Cumulative risk assessment in unstable angina: clinical, electrocardiographic, autonomic, and biochemical markers

S Kennon, C P Price, P G Mills, P K MacCallum, J Cooper, J Hooper, H Clarke, A D Timmis

Objective: To determine the incremental value of clinical data, troponin T, ST segment monitoring, and heart rate variability for predicting outcome in patients with non-ST elevation acute coronary syndromes.

Methods: Prospective cohort study of 304 consecutive patients. Baseline clinical and electrocardiographic data were recorded, serial blood samples were obtained for troponin T assay, and 48 hour Holter monitoring was performed for ST segment and heart rate variability analysis. End points were cardiac death and non-fatal myocardial infarction during 12 months’ follow up.

Results: After 12 months, 7 patients had died and 21 had had non-fatal myocardial infarction. The risk of an event was increased by troponin T > 0.1 µg/l, T wave inversion on the presenting ECG, Holter ST shift, and a decrease in the standard deviation of 5 minute mean RR intervals. Positive predictive values of individual multivariate risk were low; however, analysis of all multivariate risk markers permitted calculation of a cumulative risk score, which increased the positive predictive value to 46.9% while retaining a negative predictive value of 96.9%.

Conclusion: A cumulative approach to risk stratification in non-ST elevation coronary syndromes successfully identifies a group in whom the risk of cardiac death or non-fatal myocardial infarction approaches 50%.

Patients with unstable angina or non-ST elevation myocardial infarction are at high risk of future events. About 10% die from cardiac causes or sustain non-fatal myocardial infarction within six months of presentation. Randomised trials of maximal antithrombotic and interventional strategies have failed to provide unequivocal evidence of benefit in unselected cohorts, and there is a clear need for simple markers of risk in order that more aggressive management may be targeted at subgroups that can benefit most.

Despite the emerging role of clinical, electrocardiographic, and biochemical markers for the risk based management of unstable angina and non-ST elevation myocardial infarction, positive predictive values (proportions of patients with positive markers who sustain events) are generally low. Incremental analysis has the potential to enhance predictive value. However, the burgeoning literature on risk stratification in unstable angina and non-ST elevation myocardial infarction documents few attempts to quantify the incremental value of clinical, electrocardiographic, and biochemical markers of risk to rationalise their application for risk based management. In the present study we have prospectively analysed clinical data, troponin T concentrations, ST shift, and heart rate variability to measure their incremental value for predicting 30 day and 12 month outcome in an unselected cohort of patients with unstable angina and non-ST elevation myocardial infarction.

Methods

Patients

Consecutive patients with non-ST elevation acute coronary syndromes were recruited if they fulfilled criteria for Braunwald class 3B unstable angina. Patients with serum creatine kinase MB (CKMB) concentrations ≥ 4.0 µg/l without Q wave development were diagnosed as non-Q wave myocardial infarction. Electrocardiographic changes (ST depression, T wave inversion) were not required for inclusion but patients who developed Q waves were excluded. Other exclusion criteria were myocardial infarction within the previous 21 days, angioplasty within the preceding six months, cardiac failure (New York Heart Association functional class III or IV), chronic severe illness, renal impairment (creatinine > 200 µmol/l), oral anticoagulation, aortic stenosis, and any abnormality preventing interpretation of ST changes on Holter analysis (left bundle branch block, paced rhythm, digoxin, severe left ventricular hypertrophy). The study protocol was approved by the local (East London and The City) research ethics committee and informed consent was obtained from all subjects before recruitment.

Data collection

Clinical data

Baseline clinical characteristics including demographic, clinical, and biochemical data were collected prospectively. Details of clinical history and inpatient management were recorded. Current smokers and those who had stopped smoking less than two weeks before presentation were classified as smokers. All others were grouped as non-smokers for this study.

Abbreviations: AUC, area under the receiver operating characteristic curve; CABG, coronary artery bypass graft; CKMB, creatine kinase MB fraction; ELISA, enzyme linked immunosorbent assay; FRISC II, Fragmin and fast revascularization during instability in coronary artery disease; PTCA, percutaneous transluminal coronary angioplasty; SDANN, standard deviation of 5 minute mean RR intervals; TIMI, thrombolysis in myocardial infarction.
Electrocardiographic analysis
Presenting ECGs recorded in the emergency department were analysed for evidence of ischaemia. ST depression was measured at 80 ms after the J point. Both ST depression and T wave inversion had to occur in at least two contiguous leads and to be at least 0.1 mV to be considered significant.

Blood sampling and biochemical analysis
In addition to samples taken for routine laboratory analysis according to hospital protocols, samples were also taken for CKMB and troponin T analysis on admission (before antithrombotic treatment) and at 12, 24, and 48 hours after admission. Serum CKMB concentrations were measured using a one step sandwich immunoassay (Bayer Immuno 1 Analyst, Bayer Plc, Newbury, UK). The lower detection limit was 0.1 µg/l. The coefficient of variation was 6.1% at 4.6 µg/l and 5.8% at 15.3 µg/l. The cut off for diagnosis of myocardial infarction was 4.0 µg/l (manufacturer's data sheet). Troponin T concentrations were determined by using an enzyme linked immunosorbent (ELISA) one step sandwich assay (Enzymun Test, Roche Diagnostics, Lewes, UK). The lower detection limit was 0.02 µg/l and the coefficient of variation was 9% at 0.35 µg/l and 3.2% at a concentration of 5.44 µg/l (manufacturer's data sheet). The cut off point used was 0.1 µg/l.

Holter monitoring
ST segment and heart rate variability were monitored continuously for 48 hours within 24 hours of admission. ST segment shift and heart rate variability were determined as previously described. Briefly, frequency modulated dual channel recorders (Marquette Series 8000, Delmar, Irvine, California, USA) were used and tapes were analysed, without knowledge of the clinical outcome, using a commercially available system (Delmar Accuplus 363). The recordings were analysed for both spectral and non-spectral measures of heart rate variability. The measures calculated were ratio of low (0.04–0.15 Hz) to high (0.15–0.4 Hz) frequency, mean of all coupling intervals between qualified beats, the standard deviation about the mean, proportion of adjacent RR intervals more than 50 ms different, root mean square of the difference of successive RR intervals, the standard deviation of five minute mean RR intervals (SDANN), and the mean of all five minute standard deviations of RR intervals (SD).

Follow up
Patients were followed up for 12 months. The primary end points were death from cardiac causes and non-fatal myocardial infarction. Myocardial infarction was diagnosed if any two of the following criteria were fulfilled: (1) cardiac chest pain lasting at least 30 minutes; (2) ≥ 0.1 mV ST elevation in at least one standard lead or ≥ 0.2 mV ST elevation in two or more contiguous chest leads; or (3) CK > 400 IU/l (upper limit of reference range: 200 IU/l) or CKMB > 4.0 µg/l.

Statistical analysis
Results for continuous variables are presented as means and standard deviations, and two sample t tests were used to compare those with and without events. For variables not normally distributed results are presented as medians and interquartile ranges and compared using the Mann-Whitney U test. Categorical variables were compared using χ² or Fisher’s exact test. Variables significant (p < 0.05) on univariate analysis were selected for testing in a stepwise multiple logistic regression model. We then looked at the effect of adding variables insigificant on univariate analysis to test whether any of these became important after adjustment. Results from the logistic regression were expressed as the odds of an event relative to a reference category for categorical variables and as the relative odds associated with a one standard deviation increase in continuous variables. Cumulative risk scores were calculated by incremental analysis of all independent predictors of ischaemic events (death, non-fatal myocardial infarction) using the selected characteristics weighted by the coefficients from the logistic regression model. Cut off points for this score were selected to give false positive rates of 5–10%. The discriminative ability of the risk scores was assessed using the area under the receiver operating characteristic (AUC) curve. This index ranges from 0.5 for a test with no discriminative ability to 1.0 for a test that discriminates perfectly. The internal validity of the model generated from the entire cohort was assessed by cross validation, whereby the cohort was randomly divided into two halves, one used to develop the model and the other to determine the fit and discriminative ability.

RESULTS
Discharge diagnosis and outcome
Discharge diagnosis
The study population consisted of 304 consecutive patients admitted with non-ST elevation acute coronary syndromes. The discharge diagnosis was non-Q wave myocardial infarction in 92 (30%) and unstable angina in 212 (70%).

Outcome: death and myocardial infarction
Thirty day follow up was obtained in 303 patients (99.7%), of whom one died and 14 had non-fatal myocardial infarction. Thirteen of these events, including the death, occurred before discharge. Twelve month follow up was obtained in 289 patients (95.1%), of whom 7 died and 21 had non-fatal myocardial infarction. All deaths during follow up were attributable to cardiac causes.

Outcome: major adverse cardiac events
During the first 30 days’ follow up an additional 39 patients underwent revascularisation procedures (23 percutaneous transluminal coronary angioplasty (PTCA) and 16 coronary artery bypass graft (CABG)). After one year, 67 patients had undergone revascularisation procedures (34 PTCA and 33 CABG). There were therefore 54 major adverse cardiac events (death, non-fatal myocardial infarction, PTCA, and CABG) after 30 days and 95 after one year.

Univariate predictors of death and non-fatal myocardial infarction
Clinical factors
Ischaemic events occurred more commonly in patients who were older and had diabetes (table 1). These events were also more common when the hospital course was complicated by left ventricular failure or chest pain that failed to settle within 12 hours of admission.

Electrocardiographic factors
Ischaemic events occurred more commonly in patients with T wave inversion on the presenting ECG (table 2). ST change was also associated with ischaemic events, particularly when recorded during Holter monitoring.

Autonomic factors
Analysis of heart rate variability showed that time domain indices tended to be lower among patients who had ischaemic events; frequency domain indices were similar between the groups (table 2).

Biochemical factors
Admission cholesterol and creatinine concentrations were, on average, higher in patients who had ischaemic events during follow up (table 3). Admission and peak CKMB concentrations were also higher in these patients. Among patients with
ischaemic events, the proportion with increased (> 0.1 µg/l) troponin T concentrations at each sampling point and at any sampling point was over twice that of patients without events.

**Multivariate predictors of death and non-fatal myocardial infarction**

**Thirty days**
Clinical, electrocardiographic, autonomic, and biochemical factors were all independently predictive of ischaemic events during the first 30 days (table 4). Thus, in patients with Holter ST elevation or chest pain that failed to settle within 12 hours of admission, the odds of having an ischaemic event were increased 10.6 and 15.1 times, respectively. Any increase of troponin T > 0.1 µg/l increased the odds of an event more than 30 times. Conversely, preservation of heart rate variability reduced the odds of an ischaemic event by 65% for every standard deviation (approximately 30 ms) increase in SDANN.

**Twelve months**
In patients with T wave inversion on the presenting ECG or Holter ST elevation or depression, the odds of an ischaemic event during the first 12 months were increased 5.8, 4.4, and 3.2 times, respectively (table 4). Any increase of troponin T

---

### Table 1
Clinical univariate predictors of death or non-fatal myocardial infarction at 30 days and 12 months

<table>
<thead>
<tr>
<th>Variable</th>
<th>30 day follow up</th>
<th>12 month follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No event (n=288)</td>
<td>Event (n=15) p Value</td>
</tr>
<tr>
<td>Age (years)</td>
<td>60.1 (11.6)</td>
<td>64.5 (9.6) 0.16</td>
</tr>
<tr>
<td>Male sex</td>
<td>170 (72.3)</td>
<td>14 (93.3) 0.11</td>
</tr>
<tr>
<td>Diabetes</td>
<td>50 (21.2)</td>
<td>5 (33.3) 0.28</td>
</tr>
<tr>
<td>Hypertension</td>
<td>107 (45.3)</td>
<td>8 (53.3) 0.55</td>
</tr>
<tr>
<td>Smoking</td>
<td>74 (31.4)</td>
<td>4 (26.7) 0.7</td>
</tr>
<tr>
<td>Chest pain &gt;12 hours*</td>
<td>15 (6.5)</td>
<td>4 (26.7) 0.01</td>
</tr>
<tr>
<td>LVF†</td>
<td>70 (30.2)</td>
<td>13 (86.7) &lt;0.0001</td>
</tr>
<tr>
<td>Arrhythmias‡</td>
<td>2 (0.9)</td>
<td>2 (13.3) 0.006</td>
</tr>
</tbody>
</table>

Data are numbers (percentages) except for age, which is mean (standard deviation). *Patients with new episodes of chest pain >12 hours after admission; †clinical evidence of left ventricular failure (LVF) during admission; ‡documented arrhythmia during admission.

---

### Table 2
Electrocardiographic and autonomic univariate predictors of death or non-fatal myocardial infarction

<table>
<thead>
<tr>
<th>Variable</th>
<th>30 day follow up</th>
<th>12 month follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No event (n=288)</td>
<td>Event (n=15) p Value</td>
</tr>
<tr>
<td>Admission ECG</td>
<td>142 (49.3%)</td>
<td>13 (86.7%) 0.005</td>
</tr>
<tr>
<td>T wave inversion</td>
<td>84 (29.2%)</td>
<td>4 (26.7) 0.84</td>
</tr>
<tr>
<td>ST depression</td>
<td>76 (28.6%)</td>
<td>9 (69.2%) 0.002</td>
</tr>
<tr>
<td>Holter monitoring</td>
<td>48 (18.1%)</td>
<td>9 (69.2%) &lt;0.0001</td>
</tr>
<tr>
<td>Any ST elevation</td>
<td>106 (39.9%)</td>
<td>12 (92.3%) &lt;0.0001</td>
</tr>
<tr>
<td>Heart rate variability</td>
<td>9.1 (3.4–17.7)</td>
<td>9.1 (5.2–12.8) 0.92</td>
</tr>
<tr>
<td>pNN50 (%)</td>
<td>9.9 (3.2–17.1)</td>
<td>9.1 (5.2–12.8) 0.92</td>
</tr>
<tr>
<td>SDNN (ms)</td>
<td>810.9 (158.1)</td>
<td>800.8 (122.9) 0.03</td>
</tr>
<tr>
<td>RMSSD (ms)</td>
<td>41.9 (22.3)</td>
<td>42.0 (19.3) 0.87</td>
</tr>
<tr>
<td>LF:HF</td>
<td>1.67 (0.98–3.52)</td>
<td>2.59 (1.1–6.44) 0.47</td>
</tr>
</tbody>
</table>

Table 2: Data for pNN50 and LF:HF are median (interquartile range) and for SDNN, mean NN, RMSSD, SD, and SDANN are mean (standard deviation).

---

### Table 3
Biochemical univariate predictors of death or non-fatal myocardial infarction at 30 days

<table>
<thead>
<tr>
<th>Variable</th>
<th>30 day follow up</th>
<th>12 month follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No event (n=288)</td>
<td>Event (n=15) p Value</td>
</tr>
<tr>
<td>Cholesterol (mmol/l)</td>
<td>5.66 (1.04)</td>
<td>6.11 (1.34) 0.1</td>
</tr>
<tr>
<td>Creatinine (µmol/l)</td>
<td>102.8 (21.6)</td>
<td>118.2 (25.8) 0.015</td>
</tr>
<tr>
<td>Glucose (mmol/l)</td>
<td>6.4 (5.7–8.3)</td>
<td>7.2 (6.5–13.0) 0.02</td>
</tr>
<tr>
<td>Admission CKMB (µg/l)</td>
<td>1.5 (0.8–3.2)</td>
<td>6.7 (4.4–9) 0.0003</td>
</tr>
<tr>
<td>Peak CKMB (µg/l)</td>
<td>1.6 (0.9–3.2)</td>
<td>3.6 (1.8–7.9) &lt;0.0001</td>
</tr>
<tr>
<td>Troponin T &gt;0.1 µg/l at:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 hours</td>
<td>47 (17.4%)</td>
<td>8 (57.1%) &lt;0.0001</td>
</tr>
<tr>
<td>12 hours</td>
<td>63 (24.3%)</td>
<td>11 (78.6%) &lt;0.0001</td>
</tr>
<tr>
<td>24 hours</td>
<td>64 (24.8%)</td>
<td>11 (78.6%) &lt;0.0001</td>
</tr>
<tr>
<td>48 hours</td>
<td>45 (21.5%)</td>
<td>10 (90.9%) &lt;0.0001</td>
</tr>
<tr>
<td>Any time</td>
<td>78 (28.7%)</td>
<td>13 (86.7%) &lt;0.0001</td>
</tr>
</tbody>
</table>

Table 3: Data for cholesterol, creatine, and CKMB are mean (SD) and for glucose are median (interquartile range).

---

Kennon, Price, Mills, et al

www.heartjnl.com
Predictive accuracy of risk markers for ischaemic events

Thirty days

Analysis of individual multivariate risk markers showed that positive predictive accuracies ranged from 8.7% for every standard deviation increase in SDANN to 15.8% for Holter ST elevation (table 5). Negative predictive accuracies (proportions of patients with negative predictors who did not sustain events) were consistently > 90%. However, incorporation of all multivariate risk markers permitted calculation of a cumulative risk score (table 6) with substantial improvement in predictive accuracy. For scores ≥ 3.75 the positive predictive accuracy for ischaemic death or non-fatal myocardial infarction in the first 12 months was 46.9%. Scores < 2.5 were associated with a negative predictive accuracy of 96.9%. Positive predictive accuracy was slightly reduced in the test model (AUC = 0.84) compared with the development model (AUC = 0.93).

Excluding data derived from continuous ECG (Holter) monitoring

The analysis was repeated after ST segment shift and heart rate variability data were excluded. The calculated cumulative risk score retained true positive rates and negative predictive values of around 70% and 95%, respectively, but positive predictive values at both 30 days and 12 months fell to 31.4% and 31.3%, respectively.

Twelve months

Positive predictive accuracies of individual multivariate risk markers for events in the first year ranged from 11.5% for every standard deviation increase in SDANN to 25.6% for troponin T > 0.1 µg/l (table 5). Again, the calculated cumulative risk score (table 6) improved predictive accuracy. For patients with risk scores ≥ 2.50, the positive predictive accuracy for ischaemic death or non-fatal myocardial infarction in the first 12 months was 49.6%. Scores < 2.50 were associated with a negative predictive accuracy of 96.9%. Positive predictive accuracy was slightly reduced in the test model (AUC = 0.84) compared with the development model (AUC = 0.93).

**DISCUSSION**

This prospective cohort study has identified a range of clinical, electrocardiographic, autonomic, and biochemical factors all independently predictive of outcome in patients with non-ST elevation coronary syndromes. However, most risk markers had a low concentration of predictive accuracy when applied independently, potentially limiting their clinical value. For example, troponin T, the best independent predictor of risk,
identified > 75% of patients who had events in the first 12 months, but 75% of those with increased concentrations had no event. Previous investigators have confirmed that troponins provide prognostic information independent of the resting ECG, but this study has extended these observations by showing that cumulative analysis of multiple independent determinants of risk, including Holter ST and heart rate variability data, can substantially improve predictive accuracy. This is of particular clinical relevance because it was applied to unselected patients with non-ST elevation acute coronary syndromes and no attempt was made to preselect high risk subgroups.

Troponin T

The minimal myocardial damage that may occur following transient or subacute thrombus formation in non-ST elevation coronary syndromes is now recognised as a major predictor of subsequent ischaemic events. In the present study, troponin T was the most powerful predictor of risk; however, its usefulness for risk stratification was limited by its low positive predictive value. Nearly 75% of patients with troponin T concentrations > 0.1 μg/l remained event-free during the first year after presentation. Thus, management programmes based on troponin assays in patients with non-ST elevation coronary syndromes would result in many relatively low risk patients receiving aggressive treatment strategies unless other predictors of risk are also taken into account. This is reflected in the recent FRISC II (fragmin and fast revascularization during instability in coronary artery disease) study in which an invasive strategy did not significantly reduce death and non-fatal myocardial infarction in the troponin positive subgroup.

Myocardial ischaemia

It is well established that clinical and electrocardiographic evidence of uncontrolled ischaemia in non-ST elevation coronary syndromes identifies patients at risk of future events and cystic fibrosis of the heart. This was confirmed in the present study. Thus, chest pain that failed to settle within 12 hours of admission and Holter ST elevation increased substantially the risk of ischaemic events in the first 30 days, while Holter ST elevation or depression was independently predictive of events at 12 months. T wave inversion on the presenting ECG was also predictive of events at 12 months but, like other investigators, we found that ST depression on the presenting ECG was not retained as an independent predictor when Holter ST data were included in the multivariate analysis, presumably because of the more prolonged sampling period provided by Holter monitoring. The relation between uncontrolled ischaemia and future events has led to calls for an ischaemia driven approach to invasive management, an approach validated by the findings of the FRISC II investigators. Nevertheless, our predictive accuracy data showed that > 75% of patients with clinical or electrocardiographic predictors of cardiac death or non-fatal myocardial infarction remained event-free at least 12 months after presentation, demonstrating important limitations of this approach.

Heart rate variability

Holter monitoring not only documented ambulatory ST change but also permitted analysis of heart rate variability, which further refined the assessment of risk. Heart rate variability, a convenient measure of autonomic function, is often deranged after myocardial infarction and the severity of the derangement is predictive of outcome. Similar findings have been reported for patients with unstable angina when prognostic correlates for in-hospital events are additional to those of ST analysis. Our own data have extended these observations by showing that reductions in time domain indices of heart rate variability early after presentation are associated with a significant increase in rates of cardiac death and non-fatal myocardial infarction during the first 12 months. The association is independent of Holter ST change, as well as of clinical, electrocardiographic, and biochemical markers.

Holter monitoring

While presenting ECG changes and biochemical markers of myocardial necrosis are well established and routinely used for risk stratification, Holter monitoring is not. With recent advances in recording technology and data analysis, however, its application in the coronary care unit has become increasingly feasible and there is no doubt that continuous ECG monitoring for ST segment shift and heart rate variability may become as routine as that for heart rhythm is currently. This study has confirmed that both ST shift and measures of heart rate variability provide important, independent prognostic information that can be obtained early after presentation to anticipate the period of greatest risk and in this respect Holter monitoring may have advantages over stress testing. The aim of the recently described TIMI (thrombolysis in myocardial infarction) risk score is to identify, as simply as possible, using readily available information, patients with unstable angina or non-ST elevation myocardial infarction at high risk of further cardiac events. In the absence of continuous ECG monitoring, however, the highest risk group identified (comprising 3.4% of the sample) has a positive predictive value of only 20%.

Conclusion

Our findings have emphasised the value of a cumulative approach to risk stratification in non-ST elevation coronary syndromes—most markers of risk have a low level of predictive accuracy when applied independently. Thus, derivation of a risk score from clinical data, troponin T concentrations, ST monitoring, and heart rate variability was powerfully predictive of short and longer term outcome, successfully identifying a subgroup of patients whose risk of cardiac death or non-fatal myocardial infarction approached 50% during the first 12 months. This high positive predictive accuracy based on readily available technology exceeds previously reported levels and has the potential to maximise the cost effectiveness of interventional strategies in patients with non-ST elevation coronary syndromes.

--------------

Authors’ affiliations

S Kennon, P G Mills, A D Timmis, Department of Cardiology, Barts and the London NHS Trust, London, UK

J Cooper, ST Price, M Clarke, Department of Clinical Biochemistry, Barts and the London NHS Trust, London, UK

P K MacCallum, J Cooper, MRC Epidemiology and Medical Care Unit, Charterhouse Square, London, UK

J Hooper, Department of Clinical Biochemistry, Royal Brompton Hospital, London, UK

REFERENCES


In the 3 year old boy was admitted for investigation of generalised cyanosis (arterial oxygen saturation to 81%), associated with abnormal density on the left upper lung field (upper panel, middle) and normal cardiac examination. Lung scanning with 99 Tc-albumin showed a large perfusion defect in the same region and presence of radiotracer in the systemic circulation. Chest computed tomography (lower panel, middle) and magnetic resonance imaging (upper panel, right) showed a huge hypervascular mass in the left hemithorax compatible with pulmonary vascular fistulas (arrows); smaller additional vascular nodules were present in the right lung. The diagnosis of pulmonary vascular fistulas was confirmed by angiography (lower panel, right; arrow).

Following successful lobotomy and embolisation of the right sided fistulae, the child improved significantly and was seen five months later with arterial oxygen saturation to 91%.

C R P de Castro
F B Jatene
N M Ikari
claudiacastro@innovision.com.br