Persistent Cardiac Troponin I Elevation in Stabilized Patients After an Episode of Acute Coronary Syndrome Predicts Long-Term Mortality

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Background—In patients with non–ST-elevation acute coronary syndrome, any troponin elevation is associated with an increased risk for cardiovascular events. However, the prevalence and prognostic importance of persistent troponin elevation in stabilized patients after an episode of non–ST-elevation acute coronary syndrome are unknown and were therefore assessed in this study.

Methods and Results—Cardiac troponin I (cTnI) was measured in 1092 stabilized patients at 6 weeks and 3 and 6 months after enrollment in the FRagmin and Fast Revascularization during InStability in Coronary artery disease (FRISC-II) trial. cTnI was analyzed with the Access AccuTnI assay with the application of different prognostic cutoffs. Outcomes were assessed through 5 years. Elevated cTnI levels (>0.01 μg/L) were found in 48% of the study patients at 6 weeks, in 36% at 6 months, and in 26% at all 3 measurements. cTnI elevation was associated with increased age and other cardiovascular high-risk features. The lowest tested cTnI cutoff (0.01 μg/L) was prognostically most useful and was independently predictive of mortality (hazard ratio, 2.1 [95% confidence interval, 1.3 to 3.3]; P = 0.001) on multivariable analysis adjusted for cardiovascular risk factors and randomization to an invasive versus noninvasive treatment strategy, whereas it was related to myocardial infarction only on univariate analysis.

Conclusions—Persistent minor cTnI elevation can be detected frequently in patients stabilized after an episode of non–ST-elevation acute coronary syndrome with the use of a sensitive assay. Elevated cTnI levels (>0.01 μg/L) predict mortality during long-term follow-up. Our results emphasize the importance of further troponin testing in non–ST-elevation acute coronary syndrome patients after hospital discharge. (Circulation. 2007;116:1907-1914.)

Key Words: coronary disease • prognosis • troponin

Several studies have demonstrated that in patients with non–ST-elevation acute coronary syndrome (ACS), any detectable cardiac troponin elevation is associated with an increased risk for adverse events.1–3 Troponin elevations of prognostic significance are also known to occur in a number of nonischemic conditions4 and have recently been described in general populations.5,6 However, it is unclear whether troponin elevation also can be detected in patients with stable coronary artery disease and, if so, whether this predicts an increased risk for cardiovascular events. We therefore performed this study to assess the prevalence and the prognostic importance of minor troponin elevation in a larger cohort of patients who were stabilized after an episode of ACS and followed up for 5 years.

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Methods

Patients and Study Design

This is a substudy of the FRagmin and Fast Revascularization during InStability in Coronary artery disease (FRISC-II) trial.7,8 In brief, this was a prospective multicenter study in which 3489 patients with non–ST-elevation ACS were randomized in a factorial design to an early invasive or noninvasive strategy and to 3-month treatment with dalteparin or placebo. Patients were eligible for study inclusion if they had symptoms of unstable coronary artery disease with objective signs of myocardial ischemia such as ECG changes (ST-segment depression ≥0.1 mV or T-wave inversion ≥0.1 mV) or elevated biochemical markers of myocardial necrosis. Patients with a history of previous open heart surgery, advanced age, or poor general health and those included after completion of patient recruitment to the
invasive versus noninvasive arm were treated primarily noninvasively and randomized only with regard to 3-month treatment with dalteparin or placebo. In the invasive strategy, the aim was to perform coronary angiography and, if appropriate, revascularization within 7 days from admission. Patients randomized to the noninvasive arm underwent coronary angiography only in case of refractory or recurrent angina or if they showed signs of severe ischemia on a predischarge exercise test. Informed consent was obtained from all patients, and the protocol was approved by all local ethics committees.

Selected study centers participated in a blood sampling program at 6 (range, 4 to 7) weeks and 3 and 6 months after randomization. Cardiac troponin I (cTnI) was analyzed in all available samples. However, for the purpose of this study, only cTnI results in patients without an acute myocardial infarction (AMI) or a revascularization procedure during the preceding 14 days were considered.

Study End Points and Follow-Up
The study end points were total mortality and AMI. Patients were assessed for outcome by outpatient visits after 6 (range, 4 to 7) weeks and 3 and 6 months and by telephone contacts after 12 and 24 months. During the first 6 months, all reported events were adjudicated by an independent clinical events committee. Thereafter, information on events was based on investigator report forms, outpatient visits, or telephone contacts with the patients. After 24 months and up to 5 years after randomization, all information on events was based on the Swedish National Registry on Mortality and the Swedish National Acute Myocardial Infarction Registry. This registry has been validated in a recent study on the correctness of AMI diagnosis. Follow-up was completed in all patients included in the present analysis.

Laboratory Analysis
cTnI was measured in frozen (−70°C) samples of EDTA plasma with the Access AccuTnI assay (Beckman Coulter, Fullerton, Calif). For this assay, 99th percentiles of 0.04 μg/L among apparently healthy subjects regardless of age and of 0.021 μg/L for subjects aged <60 years have been described.6,10,11 The lowest concentration measurable with this assay with a 10% coefficient of variation is 0.06 μg/L.10,11 However, minor modifications have been introduced to the AccuTnI assay recently. A change of the manufacturing process combined with a slight increase in incubation time (36 seconds) has enhanced the signal-to-dose relationship, thereby providing a more robust assay at the low end of its range. Our validation of the modified assay confirmed this. We obtained an analytical sensitivity of 0.006 μg/L (defined as the mean+2 SD of a buffer sample containing no cTnI; n=20). The imprecision profile of 839 duplicate samples showed 10% and 20% coefficient of variation values of 0.014 and 0.008 μg/L, respectively. Measurements in previously not thawed duplicate cTnI samples (n=18) showed a correlation coefficient of 0.98 to samples used in the present analysis, indicating that no in vitro cTnI degradation processes had occurred during the time of storage.

Statistical Analysis
The following cTnI cutoffs were assessed in this study: cTnI >0.04 μg/L, >0.02 μg/L, and >0.01 μg/L, which is in the range measurable with a coefficient of variation of 10% to 20%. The prevalence and prognostic importance of cTnI elevation relative to the respective cutoffs were evaluated (1) in all available samples at each measurement instance and (2) in patients with cTnI results available at all measurement instances. In the latter analyses, the patients were divided into subgroups according to cTnI levels over time, ie, negative cTnI at all measurements, elevated cTnI at 1 to 2 measurements ("temporary cTnI elevation"), and elevated cTnI at all measurements ("persistent cTnI elevation"). Because only first-time AMI after blood sampling was counted as an end point, all patients with an AMI between randomization and the respective measurements were excluded from analyses of this end point.

Continuous variables are described as medians and 25th and 75th percentiles. Categorical variables are expressed as frequencies and percentages. Differences between categorical variables were analyzed with the χ² test. Receiver operating characteristic curve analysis was applied to assess the prognostic value of cTnI levels during follow-up. Kaplan-Meier plots were used to illustrate the timing of events.

The prognostic importance of cTnI results at selected time points and of cTnI levels over time was analyzed by Cox proportional hazards analysis. Adjustment was made in a first model for age, gender, congestive heart failure, diabetes, creatinine clearance on admission, and treatment strategy. In a second model, results were adjusted additionally for a previous AMI, defined as a history of AMI before the index event, or elevated cardiac troponin T, applying a diagnostic cutoff of 0.035 μg/L (10% coefficient of variation level) at randomization (Elecsys 2010, Roche Diagnostics, Mannheim, Germany).11 In all tests, a probability value <0.05 was considered significant. All data analyses were performed by K.M.E., using the Statistical Package for Social Sciences (SPSS 12.0.1 and 14.0 software program (SPSS Inc, Chicago, Ill).

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

Results

Patient Characteristics
The study population consisted of 1092 patients. cTnI results at 6 weeks and 3 and 6 months were available in 1086, 1026, and 961 patients, respectively. According to the predefined requirements, 1072, 1017, and 953 patients, respectively, were eligible for analysis of the prevalence of cTnI elevation and of mortality. An AMI had been documented in 66, 75, and 88 patients before the measurements at 6 weeks and 3 and 6 months, respectively, leaving 1006, 942, and 864 patients eligible for analysis of the end point of AMI. A flow diagram illustrating the sample sizes is given in Figure 1. cTnI results were available at all measurement instances in 898 patients. Of these, 823 patients were eligible for analysis of the end point of AMI.

In total, 546 patients were randomized to 3-month treatment with dalteparin and 546 to placebo. Four hundred fifty-three patients were randomized to the invasive strategy, 442 patients were randomized to the noninvasive strategy, and 197 patients were not randomized to invasive versus noninvasive strategy. The clinical characteristics of the study population are given in Table 1. Patients not randomized to the invasive versus noninvasive strategy were older and had a higher prevalence of several cardiovascular risk features. Patients randomized to the invasive versus noninvasive strategies, in contrast, differed only in discharge medications of digitalis (P=0.04) and long-acting nitrates (P<0.001).

cTnI Results
At 6 weeks after randomization, cTnI elevations >0.01 μg/L, >0.02 μg/L, and >0.04 μg/L were found in 512 (48%), 230 (21%), and 107 patients (10%), respectively. The pattern of cTnI elevation over time is shown in Figure 2. Three-hundred fifty patients (74%) with cTnI >0.01 μg/L at 6 weeks also had cTnI levels >0.01 μg/L at 3 months, whereas 121 patients (26%) with cTnI levels >0.01 μg/L at 6 weeks had
cTnI levels ≤0.01 µg/L at 3 months. New cTnI elevation >0.01 µg/L at this measurement was found in 81 patients (15%) with cTnI ≤0.01 µg/L at 6 weeks. Of the patients with cTnI levels >0.01 µg/L at 3 months, 270 patients (69%) also had cTnI >0.01 µg/L at 6 months, whereas cTnI levels decreased to ≤0.01 µg/L in 123 patients (31%), among whom were 41 of the 81 patients with new cTnI elevation >0.01 µg/L at 3 months. New cTnI elevation >0.01 µg/L at 6 months was found in 55 patients (11%). In total, 377 patients (42%) had cTnI levels ≤0.01 µg/L at all 3 measurements, 288 (32%) had temporary cTnI elevation >0.01 µg/L, and 233 (26%) had persistent cTnI elevation >0.01 µg/L. Six hundred thirty-two patients (70%) had cTnI levels ≤0.02 µg/L at all measurements, whereas 207 (23%) and 59 patients (7%) had temporary and persistent cTnI elevation >0.02 µg/L, respectively.

According to univariate analysis, cTnI elevation >0.01 µg/L at any measurement was associated with higher age (P<0.001), male gender (P<0.02), hypertension (P<0.02), a previous AMI (P<0.005), and a discharge medication with angiotensin-converting enzyme inhibitors (P<0.005), diuretics (P<0.01), or digitalis (P<0.005). cTnI elevation >0.01 µg/L was inversely related to a discharge medication with lipid-lowering drugs (P<0.05). These associations remained unchanged when a cTnI threshold of >0.02 µg/L was considered. Anginal complaints were reported by 39%, 35%, and 33% of the patients at 6 (range, 4 to 7) weeks and 3 and 6 months, respectively, but were not significantly more common in patients with cTnI elevation at any of these follow-up instances (data not shown). Patients not randomized to the invasive versus noninvasive strategy had the highest prevalence of cTnI elevation (Figure 2).

### Table 1. Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Noninvasive Strategy (n=453)</th>
<th>Invasive Strategy (n=442)</th>
<th>Not Randomized (n=197)</th>
<th>P*</th>
<th>Total (n=1092)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age, y (25th to 75th percentiles)</strong></td>
<td>65.5 (58.3–71.5)</td>
<td>66.8 (58.7–72.4)</td>
<td>76.4 (65.6–81.1)</td>
<td>&lt;0.001</td>
<td>67.4 (59.3–73.9)</td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td>319 (70.4)</td>
<td>329 (74.4)</td>
<td>132 (67.0)</td>
<td>0.14</td>
<td>780 (71.4)</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>148 (32.7)</td>
<td>132 (29.9)</td>
<td>82 (41.6)</td>
<td>0.006</td>
<td>362 (33.2)</td>
</tr>
<tr>
<td><strong>Congestive heart failure</strong></td>
<td>12 (2.6)</td>
<td>10 (2.3)</td>
<td>25 (12.7)</td>
<td>&lt;0.001</td>
<td>47 (4.3)</td>
</tr>
<tr>
<td><strong>Diabetes mellitus</strong></td>
<td>63 (13.9)</td>
<td>56 (12.7)</td>
<td>28 (14.2)</td>
<td>0.73</td>
<td>147 (13.5)</td>
</tr>
<tr>
<td><strong>Smoking</strong></td>
<td>284 (62.7)</td>
<td>277 (62.7)</td>
<td>84 (42.6)</td>
<td>&lt;0.001</td>
<td>645 (59.1)</td>
</tr>
<tr>
<td><strong>Previous AMI</strong></td>
<td>100 (22.1)</td>
<td>109 (24.7)</td>
<td>98 (49.7)</td>
<td>&lt;0.001</td>
<td>307 (28.1)</td>
</tr>
<tr>
<td><strong>Previous stroke</strong></td>
<td>16 (3.5)</td>
<td>26 (5.9)</td>
<td>12 (6.1)</td>
<td>0.47</td>
<td>54 (4.9)</td>
</tr>
<tr>
<td><strong>Previous revascularization</strong></td>
<td>10 (2.2)</td>
<td>17 (3.8)</td>
<td>89 (45.2)</td>
<td>&lt;0.001</td>
<td>116 (10.6)</td>
</tr>
<tr>
<td><strong>Treatment at discharge</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Antithrombotic drugs</strong></td>
<td>434 (95.8)</td>
<td>428 (96.8)</td>
<td>189 (95.9)</td>
<td>0.84</td>
<td>1051 (96.2)</td>
</tr>
<tr>
<td><strong>β-Blockers</strong></td>
<td>404 (89.2)</td>
<td>374 (84.6)</td>
<td>158 (80.2)</td>
<td>0.02</td>
<td>936 (85.7)</td>
</tr>
<tr>
<td><strong>ACE inhibitors</strong></td>
<td>81 (17.9)</td>
<td>71 (16.1)</td>
<td>59 (29.9)</td>
<td>&lt;0.001</td>
<td>211 (19.3)</td>
</tr>
<tr>
<td><strong>Calcium antagonists</strong></td>
<td>75 (16.6)</td>
<td>56 (12.7)</td>
<td>68 (34.5)</td>
<td>&lt;0.001</td>
<td>199 (18.2)</td>
</tr>
<tr>
<td><strong>Digitalis</strong></td>
<td>11 (2.4)</td>
<td>23 (5.2)</td>
<td>13 (6.6)</td>
<td>0.08</td>
<td>47 (4.3)</td>
</tr>
<tr>
<td><strong>Diuretics</strong></td>
<td>66 (14.6)</td>
<td>71 (16.1)</td>
<td>76 (38.6)</td>
<td>&lt;0.001</td>
<td>213 (19.5)</td>
</tr>
<tr>
<td><strong>Long-acting nitrates</strong></td>
<td>188 (41.5)</td>
<td>73 (16.5)</td>
<td>126 (64.0)</td>
<td>&lt;0.001</td>
<td>387 (35.4)</td>
</tr>
<tr>
<td><strong>Lipid-lowering drugs</strong></td>
<td>203 (44.8)</td>
<td>182 (41.2)</td>
<td>75 (38.1)</td>
<td>0.23</td>
<td>460 (42.1)</td>
</tr>
</tbody>
</table>

Values are expressed as n (%) unless otherwise indicated. ACE indicates angiotensin-converting enzyme.

*P values refer to comparison between patient cohorts randomized and not randomized regarding the invasive versus noninvasive strategy.
tion to either prolonged treatment with dalteparin versus placebo or to the invasive versus noninvasive strategy did not affect the prevalence of cTnI elevation at any measurement apart from results at 6 weeks (cTnI >0.01 μg/L invasive versus noninvasive strategy: 52% versus 41%; P=0.001).

**Prognosis**

**Mortality**
At 5-year follow-up, 106 patients (9.7%) had died. According to receiver operating characteristic curve analysis, cTnI was predictive for mortality, with areas under the curves of 0.63 (95% confidence interval [CI], 0.57 to 0.69), 0.65 (95% CI, 0.59 to 0.71), and 0.63 (95% CI, 0.56 to 0.70) at 6 weeks and 3 and 6 months, respectively. Mortality in relation to the tested cTnI cutoffs is shown in Table 2. According to multiple Cox regression analysis (model 1), cTnI elevation at 3 months independently predicted mortality at cutoffs of both >0.01 μg/L (hazard ratio [HR], 2.1 [95% CI, 1.3 to 3.3]; P=0.001) and >0.02 μg/L (HR, 1.9 [95% CI, 1.2 to 2.9]; P=0.008). Additional adjustment for a previous AMI (model 2) did not affect these associations considerably (data not shown).

**Myocardial Infarction**
During 5-year follow-up, 258 patients (24%) suffered an AMI. The areas under the cTnI receiver operating characteristic curves for AMI were 0.58 (95% CI, 0.53 to 0.62), 0.59 (95% CI, 0.54 to 0.64), and 0.57 (95% CI, 0.51 to 0.63) at 6 weeks and 3 and 6 months, respectively. cTnI levels >0.01 μg/L and >0.02 μg/L, but not >0.04 μg/L, were predictive for AMI in the univariate analysis (Table 2). However, on multiple Cox regression analysis (model 1), AMI was not independently related to either cTnI >0.01 μg/L (HR, 1.4

### Figure 2. Prevalence of cTnI elevation at 6 weeks, 3 months, and 6 months. The percentage of patients with cTnI levels within the indicated range is shown in each bar. Non-inv. indicates noninvasive strategy; inv., invasive strategy; and not rand., patients not randomized to noninvasive vs invasive strategy.

### Table 2. Total Mortality and AMI at 5 Years in Relation to cTnI Levels at 6 Weeks, 3 Months, and 6 Months

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>6 Weeks</th>
<th>P</th>
<th>n</th>
<th>3 Months</th>
<th>P</th>
<th>n</th>
<th>6 Months</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cTnI ≤0.01 μg/L</td>
<td></td>
<td></td>
<td></td>
<td>560</td>
<td>35 (6.3)</td>
<td>&lt;0.001</td>
<td>573</td>
<td>31 (5.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>cTnI &gt;0.01 μg/L</td>
<td>512</td>
<td>68 (13.3)</td>
<td>0.65</td>
<td>444</td>
<td>58 (13.1)</td>
<td>0.001</td>
<td>342</td>
<td>43 (12.6)</td>
<td>0.05</td>
</tr>
<tr>
<td>cTnI ≤0.02 μg/L</td>
<td>842</td>
<td>66 (7.8)</td>
<td>&lt;0.001</td>
<td>843</td>
<td>60 (7.1)</td>
<td>&lt;0.001</td>
<td>829</td>
<td>57 (6.9)</td>
<td>0.05</td>
</tr>
<tr>
<td>cTnI &gt;0.02 μg/L</td>
<td>230</td>
<td>37 (16.1)</td>
<td>0.05</td>
<td>174</td>
<td>29 (16.7)</td>
<td>0.001</td>
<td>124</td>
<td>15 (12.1)</td>
<td>1.00</td>
</tr>
<tr>
<td>cTnI ≤0.04 μg/L</td>
<td>965</td>
<td>90 (9.3)</td>
<td>0.05</td>
<td>946</td>
<td>77 (8.2)</td>
<td>0.04</td>
<td>907</td>
<td>69 (7.6)</td>
<td>0.05</td>
</tr>
<tr>
<td>cTnI &gt;0.04 μg/L</td>
<td>107</td>
<td>13 (12.1)</td>
<td>0.05</td>
<td>77</td>
<td>12 (15.6)</td>
<td>&lt;0.001</td>
<td>46</td>
<td>3 (6.5)</td>
<td>0.05</td>
</tr>
<tr>
<td>AMI</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>cTnI ≤0.01 μg/L</td>
<td>542</td>
<td>85 (15.7)</td>
<td>0.03</td>
<td>543</td>
<td>69 (12.7)</td>
<td>&lt;0.001</td>
<td>575</td>
<td>62 (10.8)</td>
<td>0.003</td>
</tr>
<tr>
<td>cTnI &gt;0.01 μg/L</td>
<td>464</td>
<td>98 (21.1)</td>
<td>0.05</td>
<td>399</td>
<td>86 (21.6)</td>
<td>0.03</td>
<td>289</td>
<td>53 (18.3)</td>
<td>0.05</td>
</tr>
<tr>
<td>cTnI ≤0.02 μg/L</td>
<td>802</td>
<td>130 (16.2)</td>
<td>0.05</td>
<td>790</td>
<td>117 (14.8)</td>
<td>0.003</td>
<td>760</td>
<td>97 (12.8)</td>
<td>0.22</td>
</tr>
<tr>
<td>cTnI &gt;0.02 μg/L</td>
<td>204</td>
<td>53 (26.0)</td>
<td>0.05</td>
<td>152</td>
<td>38 (25.0)</td>
<td>0.001</td>
<td>104</td>
<td>18 (17.3)</td>
<td>0.05</td>
</tr>
<tr>
<td>cTnI ≤0.04 μg/L</td>
<td>914</td>
<td>164 (17.9)</td>
<td>0.05</td>
<td>874</td>
<td>139 (15.9)</td>
<td>0.12</td>
<td>827</td>
<td>109 (13.2)</td>
<td>0.05</td>
</tr>
<tr>
<td>cTnI &gt;0.04 μg/L</td>
<td>92</td>
<td>19 (20.7)</td>
<td>0.05</td>
<td>68</td>
<td>16 (23.5)</td>
<td>&lt;0.001</td>
<td>37</td>
<td>6 (16.2)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Values are expressed as n (%) unless otherwise indicated. P values refer to patient subgroups with and without marker elevation beyond indicated cutoff.
[95% CI, 0.9 to 2.1]; P=0.10) or cTnI >0.02 μg/L at 3 months (HR, 1.5 [95% CI, 1.0 to 2.4]; P=0.08).

Prognostic Importance of Elevated cTnI Levels Over Time

As demonstrated in Table 3, cTnI levels over time with application of the 0.01 μg/L cutoff provided a better prognostication than cutoffs of 0.02 or 0.04 μg/L. This cutoff allowed the stratification of patients into different risk groups, ie, patients with negative cTnI (≤0.01 μg/L) at all measurements and with temporary and persistent cTnI elevation >0.01 μg/L (Figure 3). Compared with patients with negative cTnI, the unadjusted HR for death at 5 years was 1.4 (95% CI, 0.7 to 2.7; P=0.3) for patients with temporary cTnI elevation and 1.8 (95% CI, 1.3 to 2.4; P<0.001) for patients with persistent cTnI elevation. The HR for death among patients with persistent cTnI elevation remained significantly elevated when the analysis was adjusted according to model 1 (HR, 1.5 [95% CI, 1.1 to 2.0]; P=0.01) and model 2 (HR, 1.4 [95% CI, 1.1 to 2.0]; P=0.02). For the end point of AMI at 5 years, the unadjusted HRs were 1.2 (95% CI, 0.7 to 2.1; P=0.61) for patients with temporary cTnI elevation and 1.3 (95% CI, 1.0 to 1.7; P=0.09) for patients with persistent cTnI elevation compared with those with negative cTnI.

Discussion

In this substudy from the FRISC-II trial evaluating stabilized patients after an episode of ACS, we found a high prevalence of cTnI elevation over at least 6 months from the index event. Elevated cTnI levels occurred frequently in cohorts randomized to prolonged treatment with dalteparin or placebo and to an invasive or noninvasive strategy. Importantly, elevated cTnI levels were strong predictors of an increased mortality during 5-year follow-up.

Our results thus expand previous findings in ACS patients1–3 because any detectable troponin level was also associated with an impaired prognosis in patients with stable coronary artery disease. However, because of the observational character of our study, at present we cannot provide explanations of causality. It may be suspected that cTnI elevation is caused by several factors. Higher age, male gender, and a higher prevalence of cardiovascular comorbidities, as found for the patient cohort not randomized to invasive versus noninvasive strategy, are conditions known to be associated with troponin positivity.4,5,12–16 In these conditions, troponin elevation may be caused by increased demand ischemia or myocardial strain because of volume and pressure overload.4,15 These mechanisms have also been described as causes for detectable troponin levels both in patients with nonischemic pathologies such as severe heart failure, tachyarrhythmia, or pulmonary embolism4,15,16 and in general populations.5,6 Apoptosis could be another explanation for measurable troponin levels in the long term after an ACS. In this condition, leakage of troponin and its degradation fragments to the blood stream is due to an ongoing disintegration of myofibrils.17 Apoptotic processes persist for months after an AMI.18,19 Accordingly, an elevated rate of cTnI cleavage over several weeks after AMI has been demonstrated in animals.20 Corresponding evidence in humans, however, is lacking to our knowledge. One could also speculate that some of the temporary elevations of cTnI might be caused by clinically silent coronary plaque fissures with thrombus formation and downstream embolization. This would translate into an increased risk of AMI. However, the prognostic relevance of this association appears to be limited because cTnI positivity was not independently related to AMI during long-term follow-up.

Our study is consistent with results from Zethelius et al,6 who evaluated an elderly general population using the 99th percentile of the original AccuTnI assay (cTnI ≥0.04 μg/L) as cutoff. In that study, cTnI elevation was found in 3.7% of the participants, increasing to 29% when a cutoff of ≥0.021 μg/L was applied. In our study, 4.8% of the patients had cTnI levels at 6 months above the 99th percentile of 0.04 μg/L, and 7.6% had cTnI >0.02 μg/L. The obvious discrepancy in the prevalence of cTnI elevation >0.02 μg/L between our and the aforementioned study may depend on population characteristics because slightly older patients and only men, known to have a higher prevalence of small cTnI elevation, were included in the study by Zethelius et al. Furthermore, the poorer analytical precision of the original AccuTnI assay at
levels of \( \approx 0.02 \, \mu g/L \) might also explain part of the diverging results.

Because of the improved analytical performance of the modified AccuTnI assay, we were able to reliably detect small cTnI elevation below commonly used cutoffs (ie, cTnI 0.011 to 0.02 \( \mu g/L \)) in a substantial proportion of our study patients. From a prognostic perspective, cTnI 0.01 \( \mu g/L \) as cutoff performed at least as well as the previously described 99th percentiles. In view of these results, the question of how to define “troponin elevation” needs to be addressed. Usually, the 99th percentile in healthy reference populations is applied as threshold.\(^\text{21}\) However, according to the findings from our and other studies, even measurable troponin levels well below the 99th percentile are prognostically relevant.\(^\text{14,22,23}\) Thus, for identification of high-risk patients, we suggest that troponin elevation should be defined by analytical issues (ie, the lowest reliably measurable concentration rather than distribution characteristics such as the 99th percentile).

Our findings evoke questions about current treatment and follow-up routines for patients with ischemic heart disease. Considering the high prognostic importance of minor cTnI elevation, we would emphasize the value of repetitive troponin testing during follow-up after an ACS, further cautious investigation, and at least intensive secondary preventive measures in

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure3}
\caption{Probability of death (A) and AMI (B) in relation to cTnI levels over time. cTnI negative indicates cTnI <0.01 \( \mu g/L \) at all measurements; temporary cTnI elevation, cTnI \( \geq 0.01 \, \mu g/L \) at 1 to 2 measurements; and persistent cTnI elevation, cTnI \( \geq 0.01 \, \mu g/L \) at all measurements. Probability value for mortality <0.001 (log rank); probability value for AMI=0.27 (log rank).}
\end{figure}
patients found to be cTnI positive. Even for patients with stable coronary artery disease, troponin testing using sensitive assays might be valuable to identify high-risk individuals. These issues, however, remain to be evaluated further in prospective trials.

The high rate of persistent cTnI elevation in our patients without evidence of an ongoing or a recent ACS raises further questions about the definition of AMI with the use of very low troponin cutoffs. When our results are considered, a considerable risk exists for misdiagnosis of AMI in patients with nonischemic chest pain when assessment is based only on troponin results. It is therefore important to emphasize that for fulfillment of the diagnosis of AMI in patients with chest pain, a significant rise and/or fall of serially measured troponin results should be observed, preferably in combination with other indicators of ongoing myocardial damage (eg, ECG changes).21

Limitations
All patients with an AMI during follow-up but before cTnI measurement were excluded for analyses related to AMI as a study end point because the FRISC-II database was originally designed to register only first-time AMI. It is therefore possible that our results are biased because the patients eligible for this analysis might have been healthier than those being excluded. cTnI was not measured with the current assay in samples obtained at randomization during the index event. However, troponin results from that measurement were only used to assess the impact of an AMI at index hospitalization on the prognostic value of continuing cTnI elevation. For this aim, we regarded the available troponin T results applying an established cutoff for defining AMI as an adequate substitute.

Conclusion
We have for the first time demonstrated that minor cTnI elevation is frequent in patients stabilized after a period of ACS and that any detectable cTnI level is associated with increased long-term mortality. Repetitive troponin testing in stabilized ACS patients after discharge appears to be useful for the identification of patients at risk.

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References
CLINICAL PERSPECTIVE

Although the role of cardiac troponin testing for the diagnosis of myocardial infarction and risk prediction in patients with an ongoing acute coronary syndrome is well established, no information exists on the prevalence and prognostic implications of troponin levels in the stable phase after an episode of acute coronary syndrome. Using a sensitive assay, we found a high prevalence of cardiac troponin I (cTnI) elevation over at least 6 months in 1092 stable post–acute coronary syndrome patients who participated in the FRagmin and Fast Revascularization during InStability in Coronary artery disease (FRISC-II) trial. During this period, the proportion of cTnI levels >0.01 μg/L (ie, the concentration measurable with a 10% to 20% coefficient of variation) subsequently decreased from 48% to 36%, and 26% of the patients had persistently elevated cTnI levels >0.01 μg/L. cTnI elevation predicted mortality during 5-year follow-up independent of baseline characteristics, including renal function. We therefore emphasize the value of repetitive troponin testing during follow-up after an acute coronary syndrome, further cautious investigation, and at least intensive secondary preventive measures in patients found to be troponin positive. Even for patients with stable coronary artery disease, measurement of troponin with sensitive assays might be valuable to identify high-risk individuals. Finally, the high rate of elevated cTnI levels among patients with coronary artery disease but without an indication of acute instability urges the need for adherence to complementary criteria for defining acute myocardial infarction to avoid diagnostic misclassification.
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