Long term risk stratification of patients with acute coronary syndromes: characteristics of troponin T testing and continuous ST segment monitoring

B L Nørgaard, K Andersen, K Thygesen, J Ravkilde, P Abrahamsson, L Grip, M Dellborg

Objective: To examine the long term prognostic characteristics of troponin T testing and continuous multi-lead ST segment monitoring in combination with clinical and 12 lead ECG risk indicators in patients with acute coronary syndromes (ACS).

Patients and design: Patients with suspected ACS (n = 213) were studied. Troponin T was analysed in blood samples collected during the first 12 hours after admission. Continuous vectorcardiography ST segment monitoring was performed for 24 hours and the number of ST vector magnitude episodes was registered. Patients were followed up for a median of 28 months. The end point was a composite of cardiac death and acute myocardial infarction.

Results: Thirty eight (18%) patients reached the composite end point. The median (interquartile range) time from study inclusion to the time of the composite end point was longer for patients predicted to be at risk by troponin T testing (n = 27) than for those predicted to be at risk by ST segment monitoring (n = 20) (8.4 (0.2–1.5) months vs 0.3 (0.1–4.3) months, p = 0.04). Significant univariate predictors of the composite end point were age > 65 years, diabetes, previous myocardial infarction, congestive heart failure, use of β blockers or diuretics at admission, 12 lead ECG ST segment depression at admission, troponin T concentration ≥ 0.10 µg/l, and > 1 ST vector magnitude episodes. Age > 65 years, previous myocardial infarction, and troponin T concentration ≥ 0.10 µg/l provided independent prognostic information after multivariate analysis of potential risk variables. The prognostic value of transient ischaemic episodes in ACS seems to be confined to the short term.

Conclusions: Both biochemical and continuous ECG markers reflect an increased risk for patients with ACS; however, the methods exhibit different temporal risk characteristics.

Both evaluation of troponin concentrations and continuous ST segment monitoring are valuable tools for early risk assessment of patients with acute coronary syndromes (ACS). Both troponin T and continuous multi-lead ST segment monitoring have independent short term prognostic value in ACS. However, no previous study has assessed the long term prognostic significance of combining troponin T testing and continuous ST segment monitoring among such patients. We have extended the follow up period in the TRIM (thrombin inhibition in myocardial ischemia) trial from 30 days to a medium of 28 months and investigated the long term prognostic significance of early troponin T testing and continuous ST segment monitoring in combination with clinical and 12 lead ECG risk indicators among patients with ACS.
Twelve lead ECG
A 12 lead ECG was obtained at admission. ECGs were interpreted by the local investigators and categorised according to the predominant ST-T segment status—that is, whether ST elevation, ST depression, T wave inversion, or any ST-T wave change were present.

Troponin T
Blood specimens for troponin T analysis were obtained at inclusion and after six and 12 hours. Plasma was kept at −80°C and sent to a core laboratory for analysis by personnel without knowledge of the patients’ status (Aarhus University Hospital, Aarhus, Denmark). Troponin T was measured with an immunoassay (ELISA troponin(e) T) on the ES 300 analyser (Boehringer Mannheim GmbH, Mannheim, Germany). The method has been described in detail elsewhere. A troponin T concentration of 0.10 μg/l during the first 12 hour period was used to differentiate between high and low risk patients.1 3 7 16

ST segment monitoring
Continuous vectorcardiography ST segment monitoring was performed for 24 hours after inclusion with the MIDA 1000 or Coronet system (Ortivus Medical AB, Täby, Sweden). The method of ischaemia monitoring by vectorcardiography has previously been described in detail.12 13 15 Briefly, ECG complexes are continuously collected, sampled for one minute periods, and averaged into three orthogonal leads, X, Y, and Z. ST vector magnitude (ST-VM) is defined as the summarised deviation of the ST segment from the isoelectric level measured 20 ms after the J point. At the end of each averaging period, ST-VM is calculated and presented as a trend curve updated continuously during the whole recording period. Recordings were stored on floppy disks and sent for core laboratory analysis by personnel without knowledge of the patients’ status (Sahlgrenska University Hospital, Östra, Gothenburg, Sweden). The presence of transient myocardial ischaemia in the present study was defined as ≥1 ST-VM episodes because this algorithm is easy to use in the clinical setting and its accuracy in discriminating between high and low risk patients with ACS has been documented as high.12 13 15

Follow up
The end point was a composite of the events cardiac death and acute myocardial infarction (AMI) occurring within the follow up period. Cardiac adverse events occurring during hospitalisation and up to 30 days after the index event were evaluated by an independent end point committee. Thereafter, information about adverse events was obtained from hospital records and registers. Median (interquartile range (IQR), range) follow up time for all patients was 28 (14–31, 0.03–52) months and averaged into three orthogonal leads, X, Y, and Z. ST vector magnitude (ST-VM) is defined as the summarised deviation of the ST segment from the isoelectric level measured 20 ms after the J point. At the end of each averaging period, ST-VM is calculated and presented as a trend curve updated continuously during the whole recording period. Recordings were stored on floppy disks and sent for core laboratory analysis by personnel without knowledge of the patients’ status (Sahlgrenska University Hospital, Östra, Gothenburg, Sweden). The presence of transient myocardial ischaemia in the present study was defined as ≥1 ST-VM episodes because this algorithm is easy to use in the clinical setting and its accuracy in discriminating between high and low risk patients with ACS has been documented as high.12 13 15

Statistical analyses
Data were analysed on an intention to treat basis. Owing to non-normal distribution, troponin T concentration and ST segment monitoring data are presented as medians (IQR, range). Group continuous variables were compared by the Mann-Whitney U test and categorical variables were compared by the χ2 or Fisher’s exact test as appropriate. Univariate predictors of the composite end point were identified by the log rank test. Survival curves were constructed by the Kaplan-Meier method. Cox regression trend analysis was used to explore the significance of the number of ST-VM episodes in relation to the troponin T concentration and to the probability of the composite end point. Forward stepwise Cox regression analysis was used to detect independent predictors of the composite end point with variables of potential significance (p < 0.10) identified in the univariate analysis. A probability value of p < 0.20 was the criterion for selection. At first, baseline variables of potential significance were evaluated (model I). Once these were accounted for, the added value of information from troponin T testing and from ST segment monitoring was explored (model II). To evaluate the potential influence on the clinical outcome of coronary revascularisations (angioplasty or coronary artery bypass grafting) performed during follow up, statistical analyses were repeated after censoring of patients at the time of revascularisation. Results are expressed as hazard ratios (HR) with 95% confidence intervals (CI) and p values. A probability value of p < 0.05 was considered significant. Data were analysed with the SAS statistical package (version 8.1, SAS Institute, Cary, North Carolina, USA).

RESULTS
General findings
In 92 (43%) patients troponin T concentration was ≥ 0.10 μg/l (median 0.52 μg/l, IQR 0.20–1.90 μg/l, range 0.10–3.69 μg/l). Admission troponin T concentration was ≥ 0.10 μg/l in 77 (36%) patients. Troponin T concentration was 0.00 μg/l in 75 (35%) patients. Sixty nine (32%) of the patients had ≥ 1 ST-VM episode (median 3, IQR 1–6, range 1–24). The median time of ST segment monitoring was 24 hours. A positive quantitative relation between the troponin T concentration and the number of ST-VM episodes was found (fig 1). Table I presents baseline clinical and 12 lead ECG characteristics according to the troponin T concentration and presence of ST-VM episodes. Comparison with the total study population, patients with ST segment depression on the admission ECG had more ST-VM episodes and patients with increased troponin T concentration less commonly had previous angina. Otherwise, the two patient groups had similar characteristics and were representative of the main study population. Of nine patients with ST elevation in the admission ECG, three were retrospectively categorised as having ST elevation AMI.

Clinical outcome
After one month 12 (5.6%) patients had died or experienced a non-fatal AMI. After one year 22 (10%) and at the end of the study period 38 (18%) patients had died or had a non-fatal AMI. Four (1.9%) patients died during the study period. Fifty seven (27%) of the patients underwent coronary revascularisation within 30 days. At the end of follow up 96 (45%) patients had undergone coronary revascularisation. No revascularisations were performed in 94 event-free patients and 23 patients who reached the composite end point. Among eight patients who underwent revascularisation before reaching the combined end point, three developed an AMI < 48 hours after the procedure. In 89 patients (revascularised event-free patients and patients undergoing revascularisation before the adverse event), revascularisation may have influenced the clinical outcome. Among these patients, there was no difference in frequency of revascularisation between patients with (38%) and patients without (45%) an increased troponin concentration (p = 0.4), nor...
between patients with (45%) and patients without (40%) ST-VM episodes (p = 0.6). Median (IQR, range) time from study inclusion to revascularisation among these patients was 1.5 (0.4–7, 0.03–24) months. In the same patient group, no significant differences in time to revascularisation according to the troponin concentration or the presence of ST-VM episodes were found.

**Predictors of cardiac death or AMI**

Significant univariate predictors of the composite end point were age \( >65 \) years, diabetes, previous myocardial infarction, congestive heart failure, use of β blockers or diuretics at admission, 12 lead ECG ST segment depression at admission, troponin T concentration \( >0.10 \) mg/l, and \( >1 \) ST-VM episodes (table 2). Figure 2 shows the cumulative percentage of patients with event-free survival according to the troponin T concentration or the presence of ST-VM episodes. Median (IQR, range) time from study inclusion to the time of the composite end point was longer for patients predicted to be at risk by troponin T testing (n = 27) than for patients predicted to be at risk by ST segment monitoring (n = 20) (8.4 (0.2–15, 0.03–27) months v 0.3 (0.1–4.3, 0.03–23) months, p = 0.04). Figure 3 shows the cumulative percentage of patients with event-free survival according to the troponin T concentration in relation to the presence of ST-VM episodes.

Multivariate analysis of baseline variables of potential significance identified age \( \geq 65 \) years, previous myocardial infarction, no previous coronary revascularisation, and congestive heart failure as independent predictors of the composite end point (table 3). With the addition of information on troponin T concentration and ST segment monitoring, only age \( >65 \) years, previous myocardial infarction, and troponin T \( >0.10 \) mg/l had significant independent prognostic significance.

### Table 1. Baseline characteristics of study patients

<table>
<thead>
<tr>
<th></th>
<th>Total (n = 213)</th>
<th>Troponin T ( &gt;0.10 ) mg/l (n = 92)</th>
<th>≥1 ST-VM episode (n = 69)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>146 (69%)</td>
<td>69 (75%)</td>
<td>44 (64%)</td>
</tr>
<tr>
<td>Age ( \geq 65 ) years</td>
<td>92 (43%)</td>
<td>46 (50%)</td>
<td>39 (57%)</td>
</tr>
<tr>
<td>Smoking (past or current)</td>
<td>128 (60%)</td>
<td>62 (67%)</td>
<td>40 (56%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>37 (17%)</td>
<td>18 (20%)</td>
<td>11 (16%)</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>68 (32%)</td>
<td>28 (30%)</td>
<td>23 (33%)</td>
</tr>
<tr>
<td>Previous angina (( &gt;4 ) weeks)</td>
<td>136 (64%)</td>
<td>46 (50%)*</td>
<td>44 (64%)</td>
</tr>
<tr>
<td>Previous MI</td>
<td>95 (45%)</td>
<td>37 (40%)</td>
<td>30 (43%)</td>
</tr>
<tr>
<td>Previous coronary revascularisation</td>
<td>38 (18%)</td>
<td>9 (10%)</td>
<td>8 (12%)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>24 (11%)</td>
<td>10 (11%)</td>
<td>12 (17%)</td>
</tr>
<tr>
<td>Use of β blockers at admission</td>
<td>94 (44%)</td>
<td>38 (41%)</td>
<td>31 (45%)</td>
</tr>
<tr>
<td>Use of calcium blockers at admission</td>
<td>62 (29%)</td>
<td>16 (17%)</td>
<td>18 (26%)</td>
</tr>
<tr>
<td>Use of diuretics at admission</td>
<td>44 (21%)</td>
<td>20 (22%)</td>
<td>18 (26%)</td>
</tr>
<tr>
<td>Admission ECG</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ST elevation</td>
<td>9 (4%)</td>
<td>5 (5%)</td>
<td>6 (9%)</td>
</tr>
<tr>
<td>ST depression</td>
<td>71 (33%)</td>
<td>39 (42%)</td>
<td>42 (61%)†</td>
</tr>
<tr>
<td>T wave inversion</td>
<td>124 (58%)</td>
<td>58 (63%)</td>
<td>44 (64%)</td>
</tr>
<tr>
<td>Any ST-T change</td>
<td>153 (72%)</td>
<td>72 (78%)</td>
<td>54 (78%)</td>
</tr>
<tr>
<td>Median (IQR) time from qualifying pain episode to inclusion (hours)</td>
<td>12 (6–18)</td>
<td>14 (19–9)†</td>
<td>13 (8–19)</td>
</tr>
<tr>
<td>Study drug (magratran)</td>
<td>162 (76%)</td>
<td>67 (73%)</td>
<td>57 (83%)</td>
</tr>
</tbody>
</table>

Between group comparisons p \( \geq 0.05 \).

* p \( <0.05 \) compared with the total group; †p \( <0.05 \) compared with troponin T \( >0.10 \) mg/l group and with the total group.

IQR, interquartile range; MI, myocardial infarction; ST-VM, ST vector magnitude.
CI 1.04 to 5.9, p = 0.04), no previous revascularisation (HR 0.30, 95% CI 0.09 to 0.83, p = 0.03), and troponin T concentration > 0.10 mg/l (HR 3.01, 95% CI 1.24 to 7.40, p = 0.015). In this subanalysis, the presence of ST-VM episodes did not reach significance (HR 1.55, 95% CI 0.79 to 4.11, p = 0.18).

DISCUSSION

Admission clinical and 12 lead ECG characteristics, biochemical markers of myocardial necrosis, and continuous ST segment monitoring have proved to be valuable short and long term indicators of worsening outcome after an episode of ACS.1–16 However, the present study is the first to investigate the long term prognostic significance of combining troponin T and ECG monitoring among such patients.

In the present study, troponin T concentration > 0.10 mg/l indicated an almost threefold increase in the risk of a long term unfavourable outcome compared with no troponin T increase. At 30 days the sensitivity, specificity, and negative predictive value of troponin T testing in predicting cardiac death or AMI were 67%, 58%, and 97%, respectively. At the end of follow up the same measures of accuracy were 71%, 63%, and 91%, respectively. That the risk of a poor outcome among patients who present with ACS and troponin T increase continues to increase for up to three years is in agreement with previous investigations.2458

The sensitivity, specificity, and negative predictive value of one or more ST episodes in predicting a poor outcome at 30 days in this study were 83%, 71%, and 99%, respectively. We found a fairly high long term specificity of 72% and negative predictive value of 88%; however, the sensitivity was only 53%. Thus, the rather low prognostic sensitivity of ECG monitoring in the present study is based on adverse events occurring over the long term. Of those adverse events predicted by ST segment monitoring, 50% occurred within 30 days after the index event. Beyond this stage it seems that there is no difference in survival rates between patients with and patients without ST episodes. These findings are consistent with a study by Patel and colleagues14 of 212 patients with unstable angina showing that the sensitivity of transient ST episodes in predicting death and AMI at six weeks was 54% (specificity 87%, negative predictive value 97%) and 28% (specificity 88%, negative predictive value 91%), respectively, at a median of 31 months' follow up. Overall discrepancies in measures of accuracy between the two studies may be explained by differences in crucial determinants for outcome (that is, study enrolment criteria, treatment protocols, and ECG monitoring techniques).

Table 2

<table>
<thead>
<tr>
<th>Relative frequency of death or AMI (%)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex Yes/No</td>
<td>16.4/20.9</td>
</tr>
<tr>
<td>Age &gt;65 years</td>
<td>29.3/9.1</td>
</tr>
<tr>
<td>Smoking (past or current) Yes/No</td>
<td>16.4/20.0</td>
</tr>
<tr>
<td>Diabetes mellitus Yes/No</td>
<td>32.0/14.7</td>
</tr>
<tr>
<td>Arterial hypertension Yes/No</td>
<td>25.0/14.5</td>
</tr>
<tr>
<td>Previous angina (&gt;4 weeks) Yes/No</td>
<td>19.1/15.6</td>
</tr>
<tr>
<td>Previous MI Yes/No</td>
<td>27.2/10.7</td>
</tr>
<tr>
<td>Previous revascularisation Yes/No</td>
<td>8.0/20.0</td>
</tr>
<tr>
<td>Congestive heart failure Yes/No</td>
<td>41.7/14.8</td>
</tr>
<tr>
<td>Admission use of β blockers Yes/No</td>
<td>24.5/12.6</td>
</tr>
<tr>
<td>Admission use of calcium blockers</td>
<td>19.4/17.2</td>
</tr>
<tr>
<td>Admission use of diuretics Yes/No</td>
<td>36.4/13.0</td>
</tr>
<tr>
<td>Admission ECG</td>
<td>22.0/17.6</td>
</tr>
<tr>
<td>ST elevation Yes/No</td>
<td>26.8/13.4</td>
</tr>
<tr>
<td>ST depression Yes/No</td>
<td>18.5/16.9</td>
</tr>
<tr>
<td>T wave inversion Yes/No</td>
<td>19.0/15.0</td>
</tr>
<tr>
<td>Any ST-T change Yes/No</td>
<td>29.0/12.5</td>
</tr>
<tr>
<td>Troponin T &gt;0.10 μg/l Yes/No</td>
<td>29.3/9.1</td>
</tr>
<tr>
<td>ST-VM ≥1 episodes Yes/No</td>
<td>29.0/12.5</td>
</tr>
<tr>
<td>Study drug (moglatran) Yes/No</td>
<td>19.7/11.8</td>
</tr>
</tbody>
</table>

Figure 2

(A) Event-free probability among patients with or without troponin T > 0.10 μg/l (log rank, p = 0.0003). (B) Event-free probability of patients with or without ST-VM episodes (log rank, p = 0.0006).

Figure 3

Occurrence of cardiac death or non-fatal AMI at a medium of 28 months’ follow up in patients with troponin T < 0.10 μg/l and no ST-VM episodes (A, n = 97), troponin T > 0.10 μg/l and ≥ 1 ST-VM episodes (B, n = 24), troponin T > 0.10 μg/l and no ST-VM episodes (C, n = 47), and troponin T > 0.10 μg/l and ≥ 1 ST-VM episodes (D, n = 45). A versus B, log rank p = 0.43; A versus C, log rank p = 0.09; A versus D, log rank p = 0.0001; B versus C, log rank p = 0.61; B versus D, log rank p = 0.02; C versus D, log rank p = 0.01.
Both troponin T and continuous multi-lead ST segment monitoring provide independent short term prognostic value in ACS.7–26 Rather unexpectedly, the presence of transient ST episodes in the present study did not have significant long term prognostic value once the information from troponin testing was taken into account. During recent years it has been shown that patients at higher risk for a subsequent poor outcome as indicated by an increased troponin concentration or the presence of ST episodes benefit the most from a strategy of early angiography and revascularisation.27–21 In the present study 45% of the study population, on the discretion of the treating physicians, underwent revascularisation during follow up. During the TRIM study period, as recommended by the 1994 unstable angina guidelines,22 referral for angiography and revascularisation should be related to the patients risk of an adverse outcome such as the presence of recurrent angina and ischaemia at rest. Therefore, it may be speculated that the lack of blinding of the treating physicians to ST (in contrast to troponin) data in this study to some extent may have influenced treatment decisions (for example, referral for angiography), thus reducing the impact of ECG monitoring on late prognosis. However, we found no differences in frequency or timing of revascularisation according to the presence or absence of transient ST episodes. Moreover, the lack of late independent prognostic value of ECG monitoring remains valid even after sensitivity analysis with the censoring of patients at the time of coronary revascularisation. Thus, it is unlikely that the lack of blinding of the treating physicians to the ECG data in this study was a major determinant of the reduced impact of ECG monitoring on late prognosis.

**PATHOPHYSIOLOGICAL ASPECTS**

In ACS, plaque rupture or erosion results in a transient or persistent thrombotic vessel occlusion and transient fluctuations in the local coronary vasomotor tone.21–24 The presence at coronary angiography in ACS of complex lesion morphology, severe coronary artery disease, or thrombus is associated with an unfavourable clinical outcome.22–26 It has been shown that either an increased troponin concentration or the presence of transient ischaemic episodes in ACS is strongly associated with such angiographic findings,27–29 thus explaining the prognostic value of troponin testing and ECG monitoring in ACS. The pathophysiological relation of troponin release and transient ischaemic episodes in ACS is further supported by the finding in this study of a positive quantitative association between the troponin T concentration and the ischaemic burden (as indicated by the number of ST episodes). Considering these concordant findings in patients with troponin increase and transient ischaemic episodes during the course of ACS, how can the different temporal risk characteristics of troponin testing and ECG monitoring as shown in this study be explained? Troponin increase in ACS probably reflects thrombus formation at the site of the plaque rupture and subsequent downstream embolisation of atherothrombotic material leading to minor myocardial necrosis.30–34 In ACS, the size of thrombus changes with time and vasomotor reactivity is impaired, especially at the site of complex coronary lesions.24 Thus, it is conceivable that transient ischaemic episodes are caused by fluctuations in the size of thrombus or by transient vasospasms. On the basis of the findings in the present study it may be hypothesised that thrombus formation (as indicated by troponin increase) indicates a poor prognosis in ACS in both the short and the long term, whereas vasoconstriction (as indicated by the presence of transient ST episodes) at the most may have a role in predicting an unfavourable short term clinical course. This thesis is partially supported by the fact that in ACS only patients with troponin increase benefit from administration of antithrombotic (dalteparin) or antiplatelet (abciximab) agents.35–36 On the other hand, no prognostic benefit has been seen with vasospasmolytics, such as the nitrates, even though these agents reduce the ischaemic burden.37 Increasing troponin concentrations are associated with decreased left ventricular function,38 a pivotal determinant of mortality.39 In a study of patients with first time AMI, Rao and colleagues38 showed that a troponin T concentration > 2.8 μg/l predicted a left ventricular ejection fraction < 40% with a specificity of 92.9% (and sensitivity of 100%). In the present study, the upper quartile among patients with an increased troponin concentration was 1.90 μg/l, thus left ventricular dysfunction was presumably not a major determinant for the prognostic value of troponin T. Accordingly, troponin T increase in this study was related primarily to an increased risk of subsequent myocardial (re)infarction, and not to mortality.

**STUDY LIMITATIONS**

The present study population was selected according to the inclusion and exclusion criteria of the TRIM trial. The TRIM trial recruited patients from 1994 to 1995,17 before the era of routine use of glycoprotein IIb/IIIa antagonists and early revascularisation of patients with ACS. The significance of immediate access of the local physicians to both troponin T and ST trend data for decision making needs to be delineated in future prospective studies. We may have underestimated the prognostic value of 12 lead ECG ST depression because we did not take the degree of ST depression into consideration.

**CONCLUSIONS**

When combining troponin T and continuous ST segment monitoring for early assessment of long term prognosis in...
patients with ACS, only troponin T testing provides significant independent prognostic information. Transient myocardial ischaemic episodes seem to be especially predictive of early cardiac adverse events. Although both biochemical and continuous ECG markers reflect an increased risk in ACS, they exhibit different temporal risk characteristics.

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