Clinical and Analytical Performance of the Liaison Cardiac Troponin I Assay in Unstable Coronary Artery Disease, and the Impact of Age on the Definition of Reference Limits. A FRISC-II Substudy

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Background: Measurements of cardiac troponins are currently used as the standard for the detection of myocardial injury. None of the current assays complies with the new requirements on assay imprecision as proposed by the European Society of Cardiology/American College of Cardiology. Our aim was to evaluate the clinical and analytical performance of the Liaison cardiac troponin I (cTnI) assay.

Methods: EDTA-plasma was used, and cardiac troponins were assayed with the first-generation AxSYM assay, the second-generation AccuTnI assay, the third-generation Elecsys assay, and the first-generation Liaison assay.

Results: In a 6-day imprecision study, the Liaison cTnI assay had mean CV <10% at 0.027 μg/L and <20% at 0.015 μg/L. The 99th percentile of the upper reference limit (URL) of a reference population was 0.041 μg/L (age range, 41–76 years). Individuals <60 years had a significantly (P = 0.001) lower 99th percentile, 0.022 μg/L. The FRISC-II study participants with cTnI ≥0.041 μg/L had a poorer outcome relating to death/acute myocardial infarction than those with cTnI <0.041 μg/L (P <0.001). Treatment with low-molecular-weight heparin (dalteparin) or an invasive strategy reduced cardiac events only in patients with concentrations >0.041 μg/L (P = 0.002 and 0.02, respectively). Comparison with the AccuTnI assay showed that a large cohort of the patients with poor prognosis was identified by the AccuTnI assay but not by the Liaison cTnI assay.

Conclusion: The Liaison cTnI assay is a sensitive assay with a CV ≤10% at the 99th percentile URL. The ability to detect age-related differences among apparently healthy individuals is unique among today’s commercial assays. The results indicate that different assays seem to identify different patient cohorts for cardiac risk in the lower range of cTnI concentrations.

The measurement of cardiac troponins in blood has rapidly become the gold standard for diagnosing myocardial damage. The National Academy of Clinical Biochemistry recommended that chest pain patients with cardiac troponin results above the 97.5th percentile upper reference limit (URL) should be labeled as having myocardial injury (1). A joint committee of the European Society of Cardiology and American College of Cardiology (ESC/ACC) has proposed that increased cardiac troponin indicative of myocardial injury should be defined as exceeding the 99th percentile of a reference control group (2). The ESC/ACC also defined the acceptable imprecision (CV) at the 99th percentile as ≤10%, an imprecision goal not met by any current assay.

The advantages of measurements of cardiac troponins over conventional methods in the clinical management of patients with myocardial disease have become particu-
larly obvious in patients with unstable coronary heart disease in whom only minor myocardial damage is observed. Thus, several studies have indicated the prognostic importance of increased troponins in blood in such patients (3–7). These studies, however, have also indicated a need for more sensitive methods because patients with even very minor increases seem to be at risk as compared with those in whom no troponin is detectable (8). In a recent report we showed that the second-generation troponin I (cTnI) assay on the Beckman Coulter Access, AccuTnI (9), was superior to the first-generation AxSYM cTnI assay from Abbott Diagnostics and the third-generation cardiac troponin T (cTnT) assay from Roche Diagnostics in identifying a cohort of patients with unstable coronary heart disease and relatively poor prognosis. The aim of this study was to evaluate the clinical and analytical performance of the Byk-Sangtec Diagnostica Liaison cTnI assay. Our hypothesis was that because of its increased sensitivity, the Liaison cTnI assay would identify more patients with a poor outcome and who would benefit from an active therapeutic intervention.

**Patients and Methods**

The present study was a substudy of the FRISC-II (Fast Revascularisation during InStability in Coronary Artery Disease) trial (10, 11). In brief, the FRISC-II was a prospective, multicenter trial that included a total of 3456 patients. Of these, 2457 patients were randomized to a noninvasive or an invasive treatment strategy. Furthermore, within each arm, the patients were randomized to a 90-day treatment with the low-molecular-weight heparin (dalteparin) or placebo.

The remaining 999 patients were not randomized to the invasive or noninvasive strategies because of clinical contraindications. These patients, however, were randomized into dalteparin or placebo treatment. Inclusion criteria included symptoms of myocardial ischemia associated with ST-depression, T-wave inversion, or increases in available cardiac markers. Major exclusion criteria included increased risk of bleeding, angioplasty performed within the last 6 months, wait listing for a coronary revascularization procedure, previous open heart surgery, other severe cardiac disease, renal insufficiency (serum creatinine >150 μmol/L), or other severe illness. Blood samples were obtained, on average, 37 h (interquartile range, 26–52 h) after admission to the hospital. Written consent was obtained from all patients, and the protocol was approved by all local ethics committees.

All patients were initially treated with either subcutaneous dalteparin or standard heparin by intravenous infusion. The patients were randomized within 48 h after the start of open-label dalteparin or standard heparin. From randomization, all patients received dalteparin subcutaneously (120 units/kg) twice daily until the early invasive procedure and for at least 5 days in the noninvasive strategy. After this initial treatment, patients received twice daily subcutaneous injections of either dalteparin in a dose adjusted for weight and gender (5000–7500 units) or placebo for a period of 3 months.

The early invasive strategy required coronary angiography and, if appropriate, revascularization within 7 days from start of open-label dalteparin. The noninvasive strategy included coronary angiography only in patients with refractory symptoms, severe ischemia at a predischarge symptom-limited exercise test, or severe angina or myocardial infarction (MI) during follow-up.

The reference population consisted of 456 apparently healthy individuals participating in the SWISCH (Sweden, Women and Men and Ischemic Heart Disease) study during 2001–2002. In this study, each FRISC-II patient included at six participating hospitals was initially matched for age and gender with five individuals randomly selected from the population registry. These individuals were then mailed a questionnaire concerning medical history. The questionnaires were later returned and screened by a single physician. Individuals reporting freedom from chronic disease and medication were asked to participate in a clinical examination conducted by a screening physician at the local participating hospitals. The clinical examination included additional investigation of health history; measurement of height, weight, and blood pressure; an electrocardiogram; and blood sampling. Individuals were excluded at the point of examination if chronic disease was manifest or suspected or they were acutely ill. Finally, individuals were excluded if analysis of routine blood chemistry (hemoglobin, white cells, platelets, creatinine) was outside of reference intervals and required follow-up. cTnI was measured in 408 of these individuals by the Liaison assay and in 436 by the Beckman-Coulter AccuTnI. Written consent was obtained from all healthy participants, and the protocol was approved by the local ethics committee.

Plasma was prepared from venous blood and anticoagulated with EDTA. In the FRISC-II study, the blood sample was obtained at randomization. Troponin measurements were made on freshly frozen samples (−70 °C) that had been thawed at the maximum only once. As shown previously with the AccuTnI assay, troponin concentrations are stable in plasma after several freeze-thaw cycles (12). The stability of troponin after three freeze-thaw cycles was confirmed with the Liaison cTnI assay. Troponin I in plasma was measured by three different assays: the first-generation AxSYM assay (Abbott Diagnostics), the second-generation AccuTnI (Beckman Coulter), and the Liaison cTnI assay (Byk-Sangtec Diagnostica). cTnT was measured by the third-generation Elecsys assay (Roche Diagnostics). All assays were performed with reagents supplied by the respective manufacturers and according to their instructions.

According to the manufacturers, the minimum detectable concentrations of cTnI were 0.3, 0.01, and 0.005 μg/L for the AxSYM cTnI, AccuTnI, and Liaison cTnI, respectively. Total imprecision (CV) was 4.9–17% (range, 2.7–
147.6 μg/L) for the AxSYM cTnI and 4.1–8% (range, 0.05–11 μg/L) for the AccuTnI. The minimum detectable cTnT concentration by the Elecsys assay, according to the manufacturer, was 0.01 μg/L, and total imprecision was 4–9% (range, 0.4–30 μg/L). In the clinical analysis, we chose cutoffs for the AxSYM cTnI and cTnT at concentrations where the CV was ≥20%, i.e., 1.0 μg/L (13) and 0.03 μg/L (multicenter evaluation of a third-generation cTnT assay; Roche Diagnostics), respectively. For the AccuTnI, we used as the cutoff the 99th percentile URL, which was 0.04 μg/L. At this value, the CV was 15% (14).

The combined clinical endpoint of death/acute MI (AMI) was used. For treatment comparisons, data were calculated for 1 month, and for comparison of the invasive vs noninvasive treatments, data were calculated for 6 months. Details about the follow-up and evaluation procedures and definitions have been published elsewhere (11).

Statistics
Within-day and total imprecisions were analyzed by ANOVA based on the analysis of a high and low control sera analyzed 20 times each day on 6 different days with two different batches of reagents. Between-day imprecision was calculated from the variation of the mean concentrations of the high and low controls, respectively. Linear regression analysis was used in the comparison between two assays, and differences between percentages were used to calculate differences in outcomes relating to death/AMI. All of these calculations were performed with the statistical software Statistica for Windows, Ver. 6.0. Bland–Altman difference plots were calculated with the statistical software Medcalc, Ver. 5.0.

Results
The imprecision of the Liaison cTnI assay was evaluated in two ways. In the first approach, the total imprecision was determined by analyzing a high and low controls 20 times each day on 6 different days with two different batches of reagents. The total CV for the high control (mean, 0.905 μg/L) was 4.1%, and the CV for the low control (mean, 0.046 μg/L) was 9.1%. Within-day imprecision was 5.7–12% for the low control and 0.7–5.1% for the high control. Between-day imprecision was 5.4% for the low control and 3.6% for the high control. The second approach involved evaluation of the variation for 3293 duplicate samples of the FRISC-II study. As is seen in Fig. 1, a CV of 10% for the duplicates occurred at 0.027 μg/L, and a CV of 20% for the duplicates occurred at 0.015 μg/L.

Reference limits were estimated for the Liaison cTnI assay from EDTA-plasma samples obtained from 408 Caucasian individuals age- and sex-matched (mean, 65 years; range, 41–76 years; 274 men and 134 women) with the FRISC-II participants. The overall 99th percentile and the 99th percentile for individuals ≥60 years of age (n = 310) for Liaison cTnI was 0.041 μg/L (Fig. 2). Individuals above 60 years had significantly higher cTnI values than those below [n = 98; mean (SD), 0.013 (0.009) μg/L vs mean 0.010 (0.006) μg/L; P = 0.001]. The 99th percentile for the individuals <60 years of age was 0.022 μg/L. Overall, 37% of all healthy individuals had detectable cTnI if the cutoff limit of 0.015 μg/L (CV <20% for duplicates) was used and 6% if the cutoff limit of 0.027 μg/L (CV ≤10% for duplicates) was used. The overall 99th percentile URL for the AccuTnI was 0.040 μg/L with no statistical differences between age groups.

On the basis of the FRISC-II samples, we compared the Liaison cTnI with AxSYM cTnI and AccuTnI as well as with cTnT. Linear correlations (r) between the Liaison cTnI assay and AxSYM cTnI and AccuTnI was also calculated with the statistical software Medcalc, Ver. 5.0.
cTnI assay and the two other cTnI assays were 0.92–0.94, whereas the correlation with cTnT was lower (r = 0.73). Comparisons of the Liaison cTnI with AccuTnI and AxSYM cTnI by Bland–Altman difference plots showed mean differences of 2.6 and 26.5 µg/L, respectively, and systematic differences without any apparent outliers (Fig. 3). The comparison of Liaison cTnI and cTnT showed a mean difference of 2.3 and a systematic negative difference with several outliers.

In the clinical evaluation of the Liaison cTnI assay, we used three cutoff values. One was the 99th percentile of our healthy reference population (0.041 µg/L), and the other two were the results obtained at imprecision (CV) cutoffs for duplicate samples of ±10% (0.027 µg/L) and ±20% (0.015 µg/L). As shown in Table 1, the 6-month outcome of the patients, irrespective of treatment strategies, was significantly poorer in the groups with increased cTnI.

We also evaluated cutoffs related to the age differences in reference limits and, as shown in Table 1, we divided the patients to those below and above 60 years of age and adopted the cutoffs of the 99th percentile URL for the respective age groups. The outcomes for the patients with concentrations below the 99th percentiles were significantly different, with significantly lower numbers of events for the younger group. We also saw this difference when we applied the CV ≤10% cutoff. In the next step, we evaluated the outcome in the two age groups at three different concentration ranges, forming an intermediate group with values between the two 99th percentile cutoffs. As seen in Fig. 4, the proportion of individuals with an outcome of death/AMI was increased in the intermediate group in both age groups and was similar to the cohort with concentrations above the 99th percentile of the URL; however, it was significantly larger than the proportion of individuals in the two age groups with concentrations below the lower 99th percentile URL.

In the group of patients treated with noninvasive strategies, a total of 2029 patients were treated with either placebo or dalteparin. The outcome after 1 month with respect to death/AMI was evaluated in relation to Liaison cTnI concentrations, using the cutoff of 0.041. In the group of patients with cTnI below the cutoff, we observed no differences in outcome between placebo or dalteparin. In the patients with increased cTnI, dalteparin significantly reduced the number who died and/or had another AMI (P = 0.002; Table 2).

We compared invasive vs noninvasive treatment for 2202 patients. Only patients given placebo (n = 1094) were included in the comparison. The outcome after 6 months with respect to death/AMI was evaluated in relation to Liaison cTnI results, using the cutoff of 0.041 µg/L. As is seen in Table 2, the number of deaths/AMI was significantly decreased in the invasive group (P = 0.02) with increased cTnI as measured by the Liaison cTnI. In the patients with concentrations <0.041 µg/L, we saw no differences in outcome. It is also apparent that invasive
treatment eliminates the predictive power of cTnI measurements because we found no difference in prognosis for the invasive group when separated into low or high cTnI concentrations.

We compared the outcomes in four cohorts, using the 99th percentile URL for the Liaison cTnI and AccuTnI assays (Table 3). There was an overall concordance of 89% between the two assays. Nineteen patients (0.8%) were identified as having increased cTnI by the Liaison cTnI assay but not by the AccuTnI assay, whereas 287 patients (10.1%) were identified as having increased concentra-

tions by the AccuTnI assay but not the Liaison cTnI assay. The outcome for the latter patient cohort was much poorer ($P < 0.001$) than for the cohort in which none of the assays measured positive results, but was not different from the patient cohort in which both assays measured increased concentrations. In the case of AxSYM cTnI and cTnT, the 99th percentile URLs were not established in the above cohorts. To compare the clinical performances of these assays with the Liaison cTnI assay, we compared the Liaison cTnI 99th percentile with the cutoffs of these two assays with the Liaison cTnI assay, we compared the clinical performances of the Liaison cTnI, Elecsys cTnT, and AxSYM cTnI assays were very similar and not significant.

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**Table 1. Outcomes in relation to various cutoff values and at different ages.**

<table>
<thead>
<tr>
<th>Age group</th>
<th>Cutoff, $\mu$g/L</th>
<th>No. of patients</th>
<th>Death/AMI after 6 months, $^a$ %</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>&lt;0.015</td>
<td>625</td>
<td>5.9</td>
</tr>
<tr>
<td></td>
<td>$\geq$0.015</td>
<td>2494</td>
<td>13.3 ($P &lt; 0.001$)</td>
</tr>
<tr>
<td></td>
<td>&lt;0.027</td>
<td>864</td>
<td>7.5</td>
</tr>
<tr>
<td></td>
<td>$\geq$0.027</td>
<td>2255</td>
<td>13.5 ($P &lt; 0.001$)</td>
</tr>
<tr>
<td></td>
<td>&lt;0.041</td>
<td>1001</td>
<td>8.2</td>
</tr>
<tr>
<td></td>
<td>$\geq$0.041</td>
<td>2118</td>
<td>13.6 ($P &lt; 0.001$)</td>
</tr>
<tr>
<td>&lt;60 years</td>
<td>&lt;0.022</td>
<td>216</td>
<td>3.7</td>
</tr>
<tr>
<td></td>
<td>$\geq$0.022</td>
<td>617</td>
<td>8.4 ($P = 0.02$)</td>
</tr>
<tr>
<td></td>
<td>&lt;0.027</td>
<td>234</td>
<td>4.7</td>
</tr>
<tr>
<td></td>
<td>$\geq$0.027</td>
<td>599</td>
<td>8.2</td>
</tr>
<tr>
<td>$\geq$60 years</td>
<td>&lt;0.027</td>
<td>630</td>
<td>8.6</td>
</tr>
<tr>
<td></td>
<td>$\geq$0.027</td>
<td>1696</td>
<td>15.5 ($P &lt; 0.001$)</td>
</tr>
<tr>
<td></td>
<td>&lt;0.041</td>
<td>733</td>
<td>8.9</td>
</tr>
<tr>
<td></td>
<td>$\geq$0.041</td>
<td>1553</td>
<td>15.8 ($P &lt; 0.001$)</td>
</tr>
</tbody>
</table>

$^a$ P values indicate significant differences in the percentages of outcomes below and above the respective cutoffs.

**Table 2. Outcome relating to death/AMI in patients with Liaison cTnI values above and below 0.041 $\mu$g/L.**

<table>
<thead>
<tr>
<th>Cutoff, $\mu$g/L</th>
<th>Death/AMI after 1 month $^b$</th>
<th>Death/AMI after 6 months $^d$</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.041</td>
<td>Dalteparin 5.4%</td>
<td>Invasive treatment 9.1%</td>
</tr>
<tr>
<td>$\geq$0.041</td>
<td>Placebo 4.8%</td>
<td>Noninvasive treatment 7.1%</td>
</tr>
<tr>
<td></td>
<td>Statistical difference between treatments NS $^c$</td>
<td>Statistical difference between treatments NS</td>
</tr>
<tr>
<td></td>
<td>$P = 0.002$</td>
<td>$P = 0.02$</td>
</tr>
</tbody>
</table>

$^a$ P values indicate significant differences between treatments or in the percentages of outcomes below and above the cutoff.

$^b$ Effects of medical treatment with either dalteparin or placebo were evaluated after 1 month in the cohort of patients receiving noninvasive treatment ($n = 1429$).

$^c$ NS, not significant.

$^d$ Effects of invasive or noninvasive treatment were evaluated after 6 months in the placebo-treated cohort of patients ($n = 1094$).

**Table 3. Clinical performance of Liaison cTnI compared with AccuTnI.**

<table>
<thead>
<tr>
<th>Cutoff, $\mu$g/L</th>
<th>Liaison cTnI $&lt; 0.041$ $/\mu$g/L</th>
<th>Liaison cTnI $\geq 0.041$ $/\mu$g/L</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n Death/AMI</td>
<td>n Death/AMI</td>
</tr>
<tr>
<td>&lt;0.040 $/\mu$g/L</td>
<td>223</td>
<td>19</td>
</tr>
<tr>
<td>$\geq$0.040 $/\mu$g/L</td>
<td>29</td>
<td>19</td>
</tr>
</tbody>
</table>

$^a$ All patients irrespective of treatment strategy were included in the calculations. Outcome data after 6 months were used.

$^b$ P values indicate differences in outcomes compared with the group without increased cTnI with either of the two assays.

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**Fig. 4. Outcome relating to death/AMI in the FRISC-II patients in relation to age and three different cTnI intervals as measured by the Liaison cTnI assay.**

The statistics indicate significant differences in the percentages of outcomes as to death/AMI comparison with the cohort with concentrations $< 0.022$ $/\mu$g/L. Black columns indicate outcome values for patients $< 60$ years; gray columns indicate the outcomes for patients $\geq 60$ years of age. Cutoffs were based on the 99th percentile URLs for individuals $< 60$ years (0.022 $/\mu$g/L) and $\geq 60$ years (0.041 $/\mu$g/L).
Discussion

We have shown in this study that the Liaison cTnI assay is a precise and sensitive assay (CV ≤10% for duplicates at the 99th percentile of a healthy reference population). Using the Liaison cTnI assay, we also confirmed previous reports of troponins being important for risk stratification because patient groups with increased cTnI benefited from active treatment and invasive strategies, in contrast to those patients in whom no increased concentrations were observed. Interestingly, however, the direct comparison of the Liaison cTnI assay with the AccuTnI showed that the latter identified a cohort of patients with poor prognosis that was not identified by the Liaison assay. This indicates that not only is the analytical sensitivity of the assay important, but probably also the configuration of the assay.

The imprecision for the Liaison assay was evaluated in two ways. One, the more conventional way, showed good imprecision even for the low control, which was close to the 99th percentile URL. This approach was slightly different from that recommended by NCCLS. Direct comparisons between our imprecision data on the Liaison cTnI and imprecision data reported with other assays adopting the NCCLS protocol, therefore, are not directly applicable. The other approach was to calculate the imprecision profile from a large number of duplicates. This latter approach is a practical approach that may be closer to reality because it provides an indication of the validity of actual patient sample measurements between days and between reagent batches. In addition, this approach showed a very good imprecision, fulfilling the ESC/ACC recommendations. At the 99th percentile URL, the mean imprecision (CV) was as low as 5–6%. The very high sensitivity of the Liaison assay was also reflected by the fact that the assay was able to reliably detect cTnI in 37% of the individuals in the healthy reference population. Most other assays for cardiac troponins detect 0–5% positives. The analytical performance of the Liaison assay has been validated in recent studies by others and confirmed our data on the high sensitivity of the assay (15, 16). These studies also showed the lack of interference of heterophile antibodies and that the assay measured different forms of cTnI equimolarly. Our conclusions from the imprecision studies are that the Liaison cTnI assay is a very sensitive and precise cTnI assay.

One unexpected finding in this study was the difference in cTnI concentrations between age groups in the apparently healthy reference population. We thus found significantly higher cTnI concentrations in individuals >60 years of age as measured with the Liaison assay. However, when the same samples were measured with the AccuTnI assay, this relationship was not that apparent, although more individuals above 60 years had concentrations close to the 99th percentile URL than in the younger group. The age relationship raises several questions. One important question is what the true URL really is. Should it be age-related, or do the increased values in the older group reflect the fact that these individuals have a subclinical myocardial disease?

Another puzzling finding was the very weak correlation that we observed between the results of the Liaison cTnI assay and those of the AccuTnI, which might indicate that the two assays partly measure different molecular forms of cTnI at the low concentrations measured by the assays. cTnI forms complexes with other cardiac troponins, and indeed it has been shown that several different molecular complexes exists in plasma and that these may affect the various assays differently (17–20). Possibly the design of the assays, e.g., use of antibodies directed against different epitopes, may favor the detection of some types of these molecular complexes. However, support for the notion that the lower 99th percentile value may actually be the more relevant one is the finding that the FRISC-II patients who had concentrations in the intermediate range, i.e., between the two 99th percentile cutoffs, had as poor a prognosis as those with concentrations above the upper 99th percentile cutoff. Adopting this lower cutoff value as the true 99th percentile URL also makes the differences between the Liaison and the AccuTnI assays much less, although the AccuTnI still identified more patients with poor prognosis.

In a previous study, we compared the clinical performances of the AccuTnI with the AxSYM cTnI and cTnT. In this comparison we also found that the AccuTnI identified a cohort of patients with poor prognosis not identified by either of the other two assays (9). One limitation in the comparisons between the different assays is the fact that the comparisons with the AxSYM cTnI and cTnT are based on cutoffs of the concentrations at which imprecision (CV) is ≤20% and not the 99th percentile URL. Still, when we adopted as cutoffs the concentrations at which the imprecision (CV) was >20%, i.e., 0.6 µg/L for the AxSYM cTnI and 0.01 µg/L for cTnT, we obtained very similar concordances with Liaison cTnI. Thus, our findings seem to indicate that not only is the analytical sensitivity of the cTnI assay important, but also the configuration of the assay because different assays seem to identify different patient cohorts in the lower range of cTnI concentrations.

Future studies may show whether slight increases in cTnI in apparently healthy individuals should be regarded as risk indicators related to future cardiac events such as cardiac death or AMI. Our data, however, would indicate that in the clinical management of older patients with unstable coronary disease, patients presenting with concentrations >0.022 µg/L should be regarded as at risk even if the concentrations are below the 99th percentile URL for that age group.

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References