FRISC II study — still waiting for the exercise test data

In the first of the January 2002 issues of the European Heart Journal important new data from the FRISC II trial are presented[1]. It is understandable that the authors emphasize the prognostic benefit obtained in invasively treated patients with ST-segment depression on the admission electrocardiogram[1]. Thus, in our opinion one major finding from this FRISC II substudy is the observation that more than half of the patients — those without ST-segment depression at entry — do not benefit from an initial invasive strategy, when it comes to hard cardiac endpoints.

(2) The FRISC II trial was designed in such a way that it was very difficult for patients in the non-invasive arm to have an early coronary angiography performed. Non-invasive treatment only allowed coronary angiography in patients who were refractory to or had recurrent symptoms despite maximum medical treatment or severe ischaemia on a symptom-limited pre-discharge exercise test[2]. The authors of the FRISC II trial base their choice of non-invasive strategy with reference to a paper by Nyman et al.[3], who studied 911 men with suspected unstable coronary artery disease. The main findings from this study are that ST-segment or T-wave changes in the resting ECG can predict future acute MI or death. Surprisingly the study does not address the use of exercise testing in risk-stratification[3].

Patients in the non-invasive arm of the FRISC II trial had to have at least 3 mm of ST-segment depression or limiting chest pain associated with a low workload in order to qualify for coronary angiography[2]. As a consequence, patients with up to 2.9 mm of exercise-induced ST-segment depression were not offered an invasive approach. Earlier studies of patients with acute coronary syndromes have shown that approximately 50% will have ≥1 mm of ST-segment depression on a maximal predischarge exercise test[4]. As previously emphasized, the exercise test results of the FRISC II trial unfortunately have still not been published[1,2,5–7]. From the original data, however, we know that only 9% of the patients in the non-invasive arm had coronary revascularization performed within the first 10 days following the acute coronary event[2]. Thus up to 40% of patients in the non-invasive arm of the FRISC II study might have demonstrated ≥1 mm of exertional ST-segment depression without undergoing early coronary angiography.

(3) In previous studies addressing patients with acute coronary syndromes, it has been demonstrated that as many as 38% of the study population for a variety of reasons are

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Figure 1 Trial profile of patient randomization in the FRISC II study. *Data from[1]; **data from[2]; ***questions from the present authors.
Table 1  Death (top) and death/MI (bottom) in the invasive and non-invasive strategy in patients with ST-depression on the admission ECG.

<table>
<thead>
<tr>
<th></th>
<th>Invasive</th>
<th>Non-invasive</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death* (n)</td>
<td>18</td>
<td>33</td>
<td>0.0499</td>
</tr>
<tr>
<td>Death** (n)</td>
<td>18</td>
<td>32</td>
<td>0.0661</td>
</tr>
<tr>
<td>Death/MI* (n)</td>
<td>65</td>
<td>104</td>
<td>0.0042</td>
</tr>
<tr>
<td>Death/MI** (n)</td>
<td>65</td>
<td>92</td>
<td>0.0513</td>
</tr>
</tbody>
</table>

*Original data from [1].

**Data calculated by the present authors using the STATA 7.0 statistical programme.

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For years it has been recommended that patients with significant myocardial ischaemia on an exercise test following an acute coronary syndrome should have a coronary angiography performed[10]. Generally ST-segment depression ≥1 mm has been considered as representing significant residual ischaemia[12]. Previously, the RISC–FRISC I/II study group themselves have shown that ST-segment depression ≥1 mm is an independent factor of future cardiac events in patients with unstable coronary disease[13,14]. If the FRISC II protocol had used the 1 mm ST-segment threshold in the non-invasive arm, it would probably have resulted in more patients undergoing early coronary angiography and in fewer cardiac endpoints. In Table 1 we have calculated, by means of chi-squared analysis as a point estimate at 12 months, how many deaths and deaths/MIs that had to have been avoided in the non-invasive arm to change the $P$-value from significant to non-significant.

It is notable that the prevention of only one additional death in the non-invasive arm would have resulted in the loss of statistical significance.

In order to place the results from the FRISC II trial in an appropriate scientific and clinical perspective, we urgently need to know more about the exercise test procedure and results. Hopefully the FRISC II authors will take the opportunity to enlighten us on this important topic.

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References


A reply

Thank you for showing interest in our paper focusing on the clinical implications of the occurrence of ST depression in unstable coronary artery disease. This was addressed in the letter from Mickley et al. but the questions deal mainly about the exercise test.

Some of these issues are addressed in three forthcoming papers. These will detail the results concerning the exercise test and, in addition, present a multivariable risk score and outcome in a 2-year perspective. One of these papers is in press and two are under consideration for publication. Hopefully, they will provide answers to some of the questions.

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on I

The timing of PCI

Ronner et al. concluded in their article that patients who had undergone percutaneous coronary intervention (PCI) on day 1 had the lowest incidence of death or myocardial infarction (MI) compared to patients who underwent PCI after day 1.

They state that longer medical stabilization is unnecessary when the decision to perform PCI has been made. However, in our opinion it is not fair to draw conclusions about timing of intervention when the definition of MI occurring before 18 h is different from the definition of MI beyond 18 h. Furthermore, it is very difficult to assess the incidence of new MI in the first 24 h after admission, especially in patients who present with elevated enzymes. This may be the explanation of the very low incidence of peri-procedural MI in the group who underwent PCI on day 1. Many of these MIs may be missed due to either elevated enzymes on admission or due to the enzyme rise related to very early intervention.

Therefore, this makes a conclusion about the timing of intervention cumbersome, and as the authors stated: answering the question about ideal timing of intervention requires well-designed trials in which the definition of MI is not dependent on the timing of intervention.

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Reference


on I

The above letter commented on our article on the timing of interventional treatment of patients with ACS without persistent ST-segment elevation in a post-hoc data-analysis from PURSUIT.

To discriminate between procedural and enrolment MI for patients undergoing very early PCI in PURSUIT, an adjusted definition for MI was indeed used during the first 18 h. This definition was used for patients with enrolment MI, and not for patients without enrolment MI. It was thereby applicable for 84 epifibatide, and 109 placebo patients, while the total number of patients undergoing PCI within 24 h was 620.

This pre-defined definition for MI included any period of 30 min of chest pain with 30 min of ST-elevation. This definition contrasted to, three times the upper limit of normal CK after PCI. One could therefore hypothesize that procedural infarction in patients treated with PCI within 18 h is likely to be over- instead of under-estimated, as the authors suggest.

This very relevant topic of adjudication of MI, as enrolment or procedural MI, was performed by an independent blinded critical event committee (CEC) and also compared to MI as defined by the principal investigators. Both definitions (CEC- and principal investigators-defined MI) led to similar results.

It is well recognized that the observed, and debated, day 1 results were important in our analysis. It should be noted that the trend of events with PCI at different intervals, as well as overall 30-day results, all pointed in the same direction. It was this combination of findings that led to our recommendation.

Our recommendation is to intervene without further medical stabilization when the choice is made to intervene. This is conceivable from our data, and also conceivable from our rationale; medical treatment alone to the time of PCI is related to a chance of events over time, while procedural risk declines over time. We thus hypothesize that this procedural chance of events in ACS without persistent ST-segment elevation is related to risk of medical management alone at a specific moment in time. As platelet GP IIb/IIIa receptor blockers markedly reduce procedural risk of MI (by approximately 40%) but only slightly reduce risk (by approximately 10%) during medical management of ACS without persistent ST-segment elevation, the greatest gain by platelet GP IIb/IIIa receptor blockers is obtained when risk of procedural events is highest. Thereby a period of stabilization in which events can occur is avoided, while procedural risk is strongly reduced by platelet GP IIb/IIIa receptor blockers.

We strongly agree, however, that a prospective well-designed randomized trial is needed to test our retrospective findings.

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