Clinical research

Troponin is more useful than creatine kinase in predicting one-year mortality among acute coronary syndrome patients

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Aims To compare the long-term prognostic value of troponins (Tn) vs. conventional cardiac biomarker creatine kinase (CK) and CK-MB across the spectrum of acute coronary syndromes (ACS).

Methods and Results In the prospective, observational Canadian ACS Registry, 4627 patients with ACS were enrolled from 51 centres. The CK, CK-MB, Tn samples were analysed in each hospital clinical laboratory and the results related to the reference levels of the individual laboratories. The study cohort comprised 3138 (67.8%) patients who had both CK (or CK-MB) and Tn measurements during the first 24 h of hospitalisation. Vital status at one-year was determined by standardized telephone interview. 61.2% and 59.0% of patients had abnormal Tn and CK (or CK-MB) levels, respectively. Vital status at one-year was ascertained for 2950 patients (6% lost to follow-up). Among patients with normal CK (or CK-MB) levels, elevated Tn was associated with increased one-year mortality (odds ratio [OR] 2.06; 95% CI 1.37–3.11; P = 0.001). Similarly, among patients with abnormal CK (or CK-MB) levels, abnormal Tn predicted higher one-year mortality (OR 1.83; 95% CI 1.14–2.93; P = 0.01). In contrast, abnormal CK (or CK-MB) was not predictive of mortality after stratification by Tn status. In multivariable analysis controlling for other known prognosticators including creatinine, abnormal Tn (adjusted OR 1.78; 95% CI 1.30–2.44; P < 0.001) but not CK/CK-MB was independently associated with increased one-year mortality.

KEYWORDS Acute coronary syndromes; Creatine kinase; Troponin; Prognosis
Introduction

The current consensus guidelines of the Joint European Society of Cardiology/American College of Cardiology state that troponins (TnT or TnI) are the preferred biomarkers of myocardial necrosis; this is because of their improved sensitivity and specificity compared with the conventional biomarkers creatine kinase (CK) and its isoenzyme MB (CK-MB). In the setting of cardiac ischaemia or coronary artery intervention, myocardial infarction (MI) is defined as a typical rise and fall of troponin (Tn); the alternative CK-MB is used only when Tn assays are not available. Although not yet widely adopted, these diagnostic criteria for MI have gradually replaced the older World Health Organization (WHO) definition. As a result, more patients with acute coronary syndromes (ACS) are now diagnosed with MI. Yet, the clinical implications of MI diagnosed on the basis of elevated Tn but normal CK-MB are not entirely clear. In a meta-analysis of clinical trials and cohort studies, which enrolled patients with suspected non-ST-elevation ACS, a positive Tn was associated with increased short-term mortality (unadjusted odds ratio [OR] = 3.1). However, uncertainty exists regarding the comparative prognostic value of Tn vs. CK/CK-MB, especially among contemporary, less selected ACS patients and in the longer term. Furthermore, these biomarkers may be elevated in the setting of renal dysfunction, which is a powerful predictor of adverse outcome in ACS. The impact of this important confounding factor on the prognostic value of various biomarkers has not been well addressed.

We therefore sought to determine and compare the long-term prognostic value of Tn and CK/CK-MB among patients enrolled in the prospective Canadian Acute Coronary Syndromes Registry. We hypothesized that Tn, being a more accurate biomarker of myocardial necrosis, would be a better independent predictor than CK/CK-MB for one-year mortality after ACS.

Methods

Canadian ACS registry

In the Canadian ACS Registry, patients were eligible if they were: (1) ≥18 years old on presentation; (2) admitted to hospital with a suspected ACS (defined by symptoms consistent with acute cardiac ischaemia within 24 h of onset); and (3) the qualifying ACS was not precipitated by a significant concurrent event such as trauma or gastrointestinal bleeding. There were no other specific exclusion criteria, and consecutive patient enrolment was encouraged at all sites. A total of 51 academic and community hospitals in 9 provinces across Canada participated in this Registry. At each site, the designated physician or study co-ordinator recorded patient demographic and clinical data, relevant laboratory results, in-hospital treatment, outcome, and discharge diagnosis and medications on standardized case report forms, which were then scanned directly into an electronic database (Teleform™, Version 7.0, Cardiff, San Diego, CA, USA) at the Canadian Heart Research Centre. The discharge diagnosis was made by the attending physician according to one of the following categories: unstable angina, Q-wave MI, and non-Q wave MI. Central data checks were performed and queries were sent for correction. The study was approved by the local hospital research ethics board, and informed consent was obtained from all patients followed after discharge.

During the enrolment period from September 1999 to June 2001, 4627 ACS patients were recruited into the Canadian ACS Registry. Of these patients, 4568 (98.7%) and 3163 (68.4%) had CK/CK-MB and Tn measurements, respectively. The present study included 3138 ACS patients who had both Tn (i or T) and CK/CK-MB (available in 98% and 61%, respectively) measured within 24 h of presentation to hospital, according to the standard local practice. Compared to patients who did not have both biomarkers measured, these patients did not differ significantly in most baseline characteristics and one-year survival. All biomarkers were measured at the local hospital laboratory using its own assays and reference ranges. Any values higher than the upper limit of normal either at initial presentation or serially within the first 24 h were considered abnormal. The study patients were divided into four groups based on the Tn and CK/CK-MB assay results: (1) normal Tn, normal CK/CK-MB; (2) normal Tn, abnormal CK/CK-MB; (3) abnormal Tn, normal CK/CK-MB; (4) abnormal Tn, abnormal CK/CK-MB.

Outcome

The primary outcome was cumulative all-cause mortality at one-year. In-hospital deaths were recorded on case report forms, and vital status at one-year follow-up was ascertained by standardized telephone interview for hospital survivors. In assessing the prognostic value of Tn and CK/CK-MB, we chose to focus on mortality alone rather than the composite endpoint of death/MI, because the diagnosis of MI itself is based on these abnormal biomarkers. Moreover, using this robust endpoint avoided the potential problems from employing different definitions of MI.

Statistical analysis

Summary statistics are presented as medians with 25th and 75th percentiles for continuous variables, and as frequencies or percentages for categorical variables. For comparisons between groups, χ² and Kruskal–Wallis tests were used for categorical and continuous variables, respectively. Tn and CK/CK-MB were entered as dichotomous independent variables (elevated vs. normal).
normal). Kendall's $\tau\cdot\beta$ correlation was used to examine the relationship between serum creatinine (as an ordinal continuous variable) and biomarker status (normal vs. elevated, as an ordinal dichotomous variable). We performed bivariate logistic regression analysis, with and without stratification, to separately examine the predictive value of Tn and CK/CK-MB for one-year mortality, and calculated odds ratios (OR) with 95% confidence intervals (CI). Multivariable logistic regression (with backward elimination for $P > 0.10$) was used to determine the independent prognostic value of Tn and CK/CK-MB, with adjustment for age, heart rate, systolic blood pressure, Killip class, creatinine, and electrocardiographic changes (ST deviation and bundle branch block). These predictor variables were selected based on a validated ACS risk model. Linearity assumption was checked by examining the $\beta$ co-efficients of the independent continuous variables that were transformed into categorical variables of equal intervals. Model discrimination and calibration were evaluated by the c-statistic and the Hosmer–Lemeshow goodness-of-fit test, respectively. A product term was added to the model to test for interaction effect between Tn and CK/CK-MB.

Results

Of the 3138 ACS patients with both biomarkers measured, 59% and 61.2% had abnormal CK/CK-MB and abnormal Tn, respectively: 887 (28.3%) had normal CK/CK-MB but abnormal Tn; 59% and 61.2% had abnormal CK/CK-MB and abnormal Tn, respectively: 887 (28.3%) had normal CK/CK-MB but abnormal Tn; 330 (10.5%) had abnormal CK/CK-MB and abnormal Tn. Thus, the biomarker results were concordant in 76.8% and discordant in 23.2% of cases. The demographic and clinical characteristics of the study population are shown in Table 1. Overall, patients with both biomarkers negative were more likely to have previous MI and revascularization, but less frequently presented with heart failure and electrocardiographic changes (all $P < 0.001$ for group comparisons). Serum creatinine was highest in the group with normal CK/CK-MB but elevated Tn ($P < 0.001$). Patients with higher creatinine were also more likely to have abnormal Tn ($P$ for trend $= 0.01$), but not abnormal CK/CK-MB ($P = 0.94$).

Cardiac interventions during admission and discharge medication use are presented in Table 2. Patients with abnormal CK/CK-MB and normal Tn had the highest rate of fibrinolysis and lowest rate of coronary angiography during hospitalisation. Patients with both biomarkers positive were more likely to undergo revascularization, predominantly by percutaneous coronary intervention. There were no significant differences in the use of aspirin, $\beta$-blockers, and lipid lowering agents at discharge, but patients with both abnormal CK/CK-MB and Tn were more frequently treated with ACE-inhibitors ($P < 0.001$).

Most ACS patients with normal biomarkers (94.4%) were given a final diagnosis of unstable angina by the local site, while the majority with both abnormal CK/CK-MB and Tn (95.1%) were diagnosed with MI (Table 2). Unstable angina rather than MI was the final diagnosis for 58% of patients with normal CK/CK-MB but abnormal Tn.

Vital status during index hospitalisation was available for all patients, with an in-hospital mortality rate of 2.4%. Survival could not be ascertained for 6.0% of patients who were lost to follow-up at one-year.
one-year mortality rate was 9.8%, and the rates according to biomarker status are depicted in Fig. 1. CK/CK-MB alone (OR = 1.34 [95% CI 1.04–1.72], \( P = 0.02 \)) and Tn alone (OR = 1.93 [95% CI 1.46–2.53], \( P < 0.001 \)) was each predictive of one-year mortality. Stratified bivariate analyses were performed separately to examine the prognostic value of CK/CK-MB and Tn. Among patients who had normal CK/CK-MB, the one-year mortality rate was 6.5% for Tn-negative patients vs. 12.5% for Tn-positive patients; the unadjusted OR for death was 2.06 (95% CI 1.37–3.11, \( P = 0.001 \)) for abnormal Tn. Similarly, among patients with abnormal CK/CK-MB, abnormal Tn was associated with higher one-year mortality rate (6.8% vs. 11.7%; unadjusted OR = 1.83, 95% CI 1.14–2.93, \( P = 0.01 \)). Therefore, abnormal Tn predicted higher mortality irrespective of CK/CK-MB status. In contrast, CK/CK-MB was not predictive of mortality once patients had been stratified by Tn status. For patients with normal Tn, one-year mortality rates were similar regardless of CK/CK-MB status (6.5% vs. 6.8%, \( P = 0.86 \)); among Tn-positive patients, the rates also did not differ significantly by CK/CK-MB status (12.5% vs. 11.7%, \( P = 0.69 \)).

In multivariable analysis, after adjustment for age, heart rate, systolic blood pressure, Killip class, creatinine and electrocardiographic changes, abnormal Tn was an independent predictor of one-year mortality (adjusted OR = 1.67, 95% CI 1.23–2.27, \( P = 0.001 \)). In contrast, CK/CK-MB was not a significant predictor (\( P = 0.44 \)) once Tn was entered into the model. There was also no significant interaction effect between Tn and CK/CK-MB status (\( P = 0.37 \)). The c-statistic was 0.81 and the \( P \)-value for Hosmer–Lemeshow goodness-of-fit test was 0.89, indicating excellent model discrimination and calibration. CK/CK-MB was a significant predictor (\( P = 0.025 \)) only when Tn was not included in the model; when CK/CK-MB was forced into the model first, Tn remained an independent prognosticator (OR = 1.57, 95% CI 1.11–2.22, \( P = 0.01 \)). When the analyses were restricted to patients with non-ST elevation ACS only, the results remained essentially unchanged. Because the treating physicians were aware of the biomarker measurements and this likely influenced treatment decisions and outcome, further adjustments were made for revascularization and discharge medications (Table 3). Percutaneous coronary intervention (PCI), coronary artery bypass graft surgery (CABG), use of aspirin and lipid lowering therapy at discharge were associated with better one-year survival. However, after further adjustment for these treatment effects, the independent prognostic value of Tn remained essentially unchanged, with an adjusted OR of 1.78 (95% CI 1.30–2.44, \( P < 0.001 \)).

### Discussion

In this contemporary observational study of a broad spectrum of ACS patients, abnormal Tn was found to be an independent predictor of higher one-year mortality, whereas CK/CK-MB status did not provide incremental prognostic value. This may reflect the enhanced sensitivity and
specificity of Tn in the detection of myocardial injury that adversely impacts on long-term outcome.\textsuperscript{1,17–20} Since a more uniform and accurate definition is crucial to facilitate epidemiological and clinical studies of MI, the Joint European Society of Cardiology/American College of Cardiology has recommended adoption of the more sensitive troponin-based diagnostic criteria.\textsuperscript{1} Several studies have since documented a substantial increase in the diagnosis of MI based on these new criteria.\textsuperscript{4–7} In addition to providing a diagnostic “label”, a practical definition of MI should also carry important prognostic information to guide clinical management.\textsuperscript{15} As pointed out in the meta-analysis by Heidenreich et al.,\textsuperscript{8} additional studies are needed to determine the incremental prognostic value of Tn, especially among unselected ACS patients. However, there are only limited data that allow direct comparison of the relative prognostic significance of Tn vs. the conventional biomarkers CK and CK-MB, on which the older definition of MI was based. A previous study showed that CK-MB, TnT and myosin light chains conferred similar prognostic information for cardiac death and MI up to 28 months of follow-up among 196 patients without a “definite” diagnosis of MI.\textsuperscript{21} However, the prognostic value of all three biomarkers was no longer evident after adjusting for electrocardiographic findings. Of note, these three biomarkers were not directly compared with each other, and the wide CIs could not exclude major incremental prognostic value beyond that supplied by the electrocardiogram. In a study by Meier et al.,\textsuperscript{4} 224 patients with elevated Tn but normal CK-MB had higher 6-month mortality than 51 patients with a conventional diagnosis of MI, although this difference was no longer significant after adjustment for other baseline characteristics. Among 2182 moderate to high-risk patients admitted to a coronary care unit, Kontos et al. found that the 30-day mortality rate of patients with Tn elevation but normal CK-MB was higher than that of non-MI patients, but lower than that of patients with elevated CK-MB.\textsuperscript{6} In a recent study of 401 consecutive ACS patients followed for 6 months, abnormal Tn was independently associated with the composite endpoint of cardiac death, MI, revascularization and re-admission for unstable angina, while CK-MB was a less potent prognosticator.\textsuperscript{3} Rao and colleagues studied 1852 patients and also showed that Tn elevation, but not isolated CK-MB elevation, was associated with an increased risk of death or MI at 30 days.\textsuperscript{22} In contrast, in another study of 542 Tn-negative patients, abnormal CK-MB independently predicted a higher risk of death, MI, stroke and cardiac re-hospitalisation at 6 months.\textsuperscript{23} However, electrocardiographic changes were not adjusted for, and incomplete follow-up (82%) precluded definitive conclusions. In the Global Registry of Acute Coronary Events (GRACE), the largest study to date, a positive Tn offered additional prognostic value (adjusted OR = 2.3) beyond that provided by CK and clinical characteristics in predicting in-hospital mortality among 13,708 patients (unpublished data), but longer-term data are not yet available.

The present study offers additional insights in several important respects. Because elevated biomarker and electrocardiographic changes were not required for enrolment into the Canadian ACS Registry, in contrast to most clinical trials,\textsuperscript{24,25} our findings may be more generalisable and confirm the independent prognostic value of Tn among a broader spectrum of ACS patients up to one year. To critically evaluate the prognostic importance of Tn and CK/CK-MB, we focused on all-cause mortality alone as the robust primary endpoint, and avoided the potential confounding effects of including cardiac death, MI and re-hospitalisation for ACS, all of which are often themselves defined by biomarker elevation.\textsuperscript{26}

### Table 3 Multivariable logistic regression model for one-year mortality

<table>
<thead>
<tr>
<th>Independent predictor</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age\textsuperscript{*}</td>
<td>1.97</td>
<td>1.71–2.27</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart rate\textsuperscript{**}</td>
<td>1.11</td>
<td>1.05–1.18</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic blood pressure\textsuperscript{a}</td>
<td>0.93</td>
<td>0.89–0.97</td>
<td>0.002</td>
</tr>
<tr>
<td>Killip class\textsuperscript{b}</td>
<td>1.94</td>
<td>1.41–2.68</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Killip class\textsuperscript{b} III</td>
<td>2.18</td>
<td>1.24–3.82</td>
<td>0.007</td>
</tr>
<tr>
<td>Killip class\textsuperscript{b} IV</td>
<td>6.14</td>
<td>2.14–17.63</td>
<td>0.001</td>
</tr>
<tr>
<td>Electrocardiographic changes</td>
<td>1.38</td>
<td>1.03–1.84</td>
<td>0.03</td>
</tr>
<tr>
<td>Creatinine\textsuperscript{c}</td>
<td>1.04</td>
<td>1.03–1.06</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Abnormal troponin</td>
<td>1.78</td>
<td>1.30–2.44</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Aspirin</td>
<td>0.42</td>
<td>0.30–0.59</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lipid lowering therapy</td>
<td>0.78</td>
<td>0.58–1.05</td>
<td>0.10</td>
</tr>
<tr>
<td>PCI</td>
<td>0.68</td>
<td>0.42–1.08</td>
<td>0.10</td>
</tr>
<tr>
<td>CABG</td>
<td>0.24</td>
<td>0.07–0.88</td>
<td>0.03</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Per 10 mmHg increase.  
\textsuperscript{b} Referent to Killip class I.  
\textsuperscript{c} Per 10 l mol/L increase.  
\textsuperscript{*} Per decade increase.  
\textsuperscript{**} Per 10 beats/min increase.

CABG, coronary artery bypass graft; CI, confidence interval; PCI, percutaneous coronary intervention.
In addition, although physicians’ treatment decisions are likely based in part on the biomarker status, we demonstrated that the superior and independent prognostic value of Tn was preserved after adjustment for treatment effects. Furthermore, as Tn and CK/CK-MB may be differentially elevated in renal dysfunction which is an established marker of adverse outcome in ACS, creatinine was included in the multivariable analysis. Our results showed that while Tn was more frequently elevated with worsening renal function, it remained a better predictor of mortality than CK/CK-MB among ACS patients.

Among CK/CK-MB negative patients, the rates of coronary angiography were similar regardless of the Tn status. Although the rate of revascularization was only slightly lower among patients with normal CK/CK-MB and abnormal Tn compared with patients with elevated CK-MB, it should be noted that a much higher proportion of patients in the latter group presented with ST elevation and received fibrinolytic therapy. While coronary angiography is not routinely indicated in the management of ST elevation ACS, mounting evidence from recent randomized clinical trials suggests that patients with non-ST elevation and abnormal Tn benefit from early invasive risk stratification and revascularization. As an early invasive approach has become more widely adopted since the time period in which the Canadian ACS Registry was undertaken, Tn is expected to play a more important role in the triage of patients for revascularization.

Our results also confirmed that inconsistency in diagnosing MI persisted in the ‘‘real world’’, albeit less than that observed in the Euro Heart Survey. A small proportion of ACS patients were given a final diagnosis of unstable angina at the local site despite having abnormal biomarkers; in particular, over half of ACS patients with abnormal Tn alone were given a diagnosis of unstable angina. However, it should be noted that the Canadian ACS Registry was initiated before the dissemination of the consensus guidelines. As the new diagnostic criteria become more widely implemented in the future, their impact on the relative prevalence of unstable angina and MI among unselected ACS patients should be re-assessed.

Finally, similar to the Euro Heart Survey experience, only 68.4% of patients in the ACS Registry had a Tn measurement within the first 24 h of admission. This observation underscores the under-utilization of a potentially useful biomarker in the management of ACS in the ‘‘real world’’.

Several study limitations should be acknowledged. First and foremost, given the observational nature of this study, the timing and frequency of biomarker measurements within the first 24 h were left to the discretion of the treating physician. These might be different for Tn and CK/CK-MB, and likely accounted for the small percentage of cases (10.5%) with abnormal CK/CK-MB but normal Tn. Indeed, it is plausible that many of these patients presented with ST elevation MI (Tables 1 and 2) with initially negative Tn, but only CK/CK-MB were measured subsequently to estimate the extent of MI. However, this bias would only result in underestimation of the prognostic value of Tn. When the biomarker status on initial presentation was used in the multivariable analysis, the results were unchanged (data not shown). All the biomarker assays were performed locally without core laboratory validation. Assay precision and reference range may vary between sites, especially with respect to Tn measurements and the use of CK-MB mass vs. activity assays. It is evident that the prevalence of MI is largely dependent on the chosen diagnostic cut-off. Yet our results showed that despite these assay limitations, Tn remained a more powerful predictor of mortality than CK/CK-MB in the ‘‘real world’’. Since the quantitative results of the biomarker assays were not available, we could not compare the prognostic significance of different degrees of Tn vs. CK/CK-MB elevation, which may predict outcome. However, even minor elevations of Tn have been shown to portend an unfavourable outcome. Moreover, a bedside multimarker strategy that incorporates both CK-MB and Tn measurements may offer several clinical advantages that cannot be addressed by the present study. Finally, Tn measurement was not available in the entire Canadian ACS cohort, and a small proportion of patients (6%) were lost to follow-up, although their baseline characteristics did not differ systematically from those of the remaining cohort (data not shown).

Conclusions

Elevated Tn is independently associated with higher one-year mortality across the broad spectrum of ACS, while CK/CK-MB does not confer any incremental prognostic value. These findings support the use of Tn both for the diagnosis of myocardial infarction as recommended by current guidelines, and for the risk stratification of contemporary unselected ACS patients. Further efforts are needed to promote more widespread use of this valuable biomarker in the management of ACS.

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References


