Recurrent ischaemia during continuous multilead ST-segment monitoring identifies patients with acute coronary syndromes at high risk of adverse cardiac events

Meta-analysis of three studies involving 995 patients

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Aims Recurrent ischaemia, detected by continuous ECG monitoring, in patients with unstable angina increases the risk of unfavourable outcome. Studies that evaluated this relationship have been limited by the small series of patients. By combining data from three studies, the present analysis aims to provide an accurate assessment of the impact of recurrent ischaemia detected by multilead ECG-ischaemia monitoring on the occurrence of death and myocardial infarction in patients with acute coronary syndromes.

Methods and Results Data were obtained from CAPTURE, PURSUIT and FROST, three trials evaluating glycoprotein IIb/IIIa blockers in patients with non-ST-elevation acute coronary syndromes. Patients were monitored for 24 h after enrolment with a computer-assisted 12-lead or a vectorcardiographic ECG–ischaemia monitoring device. In a retrospective blinded analysis, recurrent ischaemic episodes were identified by a computer algorithm. The number of ischaemic episodes was normalized to 24 h. Ischaemic episodes were detected in 271 (27%) of 995 patients. There was a direct proportional relationship between the number of ischaemic episodes per 24 h and the probability of cardiac events at 5 and 30 days. The 30-day composite of death and myocardial infarction occurred in 5.7% of patients without episodes and increased to 19.7% in patients with ≥5 episodes. After adjustment for baseline predictors of adverse outcome, the relative risk of death or myocardial infarction at 5 and 30 days increased by 25% for each additional ischaemic episode per 24 h.

Conclusions This analysis emphasizes the need for integration of multilead ECG–ischaemia monitoring systems in coronary care units and emergency wards to improve early risk stratification in patients with acute coronary syndromes.

Key Words: Electrocardiography, ischaemia, acute coronary syndromes, unstable angina, ECG monitoring, prognosis.

Introduction

Recurrent ischaemia, detected by Holter monitoring or computer-assisted ECG analysis, in patients with unstable angina carries an increased risk for an unfavourable outcome, including death and myocardial infarction[1–9]. Computer-assisted multilead ECG monitoring offers an accurate, continuous real-time measurement of the QRS complex and the ST segment[10,11], and can be used as a non-invasive tool for on-line risk stratification in patients with acute coronary syndromes[12–19]. In contrast, Holter monitoring is restricted to two or three ECG leads and allows for retrospective analysis only[10,11].
Studies that evaluated the relationship between recurrent ischaemia detected during continuous multilead ECG–ischaemia monitoring (or Holter monitoring) and adverse outcome have been limited by the small series of patients. By combining data from three studies, the present analysis aims to provide an accurate assessment of the impact of recurrent ischaemia detected by multilead ECG–ischaemia monitoring on the occurrence of death and myocardial infarction in patients presenting with an acute coronary syndrome.

Methods

Patients and treatment

Data were obtained from the ECG-ischaemia monitoring substudies of the CAPTURE (c7E3 Fab Anti Platelet Therapy in Unstable REFRACTORY angina) and PURSUIT (Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy) trials, as well as from the FROST (Fibrinogen Receptor Occupancy STudy) trial. The protocols and results of the three studies have been published. All patients were monitored using a multilead ECG–ischaemia monitoring device as described below.

In brief, the studies were designed as double-blind, placebo-controlled, randomized trials to evaluate glycoprotein IIb/IIIa inhibitors in patients presenting with an acute coronary syndrome without persistent ST-segment elevation. CAPTURE evaluated abciximab in patients with unstable angina refractory to conventional medical therapy for whom percutaneous coronary intervention was planned and performed after approximately 24 h of pre-treatment with abciximab. PURSUIT tested the hypothesis that inhibition of platelet aggregation with eptifibatide would have an incremental benefit beyond that of heparin and aspirin in reducing the incidence of adverse outcomes in patients with unstable angina or non-ST-segment elevation myocardial infarction. A similar patient population was studied in FROST which assessed the safety and preliminary efficacy of 1 month of treatment with the oral glycoprotein IIb/IIIa blocker lefradafiban.

All ECG–ischaemia monitoring studies excluded patients who presented with ECG abnormalities that interfered with ST-segment interpretation such as left bundle branch block, persistent arrhythmias, or pacemakers. The protocols were approved by the institutional review board at each center and all patients gave informed consent.

Continuous ECG–ischaemia monitoring

ECG monitoring was started at the beginning of study drug administration and continued for 24 h in all studies, and in CAPTURE at least until 6 h after completion of the percutaneous coronary intervention.

In the latter study, ECG monitoring was performed using the MIDA-1000 vectorcardiographic ECG monitoring device (Ortivus Medical, Täby, Sweden). This system calculates and stores averaged QRS-T complexes from the Frank orthogonal X-Y-Z leads at 1-min intervals. In PURSUIT and FROST, patients were monitored with the ELI-ST100 continuously updated 12-lead ECG recording system (Mortara Instruments, Milwaukee, U.S.A.). This system automatically calculates the median ECG complexes of the 12 ECG leads every 20 s. The system was programmed to store the median ECG complexes and ST-trend data every 20 s if a ≥ 100 μV ST-segment shift was present in one lead relative to the preceding ECG of that patient, or if a ≥ 50 μV ST-shift was present in any two leads of the 12-lead ECG. A baseline median ECG was stored every 5 min if ST change was below these levels or absent altogether.

Data management

Recordings were stored on hard disk, subsequently downloaded to floppy disk and sent to the Cardialysis ECG core laboratory for editing and analysis. The timing of the start of study drug administration and the coronary procedures, as well as the presence of episodes of chest pain during ECG monitoring were obtained from the case report forms. All personnel involved in the analysis remained blinded to study treatment and patient outcome.

Editing and analysis of recorded data

The procedures of editing the continuous ECG monitoring data and the analysis with an automated computer-driven ischaemic ST-episode detection programme have been described in detail. After editing, the trends in the ST-segment level measured at the J-point +60 ms were generated for each lead of the 12-lead ECG (except aVR) in PURSUIT and FROST, and for each lead of the derived 12-lead ECG (except aVR) in CAPTURE, which was calculated from the X-Y-Z leads using the transformation formulas of Dower et al.
algorithm programmed according to these criteria for ischaemia was used to detect ST episodes, followed by visual confirmation afterwards. Examples of the ST-trend analysis have been published previously\textsuperscript{[6,10]}. Patients were excluded from the present analysis if the recording started >12 h after the start of study drug administration in PURSUIT and FROST and >1 h in CAPTURE. Recordings with <50\% analysable data or with a duration of <12 h were also excluded. ST episodes occurring during coronary procedures were excluded.

The ischaemic burden was calculated in different ways: the total duration of all ST episodes per patient, the sum of the area under the curve of all 12 ECG leads during ST episodes per patient, and the area under the curve of the ST-vector magnitude of all episodes per patient, calculated from the X-Y-Z leads (CAPTURE) or the eight independent leads with use of the inversed Dower transformation formula (PURSUIT and FROST)\textsuperscript{[16]}. The area under the curve was measured from the baseline ST level directly preceding the episode.

End-points

The relationship between recurrent ischaemia and mortality, as well as the composite of death and myocardial infarction was investigated at 5 and 30 days following randomization. In all studies, a blinded Clinical Events Committee adjudicated suspected myocardial infarctions within 30 days according to previously published criteria\textsuperscript{[12–14]}. Statistical analysis

Continuous variables are summarized using the median and interquartile range (25th and 75th percentiles) and were compared using Wilcoxon two-sample test. Discrete variables are described as percentages and were compared using Fisher’s exact test. A two-sided \( P \) value of less than 0.05 was required for significance. The relationship between recurrent ischaemia and adverse outcome was evaluated univariably and after adjustment for baseline variables known to be independent predictors of death and myocardial infarction in patients with non-ST-elevation acute coronary syndromes, based on an established risk model for this patient population\textsuperscript{[17]}. These included age, gender, pulse, type of ECG changes at enrolment (ST-segment depression, transient ST-segment elevation, T-wave inversion), smoking status, history of diabetes mellitus or congestive heart failure, as well as previous myocardial infarction, percutaneous coronary intervention or bypass surgery\textsuperscript{[17]}. To assess the increase in risk associated with each additional ischaemic episode during the monitoring period in a multivariate model, the number of ST episodes was normalized to a period of 24 h. Patients were subsequently classified by the number of ST episodes per 24 h into one of the following categories: 0, 0–1, 1–2, 2–3, 3–4, 4–5 and \( \geq 5 \). Results of the multivariate analysis are presented as odds ratios with 95\% confidence intervals.

Results

A total of 1181 patients were enrolled in the three studies. One hundred and eighty-six (16\%) patients were excluded from the present analysis for the following reasons: (1) the recording began too late or contained <12 h or <50\% of analysable ECG data (n=58), (2) technical failures due to incorrect user operation of the monitoring system (n=124), and (3) left bundle branch block that prevented interpretation of the ST segment (n=4). Thus, ECG recordings suitable for ST analysis were available in 995 (84\%) patients. Outcomes among patients included in the ST analysis were comparable to those in patients excluded from this analysis. The median total recording time suitable for ST analysis was 25 h (25th and 75th percentiles, 24 and 28 h).

Ischaemic episodes during continuous ECG monitoring were detected in 271 (27\%) of the 995 patients. Almost half (49\%) of the patients who exhibited recurrent ischaemia had two or more ischaemic episodes per 24 h. Patients with recurrent ischaemia had a worse cardiovascular baseline risk profile including older age, higher heart rate and a higher frequency of previous myocardial infarction and coronary revascularization when compared with patients without ischaemia (Table 1). Episodes of recurrent chest pain during monitoring were reported by the investigator in 216 (22\%) of the 995 patients.

Relationship between recurrent ischaemia and outcome

Eight patients (0.8\%) died within 5 days of follow-up. The incidence of the composite of death and myocardial infarction was 4.7\%. At 30 days, the incidence of death was 2.2\%, while the composite of death and myocardial infarction occurred in 76 patients (7.6\%).

Patients who exhibited recurrent ischaemia during ECG monitoring more frequently died or suffered from a myocardial infarction (Table 2). The differences in cardiac event rates between patients with recurrent ischaemia and those without were substantial, and all comparisons were statistically significant. The results were consistent for death alone and for the composite of death and myocardial infarction, as well as for events occurring during short-term (5 days) and long-term (30 days) follow-up. The association between recurrent ischaemia and adverse outcome was even more apparent in patients with frequent recurrent ischaemia, as represented by two or more and three or more ST episodes during ECG monitoring (Table 2). In fact, there was a direct relationship between the number of recurrent ischaemic episodes per 24 h and the probability of
adverse cardiac events (Fig. 1). At 5 days, the incidence of the composite of death and myocardial infarction was 3.3% among patients without ST episodes, and increased to 15.5% in patients with more than five ST episodes. At 30 days, these figures were 5.4% and 19.7%, respectively.

Both in univariable and multivariable analysis, the relationship between recurrent ischaemia and unfavourable outcome was remarkably consistent (Fig. 2). All ischaemia parameters univariately associated with impaired outcome remained independent predictors in the multivariable analysis, with comparable odds ratios. After multivariable adjustment, the relative risk of death or myocardial infarction both at 5 and 30 days increased by 25% for each additional ischaemic episode per 24 h (Fig. 2). The risk of death at 30 days increased by almost 40%. The number of deaths in the first 5 days was too low for a meaningful multivariable assessment.

Patients with recurrent episodes of chest pain exhibited a trend towards an increased risk of death and myocardial infarction (Table 2). Although the association between chest pain and adverse cardiac outcome did not reach statistical significance in most comparisons, the directionality of the effect on outcome parallels that of recurrent ischaemia detected by ECG-ischaemia monitoring.

In patients with ischaemia, those who had a greater ischaemic burden more often died or developed a myocardial infarction than did those with a lower ischaemic burden (Table 3).

**Discussion**

The present analysis of almost 1000 patients with acute coronary syndromes without persistent ST elevation...
currently represents the largest study of the prognostic implications of recurrent ischaemia as detected by computer-assisted continuous multilead ECG–ischaemia monitoring in this patient population. The results confirm that recurrent ischaemia is an independent and important predictor of death and myocardial infarction. In addition, the present analysis demonstrates that almost 75% of all patients admitted with a non-ST-elevation acute coronary syndrome do not exhibit any episode of recurrent ischaemia. Despite the fact that these patients met the electrocardiographic or enzymatic criteria for enrolment in the respective studies, they had a relatively low risk of death and myocardial infarction (3.3% at day 5 and 5.7% at day 30). The results also confirm previous observations that recurrent ischaemia detected by multilead ECG monitoring is a more sensitive and better prognostic marker than recurrence of chest pain[1,8].

Previous studies have shown that recurrent ischaemia, either silent or symptomatic and detected by either Holter or computer-assisted multilead ECG monitoring, during the first few days after admission with an acute coronary syndrome, portends an unfavourable outcome[1–9]. In some of these studies, the prognostic information of recurrent ischaemia appeared to be independent of and additive to that of the baseline characteristics as well as to the presence of ST depression on the enrolment ECG and to the biochemical markers of myocardial necrosis at admission, including the creatine kinase-MB and troponin levels[7,8]. However, the small sample sizes of the individual studies with relatively few cardiac events during follow-up limited the assessment of the magnitude of the risk associated with recurrent ischaemia after multivariable adjustment. Consequently, the odds ratios varied considerably across the studies and the 95% confidence intervals were wide. Accordingly, all previous studies evaluating multilead ECG–ischaemia monitoring in acute coronary syndrome patients failed to demonstrate a direct relationship between the number of ischaemic episodes and the risk of adverse outcome. By combining three studies on multilead ECG–ischaemia monitoring in almost 1000 patients, the present analysis was able to provide an accurate assessment of the impact of recurrent ischaemia on outcome and to establish a direct proportional relationship between the number of recurrent ischaemic episodes and the risk of death or myocardial infarction. After multivariable adjustment, the relative risk of death or myocardial infarction both at 5 and 30 days increased by 25% for each additional ischaemic episode per 24 h. The large sample size also allowed a risk assessment for death alone: the risk of death at 30 days was particularly high in patients with ≥5 episodes of recurrent ischaemia (5.6% at day 5 and 9.9% at day 30). The results were obtained in the full spectrum of patients presenting with a suspected non-ST-elevation acute coronary syndrome,
varying from patients with non-significant coronary artery disease during subsequent coronary angiography and a low risk profile\(^1\), to those with unstable angina at intermediate risk, as well as patients at high risk of adverse outcome because of refractory unstable angina or non-Q-wave myocardial infarction.

Incorporation of continuous multilead ECG–ischaemia monitoring in patient triage

Patients who present with chest pain or other symptoms suggestive of an acute coronary syndrome and do not have persistent ST-segment elevation on the electrocardiogram, encompass a heterogeneous group that varies considerably with respect to diagnosis as well as future risk for cardiac events. Early risk stratification in these patients is important for tailoring pharmacological and invasive treatment to an individual need based on the expected prognosis. Baseline characteristics, the admission 12-lead electrocardiogram, biochemical markers of myocardial necrosis as well as continuous multilead ECG-ischaemia monitoring have all independently proven useful in risk stratification and could be combined in an emergency department protocol for patient triage as suggested in Fig. 3\(^2\).

Recent clinical trials indicate that patients identified as having a high risk of subsequent cardiac events based on ST depression on the admission ECG or an elevated troponin T or I level, may particularly benefit from a more aggressive therapeutic approach, including early percutaneous coronary intervention with concomitant administration of a glycoprotein IIb/IIIa receptor inhibitor\(^23\).–\(^27\).

Patients admitted with a low-risk profile and a non-elevated troponin level should undergo continuous multilead ECG-ischaemia monitoring while receiving standard medical therapy (Fig. 3\(^2\)). Measurement of troponin level should be repeated after approximately 6–8 h. Patients who stabilize and do not exhibit recurrent ischaemia have a low risk of death and myocardial infarction. In these patients, a non-invasive management strategy might be preferred\(^7\),\(^22\),\(^24\),\(^27\). Early transfer to a low level of care and early hospital discharge may result in economic gains without jeopardizing safety. By contrast, in patients with an initial low-risk profile who do exhibit recurrent ischaemia, the risk of adverse outcome increases with the number of ischaemic episodes. These patients should be considered high-risk even when the serum troponin level is not elevated\(^7\),\(^8\),\(^28\). A more aggressive treatment strategy should be considered in these patients. This would particularly apply to those

![Figure 2](image-url)
Table 3  Relationship between ischaemic burden and clinical outcome in patients with recurrent ischaemia

<table>
<thead>
<tr>
<th></th>
<th>5 days</th>
<th></th>
<th>30 days</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No death (n=264)</td>
<td>Yes death (n=7)</td>
<td>P</td>
<td>No death (n=259)</td>
</tr>
<tr>
<td>Frequency of ischaemia</td>
<td>No death/MI (n=248)</td>
<td>Yes death/MI (n=23)</td>
<td></td>
<td>No death/MI (n=236)</td>
</tr>
<tr>
<td>Number of ST episodes</td>
<td>2 (1,5)</td>
<td>6 (2,11)</td>
<td>0.09</td>
<td>2 (1,5)</td>
</tr>
<tr>
<td>Ischaemic burden</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration (min)</td>
<td>6</td>
<td>32</td>
<td>0.47</td>
<td>6</td>
</tr>
<tr>
<td>ST-VM (µV . min)</td>
<td>2052</td>
<td>7722</td>
<td>0.03</td>
<td>1745</td>
</tr>
<tr>
<td>12-lead ST area (µV . min)</td>
<td>8550</td>
<td>46259</td>
<td>0.02</td>
<td>8048</td>
</tr>
</tbody>
</table>

Data are provided only for patients with any ischaemic episode per 24 h. The number of ST episodes is presented as median value with 25th and 75th percentiles in parentheses. Median values are provided for ischaemic burden variables. MI = myocardial infarction; ST-VM = area under the curve of ST-vector-magnitude during ST episodes per patient; 12-lead ST area = sum of area under the curve of all 12 ECG leads during ST episodes per patient. P values provided for Wilcoxon two-sample test.
who exhibit frequent recurrent ischaemia, as the present analysis shows that the 30-day event rate of almost 20% in this group surpasses the risk associated with an early coronary intervention protected by a glycoprotein IIb/IIIa blocker. This therapeutic concept was confirmed by recent data from a FRISC-II substudy which demonstrated that enhanced antithrombotic treatment was predominantly effective in reducing adverse outcome among the subset of acute coronary syndrome patients with recurrent ischaemia during continuous ECG monitoring in the first 24 h [29]. Clearly, the protocol for patient triage presented here should be considered as a suggestion and it needs to be evaluated for its feasibility as well as its safety and efficacy in prospective studies.

**Limitations**

The present analysis was limited by the fact that the troponin level at admission could not be included in the multivariable analysis as this information was not systematically available in the three studies. However, two recent studies have shown that the presence of ischaemic episodes during multilead ECG monitoring has predictive value independent from and additive to that afforded by the troponin level [7,8].

An inherent limitation of ST-segment monitoring is that patients with ECG abnormalities interfering with ST segment interpretation (e.g. left bundle branch block or ventricular pacemakers) are excluded. However, the baseline characteristics and outcomes of patients included in the ECG monitoring substudies were comparable with those of patients not included in these substudies. Similarly, the outcomes of the 186 patients included in one of the substudies but excluded from the ST analysis due to inadequate registrations were comparable with those of the patients included in the analysis. This suggests that exclusion from the ST analysis was not confounded by the risk of an unfavourable outcome.

Furthermore, registration data from two different monitoring systems were merged for the present analysis. The shorter sampling interval of the standard 12-lead ECG recording system enhances detection of rapid, brief changes in the ST-segment amplitude as compared with the vectorcardiographic device. Users of ECG monitoring systems should therefore be aware of the technical features of the systems for correct data interpretation. However, it should be emphasized that there was homogeneity in the relationship between the occurrence of episodes of recurrent ischaemia and adverse cardiac outcome among the three studies, i.e. each of the three studies separately showed the adverse prognostic implications of recurrent ischaemia, independent of the type of ECG monitoring device used. This observation is supported by recent data from another ECG monitoring study which indicated that in patients with a non-ST-elevation acute coronary syndrome continuous vectorcardiography and continuous 12-lead ECG monitoring identify the same high-risk population [30].
Another potential limitation of the ECG monitoring studies is that the ST-trend data could not be blinded during the recording. However, clinicians were only instructed on how to operate the monitoring function of the ECG system and no information was provided on how the ST-trend data could be retrieved. Furthermore, the monitoring devices were specifically introduced in most investigational centres for these studies and were not used for routine monitoring of patients. Finally, decisions based on ST-trend data or the on-line observation of ischaemic episodes would more likely have resulted in an under-estimation rather than an over-estimation of the prognostic value of ischaemic episodes detected by multilead ECG–ischaemia monitoring.

Conclusion

The profound impact of recurrent ischaemia on survival and the incidence of myocardial infarction among patients treated for acute coronary syndromes emphasises the need for continuous on-line ECG–ischaemia monitoring. Therefore, integration of continuous multilead ECG–ischaemia monitoring systems in coronary care units and emergency wards will identify patients at increased risk of an unfavourable outcome, and allow for better prognostic triage and more appropriate selection of therapeutic strategies.

References


