


24. Kayaba K, Ishikawa S, Gotoh T, Nago N, Kaji E, Nakamura Y, et al. Five-year mortality of cTnI and cTnT in ACS patients admitted in routine clinical practice for all-cause death, cardiac death, and cardiac events and evaluated the cutoffs at the 99th percentile and at the 10% CV.

In a consensus document from the European Society of Cardiology (ESC) and the American College of Cardiology (ACC), myocardial infarction (MI) was redefined as any amount of myocardial necrosis in the presence of myocardial ischemia, as indicated by an increased cardiac troponin (I or T) above the 99th percentile of a reference population (9). Because many troponin assays lack acceptable precision at the 99th percentile cutoff and assay precision may be important for risk stratification, a revised cutoff has been recommended as the index for myocardial damage, as the lowest troponin concentration closest to the 99th percentile that can be measured with 10% imprecision (CV) (5). We investigated the prognostic value of a whole-blood quantitative POCT assay for risk stratification of ACS patients admitted in routine clinical practice for all-cause death, cardiac death, and cardiac events and evaluated the cutoffs at the 99th percentile and at the 10% CV.

This retrospective study was performed at four sites: Hennepin County Medical Center (Minneapolis, MN); Alameda County Medical Center–Highland Campus (Oakland, CA); Medical College of Virginia (Richmond, VA); and Mayday University Hospital (Surrey, United Kingdom). All sites obtained approval for human subject research from their respective institutional review boards. We enrolled 382 patients consecutively evaluated for ACS. No follow-up information was available for 15 patients, leaving 367 patients for analysis. Whole-blood cTnI measurements by the First Medical Alpha Dx device (Mountain View, CA) (12) were obtained at baseline (admission) and every 4–8 h after 24 h after admission. Specimens were analyzed within 30 min. The baseline and maximum concentrations were used to stratify patients. In addition, whole blood was collected from 402 healthy individuals (187 males and 215 females) to estimate the 99th percentile cutoff for cTnI (0.15 µg/L) determined by nonparametric analysis (8, 13). The median ages for males and females were 48 years (range, 35–69 years) and 46 years (range, 35–67 years), respectively. Reference individuals were not age or sex matched with the ACS population.

Two cutoffs were used for stratification, 0.15 and 0.3 µg/L. The first was at the 99th percentile as recommended in the guidelines of the ESC/ACC (9); the second, recommended by Apple and Wu (5), was the lowest concentration (above the 99th percentile) that gave a 10% CV according to the manufacturer (7). Patient
RRs of death and cardiac events within 30, 60, and 180 days were all significantly increased in the increased cTnI group, using either baseline or maximum cTnI and at both cutoffs (Table 1). The RRs of death and cardiac events within 180 days for patients with cTnI ≥0.15 μg/L at baseline were 4.2 (95% CI, 1.8–9.6) and 3.3 (95% CI, 1.9–5.7), respectively. Results were similar when we used the cutoff of 0.30 μg/L. Thirty-one percent of patients with a cTnI ≥0.15 μg/L at baseline had a cardiac event within 180 days vs 11% of those with cTnI <0.15 μg/L; death occurred in 15% and 4%, respectively. Kaplan–Meier curves (Fig. 1) by baseline cTnI at the 99th percentile cutoff (0.15 μg/L) showed early separation (before 30 days) for cardiac events (Fig. 1A), all-cause death (Fig. 1B), and cardiac death (Fig. 1C).

Electrocardiographic data were available for 336 (of the total 367) ACS patients, 79 of whom presented with ST elevation. The 180-day mortality rates in participants with and without ST elevation were similar (5.1% vs 5.8%, respectively; \( P = 0.8 \)), whereas the 180-day cardiac event rate was higher in participants with ST elevation (23% vs 13%, respectively; \( P = 0.03 \)). Adjustment for ST elevation in a multivariate model did not appreciably alter RR estimates of death or cardiac events during the 180-day follow-up (data not shown).

Patients with a baseline cTnI between 0.15 μg/L (99th percentile) and 0.3 μg/L (10% CV; \( n = 11 \)) had a significantly higher 180-day mortality rate than did those with a cTnI <0.15 μg/L (\( n = 292 \); 18% vs 3.8%; \( P = 0.02 \)), as well as a higher cardiac event rate (36.4% vs 10.7%; \( P = 0.006 \)). Patients with a maximum cTnI of at least 0.15 μg/L but a baseline below this (\( n = 32 \)) had a higher rate of cardiac event than did those with a maximum cTnI <0.15 μg/L (\( n = 260 \); 28% vs 8.5%; \( P < 0.001 \)). Mortality rates were not significantly different between these groups (6.3% vs 3.5%; \( P = 0.4 \)), but power to detect smaller differences was limited.

### Table 1. RRs of death and cardiac events based on POC cTnI at baseline (B) and maximum (M) concentrations over 180 days.

<table>
<thead>
<tr>
<th>Time</th>
<th>RR cardiac event (95% CI)</th>
<th>( P )</th>
<th>RR death (95% CI)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>180 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.15 B*</td>
<td>3.3 (1.9–5.7)</td>
<td>&lt;0.001</td>
<td>4.2 (1.8–9.6)</td>
<td>0.001</td>
</tr>
<tr>
<td>0.15 M</td>
<td>4.1 (2.4–7.1)</td>
<td>&lt;0.001</td>
<td>3.7 (1.6–8.7)</td>
<td>0.002</td>
</tr>
<tr>
<td>0.3 B</td>
<td>3.0 (1.7–5.2)</td>
<td>&lt;0.001</td>
<td>3.5 (1.5–8.2)</td>
<td>0.007</td>
</tr>
<tr>
<td>0.3 M</td>
<td>4.5 (2.6–7.7)</td>
<td>&lt;0.001</td>
<td>3.6 (1.5–8.2)</td>
<td>0.004</td>
</tr>
<tr>
<td>60 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.15 B</td>
<td>3.7 (2.1–6.6)</td>
<td>&lt;0.001</td>
<td>8.1 (2.8–24)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>0.15 M</td>
<td>4.4 (2.4–7.9)</td>
<td>&lt;0.001</td>
<td>10.2 (2.9–36)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>0.3 B</td>
<td>3.4 (1.9–6.2)</td>
<td>&lt;0.001</td>
<td>7.4 (2.6–21)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>0.3 M</td>
<td>4.6 (2.6–8.3)</td>
<td>&lt;0.001</td>
<td>8.0 (2.6–25)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>30 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.15 B</td>
<td>4.0 (2.1–7.7)</td>
<td>&lt;0.001</td>
<td>7.3 (2.4–22)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>0.15 M</td>
<td>5.7 (2.9–11)</td>
<td>&lt;0.001</td>
<td>9.3 (2.6–33)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>0.3 B</td>
<td>3.5 (1.8–6.8)</td>
<td>&lt;0.001</td>
<td>6.6 (2.3–19)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>0.3 M</td>
<td>5.8 (3.0–11)</td>
<td>&lt;0.001</td>
<td>7.3 (2.3–23)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*For example, 0.15 B refers to the patient group with cTnI concentration ≥0.15 μg/L at baseline; 0.15 M refers to the patient group with maximum cTnI concentration ≥0.15 μg/L.
The current study demonstrates that ACS patients who have increased cTnI measured on a POC whole-blood assay show a significant increase in risk over 30–180 days for all-cause death, cardiac death, and cardiac events in the presence or absence of ST elevation. These findings add to the evidence-based metaanalyses that demonstrate that increased cTnI and cTnT (measured using central laboratory instrumentation) predict the risk of adverse outcomes in ACS patients (1, 2). Our findings complement the diagnostic study for this POC assay, which revealed similar clinical sensitivities for ST-elevation and non-ST-elevation MI patients (12).

The current study demonstrates that maximum cTnI during 12–24 h of monitoring provides added risk prediction for adverse cardiac events and death in patients whose baseline cTnI is below the 99th percentile (15). The current POC findings complement previous studies (11, 16, 17) of POC testing assays for risk assessment (30-day outcomes) in chest pain patients admitted for emergency room triage; these studies used qualitative cTnI and cTnT assays (11) and a quantitative cTnI assay (Stratus CS) (16, 17). The current study provides evidence in support of the ESC/ACC consensus document (7–9) for utilizing the 99th percentile as a risk assessment cutoff for cTnI. Our findings reveal that patients with small increases above the 99th percentile but below the 10% CV cutoff are at greater risk of cardiac events and death than are patients with cTnI below the 99th percentile. Our data further support the FRISC II and TACTICS trials, which demonstrated that small increases in cardiac troponin above the 99th percentile are predictors of adverse cardiac events (3, 18, 19).

Clinical data regarding the onset of chest pain, medications, and renal function were not documented during data collection. Although the current study supports the risk-stratification value of small increases above the 99th percentile reference limit for this POC testing device, it is possible that more analytically sensitive assays may provide better prognostication, as reported by Venge et al. (18), who used a second-generation central laboratory cTnI assay. The current demonstration of value of this method for risk assessment complements its use as a
diagnostic tool for MI, thus allowing its implementation in routine clinical practice where cardiac troponin tests are used for both purposes.

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References

β-Thalassemia is characterized by the reduced production of β-globin chains as a result of mutations in the β-globin gene (1). This reduction is predictable when mutations occur in the coding sequence, but not when they occur in the 5’- and 3’-untranslated regions (UTRs), the locus control region (LCR), the promoter, or the introns. Whether such mutations are involved in the reduction of the β-globin chain production or are simple polymorphisms cannot always be inferred from clinical data. Transient transfection studies with a β-globin promoter and an heterologous reporter gene have shown that promoter mutations can decrease transcription (2) and are then associated with the β-thalassemia phenotype, as illustrated by the −30T→A mutation (3). However, such studies have often failed to provide clear-cut data regarding the transcriptional effect of a mutation or a deletion occurring in a noncoding sequence (4), and quantitative data are lacking.

To bypass these limitations and to mimic as closely as possible the regulatory mechanisms of β-human globin gene expression in vivo, we created a construct (pBLAG), in which the entire human β-globin gene was cloned behind the β-μLCR. Whereas previous assays used constructs bearing HS2 as a single LCR enhancer element (5, 6), we used the entire β-μLCR because it has been shown that the other three HS elements play also a key role in β-globin transcription (7–11).