Optimal timing of invasive angiography in stable non-ST-elevation myocardial infarction: the Leipzig Immediate versus early and late Percutaneous coronary Intervention trial in NSTEMI (LIPSIA-NSTEMI Trial)

Holger Thiele1*, Justus Rach1, Norbert Klein2, Dietrich Pfeiffer2, Andreas Hartmann3, Rainer Hambrecht4, Peter Sick5, Ingo Eitel1, Steffen Desch1, and Gerhard Schuler1, for the LIPSIA-NSTEMI Trial Group

1Department of Internal Medicine/Cardiology, Heart Center, University of Leipzig, Stru¨mpellstr. 39, 04289 Leipzig, Germany; 2University of Leipzig, Leipzig, Germany; 3Krankenhaus St. Georg, Leipzig, Germany; 4Klinikum Links der Weser, Bremen, Germany; and 5Krankenhaus der Barmherzigen Brüder, Regensburg, Germany

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Aims
The optimal timing of intervention in non-ST-elevation myocardial infarction (NSTEMI) remains uncertain. The aim of this multicentre trial was to assess whether an immediate invasive approach is superior to an early invasive or a selective invasive approach with respect to reduction of large infarction.

Methods and results
Patients with NSTEMI were randomized to either an immediate (<2 h after randomization; n = 201), an early (10–48 h after randomization; n = 200), or a selective invasive approach with high invasive percentage (n = 201). The primary outcome was the peak creatine kinase (CK)-myocardial band (MB) activity during index hospitalization; key secondary clinical endpoints were the composite of (i) death and non-fatal infarction; (ii) death, non-fatal infarction, and refractory ischaemia; (iii) death, non-fatal infarction, refractory ischaemia, and rehospitalization for unstable angina within 6 months.

The median time from randomization to angiography was 1.1 h in the immediate vs. 18.6 h in the early and 67.2 h in the selective invasive group (P < 0.001). There was no significant difference in the peak CK-MB activity between groups. The key secondary clinical endpoints were similar between groups at 6-month follow-up: death and infarction: 21.0% vs. 16.0% vs. 14.5%; P = 0.17; death, infarction, refractory ischaemia: 20.9% vs. 21.5% vs. 22.0%; P = 0.98; death, infarction, refractory ischaemia, rehospitalization: 26.0% vs. 26.5% vs. 24.5%; P = 0.91, respectively.

Conclusions
In NSTEMI patients, an immediate invasive approach does not offer an advantage over an early or a selective invasive approach with respect to large myocardial infarctions as defined by peak CK-MB levels, which is supported by similar clinical outcomes.

ClinicalTrials.gov NCT00402675

Keywords
Acute myocardial infarction • Acute coronary syndrome • Revascularization • Non-ST-segment elevation acute coronary syndromes • Timing
Introduction

Several randomized trials and meta-analyses have shown a benefit of an early invasive strategy followed by revascularization over a conservative or selective invasive approach with respect to death and myocardial infarction (MI) in non-ST-elevation acute coronary syndromes (NSTE-ACS). Several recent guidelines recommend an early invasive strategy within 12–24 h for most NSTE-ACS patients. However, the optimal timing of such intervention is not well established.

Recently, some randomized trials have investigated the timing of intervention (immediate vs. early and late and high-risk NSTE-ACS patients. Based on these trials and subgroup analysis from the Timing of Intervention in Patients With Acute Coronary Syndromes (TIMACS) trial, current updated guidelines recommend an early invasive strategy within 12–24 h for patients with high-risk features defined by a GRACE score >140 and within 72 h for those at lower risk with GRACE score <140.

These timing trials showed substantial heterogeneity in a number of aspects such as (i) non-uniform endpoint definitions, (ii) comparison of either immediate vs. early/late or early vs. late intervention, and (iii) the inclusion of a substantial portion of patients without elevated troponin ranging from 33–54% indicating a low-risk population. Moreover, the advantages of a routine early invasive strategy in NSTE-ACS over a selective invasive strategy with high invasive rates are not as clear cut as demonstrated in meta-analyses and the Invasive vs. Conservative Treatment in Unstable Coronary Syndromes (ICTUS) trial. The actual revascularization rate might have a higher impact on outcome than the exact timing of an invasive strategy.

Given these uncertainties, we designed a multicentre, randomized trial to determine the optimal timing in patients with high-risk non-ST-elevation MI (NSTE-MI). For this purpose, we examined whether the use of immediate coronary angiography and revascularization—similar to the approach in ST-elevation MI (STEMI)—is superior to an early invasive approach performed on the next working day or a selective invasive strategy with a high invasive rate excluding low-risk patients without troponin elevation.

Methods

The LIPSIA-NSTEMI trial randomized patients with NSTEMI admitted at six tertiary care centres in Germany with 24 h percutaneous coronary intervention (PCI) facilities.

Included were patients with NSTE-MI with ischaemic symptoms that were increasing or occurred at rest, with the last episode <24 h before randomization plus elevated troponin T level ≥0.1 ng/mL. Exclusion criteria were age <18 and >90 years, refractory ischaemia, haemodynamic instability, overt congestive heart failure, major arrhythmias requiring immediate catheterization, oral anticoagulation, contraindications to heparin, aspirin, clopidogrel, and glycoprotein IIb/IIIa inhibitors, comorbidity with life expectancy <6 months, and alternate possibilities of troponin elevation such as suspected myocarditis, secondary to congestive heart failure or hypertensive crisis.

The study was approved by the local Ethics Committees at each participating institution and all patients gave written informed consent. The trial was coordinated by the LIPSIA Research Institute.

Randomization and study treatment

At the earliest time point after admission and initial NSTEMI diagnosis, patients were randomly assigned by the use of a web-based randomization system to one of the three treatment arms: immediate invasive; early invasive; selectively invasive. Permuted block randomization was performed with stratification according to site. Patients assigned to the immediate invasive strategy were scheduled to undergo angiography as soon as possible within the first 2 h after randomization and patients in the early invasive strategy on the next working day which was defined by a time window of 10–48 h after randomization. Patients assigned to the selectively invasive strategy were initially treated medically.

Patients assigned to the early and selective invasive strategy were allowed to undergo immediate intervention, if the patient met prespecified criteria (see Supplementary material online).

Decisions regarding the revascularization method were left to the discretion of the interventionists. In the three groups, when PCI was believed appropriate on the basis of coronary anatomy, culprit vessel PCI was performed in the same setting. In case of multivessel PCI, non-culprit vessels could be revascularized in the same setting or in a staged procedure. The use of bare-metal or drug-eluting stents and thrombectomy was left to the interventionists discretion. When revascularization with coronary artery bypass graft (CABG) surgery was preferred, it was recommended to be performed as soon as possible regardless of the randomized group.

In all study groups, antithrombotic pre-treatment consisted of (i) unfractionated heparin, initial bolus of 60 U/kg followed by infusion adjusted to aPTT of 60–80 s for at least 24 h. In case of PCI, additional heparin doses were given adjusted to the activated clotting time (target 200–250 s); (ii) aspirin, initially 500 mg followed by 100 mg indefinitely; (iii) oral clopidogrel, 600 mg loading dose followed by 75 mg daily for 12 months (during the last 7 months of the study also prasugrel was allowed at 60 mg loading dose followed by 10 mg/day); and (iv) intravenous tirofiban, initial bolus of 25 μg/kg followed by continuous infusion of 0.15 μg/kg/min for 24 h. In patients undergoing medical treatment or CABG, tirofiban was stopped after catheterization; heparin could be continued until surgery, if indicated.

For all study groups, the study protocol mandated β-blockers, angiotensin-converting enzyme-inhibitors or angiotensin-I antagonists, and high-dose statins as concomitant treatment.

Time zero was defined as the time of randomization. The following additional times were recorded: onset of angina, last ischaemic symptoms, hospital admission, first sheath insertion, day of hospital discharge.

Biochemical marker and electrocardiographic assessment

Biochemical markers of myocardial damage, such as troponin, creatine kinase (CK), and CK myocardial band (CK-MB) activity, were collected at hospital admission. After randomization, CK-MB activity was measured every 6 h for the first 48 h using an in vitro immune inhibition test (Roche Diagnostics, Germany) with the upper limit of normal <0.14 μkat/L. All measurements complied with the rules of the International Federation of Clinical Chemistry. Thereafter, blood sampling was repeated in case of recurrent ischaemic episodes during hospitalization and in case of any revascularization performed >48 h after randomization at 6 and 12 h. For three centres enrolling 85% of patients, measurements were performed in a central laboratory. In the other centres, measurements were performed locally using the same assay and entered in a central computer database. In addition to the peak CK-MB activity, the area under the curve was calculated using a linear trapezoid method. All patients underwent conventional
12-lead ECG on admission, immediately after revascularization, and at least once daily during the initial first 2 days. In case of any event, the ECG was centrally analyzed by observers blinded to treatment allocation.

**Outcomes and follow-up**

The primary endpoint was the peak CK-MB activity during index hospitalization for each patient. In addition, the infarct size was estimated on the basis of the area under the curve of CK-MB release. Key secondary endpoints were the composite of (i) death and non-fatal MI; (ii) death, non-fatal MI, and refractory ischaemia; (iii) death, non-fatal MI, refractory ischaemia, and rehospitalization for unstable angina within 6 months.

Major safety endpoints were in-hospital severe/life-threatening or moderate bleeding occurring either spontaneously, PCI-related, or CABG-related as assessed by the GUSTO definition and the occurrence of any ischaemic stroke.

Post-hospital follow-up included one 6-month outpatient visit. All clinical endpoints were adjudicated by a central committee unaware of the patient treatment assignments.

**Statistical analysis**

The number of patients included was based on the sample size estimation for the primary study endpoint peak CK-MB. Using a one-way analysis of variance model, we calculated that a sample size of 190 in each group would ensure a power of at least 85% at a two-sided \( \alpha \)-value of 0.05 to detect a difference in peak CK-MB values of 5% at an SD of 17% between any of the three treatment groups. To account for potential dropouts, 200 patients were scheduled for randomization in each group.

All analyses were performed by the intention-to-treat principle. In case of missing values, a sensitivity analysis was carried out to check the robustness of the conclusions.

A predefined subgroup analysis was performed for male/female, diabetes absent/present, age (<65 vs. ≥65 years) and GRACE score <median vs. >median.

Several continuous variables had non-normal distribution. For reasons of uniformity, summary statistics for all continuous variables are therefore presented as medians with inter-quartile range (IQR). Categorical variables were compared with the \( \chi^2 \) test or Fisher’s exact test. Continuous variables were compared with the Kruskal–Wallis one-way analysis of variance on ranks. In case of multiple comparisons, Tukey’s post hoc testing was done. Time-to-event distributions for the combined secondary clinical endpoints were displayed according to the Kaplan–Meier method and were compared with the use of the log-rank test.

All statistical tests were performed with the SPSS software, version 17.0 (Chicago, IL, USA). A two-tailed \( P \)-value <0.05 was considered statistically significant.

**Results**

Of the 602 patients in the study, 201 were randomized to immediate, 200 to early, and 201 to the selective invasive group. Owing to withdrawal of consent, two patients were excluded, leading to 200 patients in each group for the final analysis (Figure 1). Baseline characteristics were well balanced between treatment groups (Table 1). Complete 6-month follow-up was obtained for >98% of patients (Figure 1). The use of evidence-based medication, including aspirin, thienopyridines, angiotensin-converting enzyme-inhibitors, and statins, was high and similar in the three treatment groups except...
for tirofiban completion, which was lower in the immediate and early invasive groups, leading to earlier disruption in case of urgent CABG or conservative therapy (Table 1).

### Procedural characteristics

Overall, 99.5% (199/200) of patients in the immediate invasive group underwent angiography, compared with 99% (198/200) in the selective invasive group (P < 0.001 vs. immediate and early invasive group). In the early invasive group, 12 (6%) patients underwent urgent angiography before the predefined 10–48 h time period. The reasons for invasive angiography in the selective invasive group are shown in Figure 1. The median time to angiography as defined by sheath insertion was 1.1 h (IQR 0.8–1.5) in the immediate, 18.3 h (14.0–21.2) in the early, and 67.2 h (35.8–89.9) in the selective invasive group (P < 0.001).

The angiographic baseline characteristics were not significantly different between the three treatment groups (Table 2).

Approximately two-thirds (62%) of the patient population had multivessel disease and the left anterior descending artery was most frequently identified as the culprit artery (Table 2). Patients undergoing PCI received 98% of stents, of which 35% were drug-eluting stents. The definitive treatment did not differ significantly between the immediate and the early invasive treatment group [PCI: 151 (76%) vs. 141 (71%); CABG: 33 (17%) vs. 34 (17%)]. The time from randomization to CABG was shortest in the immediate invasive group (P = 0.001 vs. early and selective invasive group, respectively). Similarly, the revascularization rates were also high in the selective invasive group, more patients were treated medically, mainly influenced by the 31 patients not undergoing angiography (Table 2).

### Primary endpoint

The peak CK-MB activity was similar between groups with 0.94 μkat/L (IQR 0.48–1.91) in the immediate vs. 0.78 μkat/L (IQR 0.47–1.60) in the early and 0.91 μkat/L (IQR 0.47–1.64; P = 0.18) in the selective invasive group (Figure 2). Similarly, the
Optimal timing of intervention in NSTEMI

Table 2  Times and results of invasive procedures

<table>
<thead>
<tr>
<th>Variable</th>
<th>Immediate invasive (n = 200)</th>
<th>Early invasive (n = 200)</th>
<th>Selective invasive (n = 200)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admission to randomization, h</td>
<td>2.1 (1.0–3.8)</td>
<td>2.5 (1.3–4.1)</td>
<td>2.2 (1.0–3.5)</td>
<td>0.71</td>
</tr>
<tr>
<td>Last symptoms to randomization, h</td>
<td>8.8 (6.3–12.9)</td>
<td>10.0 (6.0–14.9)</td>
<td>9.5 (5.9–13.4)</td>
<td>0.62</td>
</tr>
<tr>
<td>Randomization to sheath insertion, h</td>
<td>1.1 (0.8–1.5)</td>
<td>18.3 (14.0–21.2)</td>
<td>67.2 (35.8–89.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Extent coronary disease, n/N (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>One-vessel disease</td>
<td>63/200 (32)</td>
<td>53/198 (27)</td>
<td>39/170 (23)</td>
<td>0.24</td>
</tr>
<tr>
<td>Two-vessel disease</td>
<td>59/200 (30)</td>
<td>64/198 (32)</td>
<td>53/170 (31)</td>
<td></td>
</tr>
<tr>
<td>Three-vessel disease</td>
<td>59/200 (30)</td>
<td>54/198 (32)</td>
<td>63/170 (37)</td>
<td></td>
</tr>
<tr>
<td>Culprit lesion, n/N (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left main</td>
<td>3/200 (2)</td>
<td>6/198 (3)</td>
<td>2/170 (1)</td>
<td>0.93</td>
</tr>
<tr>
<td>Left anterior descending</td>
<td>64/200 (32)</td>
<td>66/198 (33)</td>
<td>57/170 (34)</td>
<td></td>
</tr>
<tr>
<td>Left circumflex</td>
<td>45/200 (23)</td>
<td>46/198 (23)</td>
<td>37/170 (22)</td>
<td></td>
</tr>
<tr>
<td>Right coronary</td>
<td>47/200 (24)</td>
<td>38/198 (19)</td>
<td>32/170 (19)</td>
<td></td>
</tr>
<tr>
<td>Bypass graft</td>
<td>2/200 (1)</td>
<td>2/198 (2)</td>
<td>3/170 (2)</td>
<td></td>
</tr>
<tr>
<td>Culprit not clearly identified</td>
<td>39/200 (20)</td>
<td>40/198 (20)</td>
<td>39/170 (23)</td>
<td></td>
</tr>
<tr>
<td>Treatment, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCI</td>
<td>151 (76)</td>
<td>141 (71)</td>
<td>114 (57)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CABG</td>
<td>16 (8)</td>
<td>25 (13)</td>
<td>25 (13)</td>
<td></td>
</tr>
<tr>
<td>Conservative</td>
<td>33 (17)</td>
<td>34 (17)</td>
<td>61 (31)</td>
<td></td>
</tr>
<tr>
<td>Time to CABG, days</td>
<td>2.0 (1.0–4.0)</td>
<td>5.0 (2.3–8.0)</td>
<td>10.0 (4.0–13.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Left ventricular EF, %</td>
<td>55 (45–63)</td>
<td>55 (45–60)</td>
<td>55 (48–60)</td>
<td>0.68</td>
</tr>
</tbody>
</table>

Continuous data are presented as median (IQR). PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; EF, ejection fraction.

Secondary clinical endpoints

The key clinical secondary endpoint combining death and non-fatal re-MI was not different between the three treatment groups (Figure 3A) despite a significantly higher re-MI rate in the immediate invasive group (Table 3). Similarly, the rate of death, non-fatal re-MI, and refractory ischaemia as well as death, non-fatal re-MI, refractory ischaemia, and rehospitalization for unstable angina was not different despite a significantly lower rate of refractory ischaemia in the immediate invasive group (Figure 3B and C; Table 3).

Patients with peak CK-MB activity ≥median had worse clinical outcome with respect to death and MI after hospital discharge at 6-month follow-up in comparison with patients with peak CK-MB activity <median (Figure 3D), underlining the prognostic validity of the primary endpoint.

There were no safety differences with respect to bleeding in the three treatment groups (severe/life-threatening 0.5 vs. 0.5 vs. 1.0%; P = 0.78; moderate non-CABG-associated 4.0 vs. 3.5 vs. 1.5%; P = 0.30; moderate CABG-associated 4.0 vs. 4.5 vs. 5.0%; P = 0.89; mild 9.5 vs. 8.5 vs. 5.5%; P = 0.30). There were two strokes (1.0%) in the immediate intervention group. The hospital stay was longest in the selective invasive group with 5.0 days (IQR 4.0–7.0) vs. 4.0 (2.0–5.0) in the immediate and 4.0 days (3.0–6.0) in the early invasive group (P < 0.001).

Discussion

This is the first randomized trial exclusively including high-risk NSTEMI patients with elevated troponin. Our trial confirms and extends previous findings, as we could demonstrate that (i) a STEMI-like immediate approach in NSTEMI patients is feasible and can be safely adopted without increased risk; (ii) an immediate invasive approach does not offer significant advantage over an early or a selective invasive approach with respect to large infarctions as defined by peak CK-MB levels; (iii) an immediate or early invasive strategy is associated with a reduced hospital stay.

Timing trials in non-ST-elevation acute coronary syndromes

The Intracoronary Stenting With Antithrombotic Regimen Cooling Off (ISAR-COOL) study was the first trial to compare immediate angiography (3 h to catheterization) with delayed angiography (4 days), demonstrating that the immediate approach was superior in preventing death or MI. However, this trial had a modest sample size and a relatively long waiting period until catheterization in the control group, which is not fully representative of contemporary practice. Interestingly, this trial had
virtually the same number of patients included in each of the two groups. In contrast, two more recent trials showed no benefit or even harm with an immediate approach (0.5 and 1.1 h to catheterization) over an early invasive approach (20.5 and 25 h).\textsuperscript{7,9} This is in line with the current trial, which showed a higher re-infarction rate in the immediate invasive group, whereas refractory ischaemia could be significantly reduced. In the largest trial, the TIMACS study, no advantage of early catheterization (14 h) over late catheterization (50 h) to prevent death, MI, or stroke at 6-month follow-up was observed.\textsuperscript{6} However, TIMACS investigated only an early vs. a later invasive approach and there was a benefit in high-risk patients with the early approach.\textsuperscript{6} Therefore, no conclusion can be drawn with respect to any benefit of an immediate STEMI-like approach.

Another important problem in timing trials is that in NSTEMI the exact symptom onset is not as clearly defined as in STEMI. Therefore, in all trials, timing is not based on symptoms leading to a large heterogeneity of timing intervals in the trial cohorts, although the timing intervals are relatively homogenous with respect to time from randomization. In the current trial, we

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**Figure 2** Subgroup analysis for the comparison of immediate (dark grey boxes) vs. early (light grey boxes) and selective invasive (black boxes) treatment. Boxes indicate 25th percentile, median, and 75th percentile, and whiskers 10th and 90th percentiles. Dots indicate outliers. P-values reported are derived from the Kruskal–Wallis one-way ANOVA on ranks test. CK-MB, creatine kinase myocardial band.
Figure 3 Kaplan–Meier cumulative risk of the clinical secondary outcomes at 6 months. (A) Death or recurrent non-fatal myocardial infarction (left upper corner). (B) Death, recurrent non-fatal myocardial infarction, or refractory ischaemia (right upper corner). (C) Death, recurrent non-fatal myocardial infarction, refractory ischaemia, or rehospitalization for unstable angina (left lower corner). (D) Death and recurrent non-fatal myocardial infarction with respect to CK-MB values < and ≥ median (right lower corner). CK-MB, creatine kinase myocardial band.

Table 3 Incidence of clinical events within 6 months

<table>
<thead>
<tr>
<th>Variable</th>
<th>Immediate invasive (n = 200)</th>
<th>Early invasive (n = 200)</th>
<th>Selective invasive (n = 200)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death, n (%)</td>
<td>9 (4.5)</td>
<td>12 (6.0)</td>
<td>13 (6.5)</td>
<td>0.66</td>
</tr>
<tr>
<td>Non-fatal MI, n (%)</td>
<td>33 (16.5)</td>
<td>20 (10.0)</td>
<td>16 (8.0)</td>
<td>0.02</td>
</tr>
<tr>
<td>In-hospital MI, n (%)</td>
<td>27 (13.5)</td>
<td>17 (8.5)</td>
<td>14 (7.0)</td>
<td>0.07</td>
</tr>
<tr>
<td>Post-discharge MI, n (%)</td>
<td>6 (3.0)</td>
<td>3 (1.5)</td>
<td>2 (1.0)</td>
<td>0.30</td>
</tr>
<tr>
<td>Refractory ischaemia, n (%)</td>
<td>0</td>
<td>13 (6.5)</td>
<td>20 (10.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Rehospitalization for unstable angina, n (%)</td>
<td>13 (6.5)</td>
<td>15 (7.5)</td>
<td>9 (4.5)</td>
<td>0.58</td>
</tr>
<tr>
<td>Death and non-fatal MI, n (%)</td>
<td>42 (21.0)</td>
<td>32 (16.0)</td>
<td>29 (14.5)</td>
<td>0.20</td>
</tr>
<tr>
<td>Death, non-fatal MI, and refractory ischaemia, n (%)</td>
<td>42 (21.0)</td>
<td>43 (21.5)</td>
<td>44 (22.0)</td>
<td>0.97</td>
</tr>
<tr>
<td>Death, non-fatal MI, refractory ischaemia, and rehospitalization for unstable angina, n (%)</td>
<td>52 (26.0)</td>
<td>53 (26.5)</td>
<td>49 (24.50)</td>
<td>0.89</td>
</tr>
</tbody>
</table>

For composite endpoint reporting in patients with more than one event, only the most severe event was counted: death > non-fatal re-infarction > refractory ischaemia > rehospitalization for unstable angina. MI, myocardial infarction.
carefully evaluated the last occurrence of symptoms showing a long delay from last symptoms to randomization of ~9 h.

**Routine early vs. selective invasive approach**

Current guideline recommendations favouring a routine early invasive over a selective invasive approach are based on older randomized clinical trials and meta-analyses.1–5 However, if the invasive rate is high in the selective invasive strategy, the benefits in the early invasive arm are not as clear as shown in the ICTUS trial and also in more recent contemporary meta-analyses.3,14,15,18 By design, the individual trials allowed for angiography and revascularization on the basis of symptoms as well as objective signs of ischaemia. Routine stress testing led to higher crossover rates in the selective invasive arm very similar to our trial, which had the highest invasive rate (85%) reported so far in a selective invasive group. In other previous trials, the invasive rate ranged from only 16 to 63% during index hospitalization.15,19 As shown previously, the actual revascularization rate might have higher impact on outcome than the timing of the invasive strategy itself.16

**Endpoint definitions**

Currently, no timing trial in NSTE-ACS was sufficiently powered to detect differences in hard endpoints. Even the largest trial was stopped early due to slow enrolment, leading to insufficient power.6 In addition, crucial for all trials is the definition of recurrent MI. Although the universal definition of MI has been introduced,20 each trial used a different MI definition (see Supplementary material online, Table).6–9,15,21,22 This is based on the difficulties to define recurrent MI if cardiac troponin is elevated before the procedure and not stable for at least two samples 6 h apart.20 In patients with evolving NSTEMI, such as in our trial, diagnosis of recurrent MI is therefore best done until the biomarkers have begun to fall. However, this is not applicable to the immediate invasive group. Thus, it would lead to an imbalance in the assessment of the recurrent MI definition, and essentially invalidate the results. We therefore aimed at a definition that only counts large infarction. Applying previous definitions, such as any CK-MB elevation or an increase of >20% or >50%, would have led to an inadequately high recurrent MI rate (up to 70% depending on definition) due to the high number of patients with elevated CK-MB levels at baseline.

As we have used CK-MB values for the definition of recurrent in-hospital MI similar to many other previous trials, we used the peak CK-MB as the primary endpoint. Peak troponin values might be superior to CK-MB values with respect to prognosis.7,23,24 However, the prognostic value of high CK-MB values could be shown in the current trial (Figure 3D) and the similar secondary clinical findings between treatment groups support the value of the primary clinical endpoint. Furthermore, a recent trial showed over-sensitivity of troponin values for re-infarction definition, whereas peak CK-MB values were more appropriate and only elevated CK-MB values were associated with evidence of myocardial necrosis using magnetic resonance imaging.25

**Up-stream glycoprotein IIb/IIIa inhibition**

Our trial was designed before the results were available that the routine use of up-stream glycoprotein IIb/IIIa inhibitors is not beneficial and that this leads to a higher risk of bleeding complications.26 The intention of administering tirofiban as early as possible was mainly to take advantage of the benefits of early platelet inhibition before cardiac catheterization and PCI, which was consistent with guideline recommendations.4,5

**Limitations**

This trial had sufficient statistical power only to assess the peak CK-MB activity, limiting the ability for definite conclusions regarding differences in clinical events. In addition, we did not use a central core laboratory mainly for logistical reasons. However, >85% of the measurements were performed in one laboratory and the same test was used in the others, limiting any adverse influence. A screening log was not kept at sites and site selection bias cannot entirely be excluded. Furthermore, the higher incidence of recurrent MI in the immediate invasive strategy might have been induced by revascularization in the early phase causing a brisk increase in the CK-MB concentration due to rapid wash-out. In contrast with delayed intervention, some wash-out will have occurred before, thereby attenuating the wash-out following PCI.

In conclusion, in NSTEMI, an immediate invasive approach does not offer an advantage over an early or a selective invasive approach with respect to large infarctions as defined by peak CK-MB levels, which is supported by similar clinical outcome between the groups.

**Supplementary material**

Supplementary material is available at European Heart Journal online.

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We are indebted to the medical and technical staff in the coronary care units, and the catheterization laboratories of the participating institutions.

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**Conflict of interest:** none declared.

**Appendix**

Optimal timing of intervention in NSTEMI


References


