A rapid troponin-I-based protocol for assessing acute chest pain

N.J. ALP, J.A. BELL and M. SHAHI

From the Cardiology Department, John Radcliffe Hospital, Oxford, and Cardiology Department, Royal Berkshire and Battle Hospitals, Reading, UK

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Summary

In a prospective randomized open trial with 30-day follow-up, we compared a troponin-I-based protocol to ‘standard management’ for the diagnosis and risk stratification of patients with acute non-ST-elevation chest pain. Patients with acute chest pain (n = 400) were randomized to standard diagnostic tests and management, or a protocol based on the admission ECG and the troponin-I result 6 h after onset of chest pain. Low-risk patients were discharged early from CCU; high-risk patients were treated with medical therapy or referred for in-patient angiography as appropriate. We measured length of CCU stay, and followed all patients for major adverse cardiac events (MACE) of death, non-fatal myocardial infarction (MI), or urgent revascularization during the admission and for 30 days post-discharge. The troponin protocol allowed earlier discharge in the low-risk group (10 vs. 30 h, \( p < 0.001 \)) with no excess of adverse events compared to standard management (3% vs. 5%, \( p = 0.32 \)). It identified a group of patients at moderate risk of cardiac events (15% MACE rate during admission and 30-day follow-up), and a high-risk group (75% MACE rate) more accurately than did standard management. The prognostic power of troponin testing in combination with the admission ECG was higher than with either test used alone. The protocol improved the efficiency of low-risk patient management, and improved patient risk stratification. This study adds to the evidence favouring troponin evaluation as part of the management of acute coronary syndromes.

Introduction

The assessment of patients with acute chest pain of possible cardiac cause continues to be a challenge. The presence of ST segment elevation in the ECG is highly specific (but only about 50% sensitive\(^1\)) for acute myocardial infarction (MI). However, many patients presenting to coronary care units have chest pain without ST elevation in the ECG. The diagnostic possibilities in these cases include: acute coronary syndrome in evolution, or ‘non-ischaemic’ chest pain (e.g. aortic dissection; pericarditis; pleurisy; pulmonary embolism; gastro-oesophageal reflux, or musculo-skeletal pain). These diagnoses are currently differentiated in many UK hospitals using clinical review, chest radiography, serial ECG analysis, and serial assessments of ‘cardiac enzymes’. In many cases, two or three days may elapse before a diagnosis of acute coronary syndrome can be excluded. In addition, the traditional biochemical ‘gold-standard’ of CK-MB levels has limited prognostic power.\(^2,3\) Hence, many patients occupy CCU beds unnecessarily, and others are discharged only to return with recurrent coronary events. Recently, several studies have shown that measurements of the cardiac-specific contractile proteins troponin I and troponin T are more sensitive than CK-MB for detecting minor myocardial injury.\(^4,5\) In addition, they may predict recurrent
cardiac events in patients with acute coronary syndromes. However, use of troponin testing has been limited by availability of laboratory-based diagnostic techniques and by relatively long processing times.

A new bedside test kit that provides a qualitative troponin I result within 15 min has recently been evaluated. Patients attending an emergency room with acute chest pain were managed using standard diagnostic techniques, but troponin T and troponin I tests were also performed at 6 h after chest pain onset. Diagnostic and management decisions were recorded and patients followed up over 30 days. Troponin I testing had better sensitivity, specificity and prognostic value than troponin T testing. A positive troponin I result was a strong predictor of cardiac events (death from cardiac causes or MI) in the next 30 days. The predictive value of a negative troponin I result was also high, with a total 30-day event rate of 0.3%, regardless of the admission ECG.

The study identified three important roles for bedside troponin I testing in patients with acute chest pain: (1) a negative result at 6 h may allow rapid discharge from the coronary care unit; (2) a positive result indicates myocardial damage (up to 10 days after a clinical event) allowing rapid diagnosis of a recent or evolving acute coronary syndrome; (3) in conjunction with the admission ECG, a positive troponin I result may allow risk stratification of acute coronary syndromes.

The present study was designed to evaluate a management strategy for patients with acute chest pain, using bedside troponin I testing in conjunction with the admission ECG for rapid diagnosis and risk stratification. The strategy was designed to permit early and safe discharge from CCU for low-risk patients, while initiating rapid treatment for patients with high-risk acute coronary syndromes.

**Methods**

**Patients**

The study was done in a 10-bed cardiac care unit (CCU) of a large district hospital in the UK (serving a population of approximately 480,000). The local research ethics committee approved the study protocol. We obtained written informed consent from all study participants. Patients aged >18 years referred to the CCU with acute chest pain (within 24 h of presentation) of possible cardiac cause were considered eligible for the study. Exclusion criteria were: evidence of ST elevation on the admission ECG, evidence of MI within the previous 2 weeks, and inability to provide informed consent.

**Troponin I testing**

Serum troponin I testing was done with a rapid-assay solid-phase kit (Spectral Cardiac STATus Troponin I Rapid Test, Spectral Diagnostics) clinically validated by Hamm and colleagues. This test uses two-colour-labelled mouse monoclonal antibodies and a biotinylated polyclonal goat capture antibody forming a sandwich complex with the troponin I molecule, which adheres to streptavidin in the signal zone. Enrichment of colour-labelled antibodies binding to troponin I (discriminator value 0.1 ng/ml) results in a colour line within 15 min at room temperature. To perform the test, 0.2 ml of whole venous blood is applied to a well on the test strip. The plasma diffuses into the test area, and the test develops within 15 min. A positive control line is compared to the troponin I line. Any colour appearing in the troponin I line represents a positive test.

Trained CCU nursing staff performed the troponin test 6 h after the onset of the worst chest pain, or 6 h after admission if the timing of chest pain was in doubt.

**Trial design**

We used a prospective randomized open design. Patient allocation was predetermined using a computerized random number generator. Patients were randomized (Figure 1) to either:

(i) A ‘standard management’ arm of serial cardiac enzymes (CK, AST) and ECGs over 24–48 h to confirm or exclude an acute coronary syndrome. Patients with a presumptive diagnosis of unstable angina or non-Q wave MI were treated with at least aspirin, beta-blockers and low-molecular-weight heparin. Further diagnostic tests (e.g. exercise testing) and treatments were organized at the discretion of the physician in charge.

Patients in whom acute coronary syndrome was excluded were then discharged to a general ward or home.

(ii) A ‘troponin’ arm where diagnosis and management was guided by the both the admission ECG (as interpreted by the duty physician) and 6-h troponin I test result, within the context of continuing clinical assessment. An ‘ischaemic ECG’ was defined as planar ST depression >1 mm in any lead, or abnormal T-wave inversion. Patients with an ECG showing ST elevation or new left bundle branch block were not included in the trial, but considered for standard treatment with thrombolysis. Patients with established left bundle branch block on the ECG were considered to have a ‘non-ischaemic’ ECG for the purposes of this study. Troponin-positive patients...
(regardless of the ECG) were managed for ‘high-risk’ acute coronary syndrome, with aspirin, beta-blockers and low-molecular-weight heparin. Troponin-negative patients with an ischaemic ECG were treated as ‘moderate-risk acute coronary syndrome (aspirin, beta-blockers, and low-molecular-weight heparin at the discretion of the physician in charge). Troponin-negative patients with a normal ECG were considered to have a ‘low-risk chest pain syndrome’, and were prepared for discharge from CCU (to a medical ward or home) at the earliest opportunity.

**Outcome measures**

The predetermined primary endpoints were the major adverse cardiac events (MACE) of cardiac death, non-fatal MI (CK 2 times upper limit of the hospital laboratory reference range), and urgent revascularization (coronary angioplasty or bypass surgery) during the index hospital admission and during 30-day follow-up. Only those patients who developed a raised CK after the first 6 h of admission were included in the ‘in-hospital MI’ endpoint. The secondary endpoint was the length of CCU stay.

**Follow-up**

The duration of the CCU admission from arrival to actual ward transfer or discharge was recorded. Patients were monitored during the index admission for adverse cardiac events. Following discharge, all patients were contacted (via their primary care physician) by telephone or letter following a structured interview. Adverse events were confirmed by reference to hospital notes or general practice records. In the event of undetermined cause of death, this was assumed to be cardiac.

**Statistical analysis**

Statistical analysis was on an ‘intention to treat’ basis. χ² analysis, with appropriate correction, was used to compare categorical variables. Standard parametric tests were used for continuous variables. Skewed data sets (for example the length of CCU stay) were transformed mathematically prior to parametric statistical analysis. Sensitivity and specificity analyses used standard equations. Data were analysed using Microsoft Excel 97 software. All reported p values are two-sided.

**Power calculation**

Assuming a 30-day MACE rate of 20%, we calculated that to detect a 10% absolute difference in outcome between management arms, with a significance level (α) of 0.05 and power (1-β) of 0.80, we would require 200 patients in each group.

**Results**

From September 1998 to August 1999, 1401 patients were admitted to the CCU, of whom 665 with non-ST-elevation chest pain were screened; and 400 gave consent and were randomized. Two patients were lost to 30-day follow-up in the ‘standard management’ arm and one patient in
the ‘troponin’ arm (99.3% complete follow-up).
The trial profile and patient diagnostic categories are shown in Figure 2.
There were no significant differences in the baseline characteristics of the two groups, including age, gender, previous cardiac history, or presenting ECG (Table 1).

### Duration of admission in CCU

Patients who were troponin-negative with a normal ECG (50% of all admissions) were discharged from CCU more quickly than patients in the ‘standard management’ arm with a normal ECG (mean 10 h (median 7 h) vs. mean 30 h (median 22 h)) (t-test on transformed dataset \( p < 0.001 \)) (Table 2). High-risk troponin-positive patients stayed longer in CCU (mean 86, median 82 h) than patients with an ischaemic ECG in the ‘standard management’ arm (mean 57, median 56 h) (t-test on transformed dataset \( p < 0.001 \)).

### Clinical outcomes

Table 2 summarizes the clinical outcomes, with 95% CIs included with the event rates.

**Comparisons within the ‘standard management’ arm**

In the ‘standard management’ arm, 61/180 patients (34%) had an ischaemic ECG (ST depression or T wave abnormalities) on admission. Of these patients, 17 (28%) went on to have a significant

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**Figure 2.** Trial profile.

**Table 1** Baseline and admission characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Standard management group (( n = 180 ))</th>
<th>Troponin I protocol group (( n = 217 ))</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (range) age</td>
<td>62.2 (30–93)</td>
<td>63.5 (30–94)</td>
<td>0.31</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>119/61</td>
<td>126/91</td>
<td>0.10</td>
</tr>
<tr>
<td>History of chronic stable angina</td>
<td>30%</td>
<td>36%</td>
<td>0.20</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>24%</td>
<td>21%</td>
<td>0.47</td>
</tr>
<tr>
<td>Previous revascularization</td>
<td>12%</td>
<td>11%</td>
<td>0.75</td>
</tr>
<tr>
<td>ST depression on admission ECG</td>
<td>18%</td>
<td>23%</td>
<td>0.19</td>
</tr>
<tr>
<td>Raised CK &lt; 6 h from admission</td>
<td>1.6%</td>
<td>2.3%</td>
<td>0.46</td>
</tr>
</tbody>
</table>
Table 2 Combined pre-discharge and 30-day follow-up outcomes

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Standard management (n = 180)</th>
<th>Troponin I (TnI) management protocol (n = 217)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>iECG (n = 61)</td>
<td>nECG (n = 119)</td>
</tr>
<tr>
<td>Admission time (h) (mean, median, IQR)</td>
<td>57, 56, 31</td>
<td>30, 22, 34</td>
</tr>
<tr>
<td>MI (95% CI)</td>
<td>35% (23–48%)</td>
<td>3% (1–7%)</td>
</tr>
<tr>
<td>Revascularization (95% CI)</td>
<td>2% (0–9%)</td>
<td>2% (0–6%)</td>
</tr>
<tr>
<td>Death (95% CI)</td>
<td>0% (0–6%)</td>
<td>0% (0–3%)</td>
</tr>
<tr>
<td>Combined MACE (95% CI)</td>
<td>37% (24–49%)</td>
<td>5% (1–9%)</td>
</tr>
</tbody>
</table>

MI, non-fatal myocardial infarction; IQR, interquartile range, iECG, ischaemic ECG; nECG, normal ECG; TnI, troponin I.

CK release during the hospital admission, compared to 4/119 patients (3%) with a non-ischaemic admission ECG (p < 0.001). Following discharge, a further 4/61 patients (7%) with an ischaemic admission ECG had a documented MI within 30 days, compared to 0/119 patients (0%) with a non-ischaemic admission ECG (p < 0.005). There were no deaths in either group of the ‘standard management’ arm, and only 2% of the patients in each group underwent urgent revascularization within 30 days of discharge.

Comparisons within the ‘troponin’ arm
In the ‘troponin’ arm, 51/217 patients (24%) were troponin-positive, of whom 45 also had an ischaemic ECG. Troponin-positive patients were thus analysed as a single group. Of these 51 patients, 29 (57%) had a significant CK release during the admission, compared to 4/57 patients (7%) who were troponin-negative but with an ischaemic admission ECG (p < 0.001), and 1/109 patients (1%) who was troponin-negative with a non-ischaemic ECG (p < 0.001). Following discharge, a further 3/51 patients (6%) who were troponin-positive had a documented MI within 30 days, compared to 1/57 patients (2%) who were troponin-negative but with an ischaemic admission ECG (p = 0.34), and 0/109 patients (0%) who were troponin-negative with a non-ischaemic ECG (p = 0.011). During admission and following discharge there were 4 deaths and 7 urgent revascularizations in the ‘troponin’ arm of the study, but no significant differences between low-risk and high-risk patients. The single post-discharge death in the low-risk ‘troponin’ arm group was an 84-year-old man who was certified dead at home by his general practitioner 3 days post discharge, although no post-mortem examination was performed. For the purposes of this study, we assumed his death to be cardiac in origin.

Comparisons between the ‘standard management’ and ‘troponin’ arms
Six of 119 patients (5%, 95% CI 1–9%) with a non-ischaemic ECG in the ‘standard management’ arm had a major adverse cardiac event during the period including admission and 30-day follow-up, compared to 3/102 patients (3%, 95% CI 1–8%) in the troponin-negative, non-ischaemic ECG group (p = 0.32). Twenty-three of 61 patients (37%) with an ischaemic ECG in the ‘standard management’ arm had a major adverse cardiac event during this period, compared to 43/102 patients (42%) in the ‘troponin’ arm who had an ischaemic ECG (regardless of troponin status) (p = 0.57).

Prognostic power of troponin I and ECG analysis
We performed analyses of the sensitivity and specificity of the admission ECG (‘ischaemic’ or ‘non-ischaemic’) alone, the 6-h troponin-I result alone, and the two tests in combination for the diagnosis of a major adverse cardiac event during the admission and for the next 30 days. The combination of the two tests was superior to either used alone, with a combined sensitivity of 91.9%, specificity of 90.5%, positive predictive value of 75.6% and negative predictive value of 97.2% (summarized in Table 3).

Discussion
Increasing acute chest pain admissions in the UK continue to pressurize limited CCU resources, hence the need to rapidly discriminate high-risk from low-risk patients. This randomized study compared a rapid protocol based on troponin-I and ECG against the pre-existing standard ‘rule out MI’...
management for patients with acute chest pain. Our aim was to validate the safety and clinical utility of the new protocol, for the rapid discharge of low-risk patients from CCU and the early identification of high-risk patients. We chose the Spectral Cardiac STATus Troponin I Rapid Test kit because it had already been shown to have high positive and negative predictive value in a large clinical study of patients with acute chest pain.11

Principal findings and comparisons

Of the patients referred to our CCU with possible acute cardiac chest pain, 50% were assigned to the low-risk group by our protocol, as judged by a negative 6-h troponin-I result and a non-ischaemic ECG. These patients were discharged significantly more quickly from CCU than control patients, assessed by serial ECG and cardiac enzyme results (mean of 10 vs. 30 h), making available almost one extra bed day per patient. In practice, this may not necessarily lead to cost savings, but should improve availability of CCU beds for patients who have most to gain from this level of care. The rapid discharge approach did not lead to an increase in adverse events compared to standard management, but there was nevertheless a 30-day MACE rate of 3% (95%CI 0–8%) in this ‘low-risk’ group. Thus, analysis of ECG and cardiac markers should be performed in the context of repeated clinical assessments, and patients with a high clinical suspicion should not be discharged early.

The 30-day MACE rate of 3% in the ‘low-risk’ group was higher than the 0.3% 30-day MI and death rate in the troponin-I negative group reported by Hamm et al.11 This may be due to differences in patient characteristics, to the additional inclusion of ‘revascularization’ as an endpoint in our study, or simply to chance.

Patients who were troponin-positive at 6 h (88% of these also had an ischaemic ECG) had a very high risk (57%) of going on to develop myocardial necrosis during the next few days. There was an additional 7% rate of documented MI and 4% rate of urgent revascularization during the 30 days post discharge in the troponin-positive group. This is similar to the post-discharge event rates reported by Hamm and colleagues19 and in the TRIM,13 CAPTURE,14 and PRISM-PLUS15 trials. Thus, a 6-h positive troponin result with ischaemic ECG changes was a marker of early minor myocardial damage and impending frank myocardial infarction, identifying a window of opportunity for early intensive medical therapy or coronary intervention. Retrospective analyses of patients’ troponin status from large studies including CAPTURE,16 FRISC-217 and EPISTENT18 suggested that the benefit from glycoprotein (GP) IIb/IIIa inhibitors and early revascularization was particularly marked in troponin-positive patients with acute coronary syndrome. However, the recently reported results from the GUSTO-IV ACS study19 suggest that adding Abciximab to aspirin and heparin (with no planned coronary intervention) may not offer any additional benefit in this patient group. Thus, a combined approach of GP IIb/IIIa inhibition with early revascularization seems appropriate for high-risk patients with ischaemic ECG changes and positive troponin results.

There was a combined in-hospital and 30-day MACE rate of 15% for patients who were troponin-negative but had an ischaemic ECG. This represents an intermediate risk group, which may be further risk-stratified using in-patient exercise testing or perfusion scintigraphy as appropriate. In our view, even those patients in this group who settle on medical therapy should be offered coronary angiography on at least an urgent elective basis, aiming to reduce their event rate further.

**Troponin I and troponin T assays**

During the development of troponin assays there has been debate about the relative value of troponin T versus troponin I testing. There are several troponin I assays available, with individual
Limitations

Our study has a number of limitations. The study was for obvious reasons not blinded, and this may have introduced bias into the management of the patients in the two arms. There was a small difference in the number of patients allocated to each arm, due to the random number generator used, but this would not in itself lead to bias. The event rate during 30-day follow-up was lower than we anticipated, so the study is underpowered to confidently exclude important differences in outcomes between low-risk patients in the two management arms. About one-third of the patients potentially eligible for the study were not recruited, which may limit the applicability of the results to the wider population. Several different physicians were involved in the interpretation of the ECGs for the inclusion of patients in the study. This may have led to errors in patient classification, as patients were managed and analysed according to the original ECG interpretation. However, retrospective review of all ECGs in the study showed >95% to be correctly classified, and it was our intention to conduct the study in a manner as close to normal clinical practice as possible.

The classification of MI was based on total CK measurements more than twice the upper reference range. We did not use CK-MB (by mass) measurements, as recommended by recent guidelines, because the assay was not routinely available in our hospital. It is therefore possible that the less-specific CK measurements may have led to some incorrect patient classifications.

The medical management of even high-risk patients was limited to aspirin, low-molecular-weight heparin, beta-blockers and other antianginal therapy as required. It did not include GP IIb/IIIa inhibitors, and immediate percutaneous intervention was not available in the majority of cases. The average waiting time for in-patients referred to our link tertiary cardiac centre was 4–7 days during the study. It is possible that the use of GP IIb/IIIa inhibitors combined with transfer for revascularisation within 48 h may have led to lower MI rates in high-risk patients than we observed. This strategy requires testing in large prospective clinical trials.

Our protocol used a single troponin-I measurement at least 6 h after chest pain onset, in conjunction with the admission ECG. Other authors have advocated an additional troponin measurement 12–16 h after admission, to reduce the false negative rate. Such an approach would likely improve the sensitivity for the diagnosis of evolving acute coronary syndrome, but would also lead to longer admission times. Our protocol was based on the study of Hamm and colleagues, who reported a very low MACE rate (0.3%) in those patients with a negative 6-h troponin I result, using an identical test kit. However, our own results suggest that repeated troponin testing 12 h after admission would be appropriate for patients with a high clinical suspicion of cardiac ischaemia or with ischaemic ECG changes.

Conclusions

This is to our knowledge the first randomized trial to compare a troponin-based acute chest pain protocol against standard management for patients with acute coronary syndrome. This protocol allowed earlier discharge in approximately 50% of patients (the low risk group) with no excess of adverse events compared to standard management. It also identified a group of patients (about 25% of the total) at moderate risk of cardiac events, for whom early angiography and intervention could be considered. Finally, the troponin protocol identified a high-risk group (about 25% of patients) more accurately than standard management for whom aggressive medical therapy and in-patient investigation/revascularization would be appropriate. We believe such a protocol should not be considered a replacement for careful clinical assessment, but rather an adjunct to it. This study adds to the accumulating evidence in favour of troponin evaluation as part of the diagnosis and risk stratification of acute coronary syndrome.

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References


