Symptom onset and treatment in acute myocardial infarction
Mahmoud, Karim

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CHAPTER 7

Timing of intervention and outcome in non-ST-elevation acute coronary syndromes

There is risk on both sides of the curve

Karim D. Mahmoud\textsuperscript{1,2}
Hans L. Hillege\textsuperscript{2}
Ryan J. Lennon\textsuperscript{3}
Bernard J. Gersh\textsuperscript{1}
David R. Holmes Jr.\textsuperscript{1}

\textsuperscript{1}Division of Cardiovascular Diseases, Mayo Clinic, Rochester, Minnesota, USA
\textsuperscript{2}Department of Cardiology, University Medical Center Groningen, The Netherlands
\textsuperscript{3}Division of Biomedical Statistics and Informatics, Mayo Clinic, Rochester, Minnesota, USA

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ABSTRACT

**Background:** In invasively treated patients with non-ST-elevation acute coronary syndromes (NSTE-ACS), the relationship between specific timing of intervention and clinical outcome remains controversial. We aimed to investigate the relationship between delay to intervention and clinical outcome in randomized trials assessing the timing of intervention in patients with NSTE-ACS managed with an initial invasive approach, using a continuous scale of time.

**Methods:** A systematic search was performed to identify published trials randomizing patients with NSTE-ACS to early versus delayed invasive management. Our primary outcome was early myocardial infarction defined as the occurrence of in-hospital or 30-day myocardial infarction. The relationship between timing of intervention and outcome was modeled by fitting a spline to a generalized linear mixed model.

**Results:** Eight trials randomizing 5904 NSTE-ACS patients were included. There was a significant association between timing of intervention and early myocardial infarction (P=0.038) that was U-shaped (P=0.033 for nonlinearity), with the most beneficial period corresponding to a delay to intervention of 20-40 hours. Myocardial infarction at 6-12 months was also associated with timing of intervention (P=0.039) and trended towards a similar U-shaped pattern (P=0.10 for nonlinearity).

**Conclusions:** In patients with NSTE-ACS treated using an invasive strategy, the relationship between specific timing of intervention and the occurrence of myocardial infarction is U-shaped. The risk of myocardial infarction is lowest when intervention is timed between 20 and 40 hours. Earlier intervention may increase the risk of periprocedural myocardial infarction, while delayed intervention may result in excess spontaneous myocardial infarction.

INTRODUCTION

An initial invasive approach consisting of routine angiography and possible revascularization by means of percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) as appropriate is now recommended for most intermediate- and high-risk patients with non-ST-elevation acute coronary syndromes (NSTE-ACS). Still, there is considerable controversy regarding the specific timing of this initial invasive intervention in NSTE-ACS patients. One large and several
smaller randomized trials have addressed this issue and their results have subsequently been studied in meta-analyses. So far, results have been inconclusive and, at times, contradictory. An important limitation of the meta-analyses is that they have studied the impact of time to intervention on outcome in a binary fashion, mainly by pooling of pairwise comparisons of early and delayed treatment arms in the trials. This approach is only valid if a linear relationship between time to intervention and outcome is assumed. However, the shape of this relation is presently unknown. We therefore aimed to investigate the relationship between delay to intervention and clinical outcome in randomized trials assessing the specific timing of intervention in patients with NSTE-ACS managed with an initial invasive approach.

**METHODS**

Two investigators (KDM and DRH) independently searched Medline and the Cochrane Library as well as ClinicalTrials.gov, Current Controlled Trials, and the Netherlands Trials Registry for clinical trials randomizing patients with non-ST-elevation acute coronary syndromes (NSTE-ACS) to early versus delayed invasive management. The following search term was used: 

("myocardial infarction" OR "non-st-elevation" OR “non-st-segment-elevation” OR “non-st-segment elevation” OR “acute coronary syndrome” OR “unstable coronary syndrome” OR “unstable angina”) AND (timing OR strategy OR (early OR immediate OR urgent AND delayed OR deferred)) AND (intervention OR “percutaneous coronary intervention” OR angioplasty OR “coronary angiography” OR angiography OR catheterization)

Additionally, references of relevant articles were reviewed. Trials were included if they were published in peer-reviewed journals up to May 20, 2014. Furthermore, analysis of a prespecified primary endpoint of an early versus delayed invasive strategy was a minimal quality requirement for inclusion. No language restrictions were applied. Trial characteristics, timing of intervention, and clinical outcome were extracted from the included trials by KDM using double data entry. Any inconsistencies were resolved in discussion with DRH. Risk of bias of the included trials was assessed according to the Cochrane Collaboration’s guidelines. Our prespecified primary outcome was early myocardial infarction defined as the incidence of in-hospital or 30-day myocardial infarction as reported in the trials. Our secondary outcome was
myocardial infarction at intermediate follow-up (6-12 months). None of the trials reported on outcome beyond 12 months. All outcomes were based on intention-to-treat analyses.

In the Optimal Timing of Coronary Intervention in Unstable Angina (OPTIMA) trial, a very high rate of myocardial infarction was seen. This could be partially explained by the lenient and broad definition of in-hospital myocardial infarction (creatinine kinase [CK]-MB ≥ once the upper limit of normal) primarily reported in this trial. To better match the definitions used in the other trials, we selected CK-MB ≥3 times the upper limit of normal as definition of in-hospital myocardial infarction, which was also reported in OPTIMA. In all other trials, the originally reported definition of myocardial infarction was used.

The relationship between timing of intervention and myocardial infarction was modeled using a 3 degree-of-freedom restricted natural cubic spline. A generalized linear mixed model was used to fit the spline using a logit link for the response and a random intercept term to account for the correlation between 2 responses from the same trial. Statistical significance was set at P<0.05 (two-tailed). Statistical analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, North Carolina).

**RESULTS**

We identified 10 clinical trials randomizing NSTE-ACS patients to early versus delayed invasive management of which 2 trials were excluded due to insufficient quality. The 8 included trials randomized a total of 5904 patients. Extended follow-up for the Early or Late Intervention in unStable Angina (ELISA) and Intracoronary Stenting With Antithrombotic Regimen Cooling-Off (ISAR-COOL) trials was published in a collaborative meta-analysis. All trials randomized patients to early versus delayed angiography with the exception of the OPTIMA trial, where eligible patients were randomized to early versus delayed percutaneous coronary intervention (PCI). The Leipzig Immediate versus
early and late Percutaneous coronary Intervention trial in Non-ST-Elevation Myocardial Infarction (LIPSIA-NSTEMI) trial only included patients with non-ST-elevation myocardial infarction (NSTEMI). The third arm of this trial, containing a selective invasive strategy (i.e. only clinically driven angiography), was excluded for the present analysis. Although treatment assignment could not be blinded during the trials, the risk of bias was generally deemed to be low (Table 1). Key baseline characteristics and timing of treatment are listed in Table 2. Median time from randomization to intervention varied from 30 minutes in the early arm of the OPTIMA trial to 86 hours in the delayed arm of the ISAR-COOL trial. In the ELISA-3 trial, the intended minimal delay to intervention of 48 hours was violated in 35% of patients assigned to delayed treatment, but median time to intervention was still 43 hours in these prematurely treated patients. Cross-over rates were otherwise low. Subsequent revascularization consisted of PCI in the majority of patients; only few underwent coronary artery bypass grafting (CABG). Follow-up and outcomes of the trials are listed in Table 3. The occurrence of early myocardial infarction was reported in all trials. There was a significant association between timing of intervention and early myocardial infarction (P=0.038) that was U-shaped (P=0.033 for nonlinearity; Figure 2A), with the most beneficial period corresponding to a delay to intervention.

Table 1. Quality and risk of bias of included trials

<table>
<thead>
<tr>
<th>Study, reference</th>
<th>Randomization</th>
<th>Setting</th>
<th>Allocation concealment</th>
<th>Blinded allocation adjudication of outcomes</th>
<th>Outcome data sufficiency</th>
<th>Selective reporting</th>
<th>Other bias</th>
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<tr>
<td>ELISA⁹</td>
<td>Yes</td>
<td>Single center</td>
<td>Unknown</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
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<td>ISAR-COOL⁴</td>
<td>Yes</td>
<td>Multicenter</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
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<td>Yes</td>
<td>Multicenter</td>
<td>Yes</td>
<td>Unknown</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
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<td>TIMACS²</td>
<td>Yes</td>
<td>Multicenter</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
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<tr>
<td>ABOARD⁶</td>
<td>Yes</td>
<td>Multicenter</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
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<tr>
<td>Zhang et al⁷</td>
<td>Yes</td>
<td>Multicenter</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>LIPSIA-NSTEMI⁸</td>
<td>Yes</td>
<td>Multicenter</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
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<td>Yes</td>
<td>Unknown</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
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<td>Study, reference</td>
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<td>ISAR-COOL</td>
<td>OPTIMA</td>
<td>TIMACS</td>
<td>ABOARD</td>
<td>Zhang et al</td>
<td>LIPSIA-NSTEMI</td>
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<td>111</td>
<td>202</td>
<td>200</td>
<td>109</td>
<td>111</td>
<td>202</td>
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<td>Age, mean, y</td>
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<td>69</td>
<td>69</td>
<td>69</td>
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<td>Male, %</td>
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<td>68</td>
<td>68</td>
<td>68</td>
<td>68</td>
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<td>Diabetes, %</td>
<td>15</td>
<td>14</td>
<td>26</td>
<td>31</td>
<td>19</td>
<td>20</td>
<td>27</td>
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<tr>
<td>Prior myocardial infarction, %</td>
<td>17</td>
<td>13</td>
<td>22</td>
<td>25</td>
<td>21</td>
<td>26</td>
<td>20</td>
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<tr>
<td>Ischemic ECG changes, %</td>
<td>N/A</td>
<td>N/A</td>
<td>66</td>
<td>65</td>
<td>52</td>
<td>52</td>
<td>81</td>
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<td>Elevated cardiac biomarker, %</td>
<td>78</td>
<td>71</td>
<td>66</td>
<td>68</td>
<td>47</td>
<td>45</td>
<td>77</td>
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</tbody>
</table>

**Table 2.** Trial characteristics and timing of intervention. Other abbreviations as in Table 1.
### Table 3. Trial outcomes

<table>
<thead>
<tr>
<th>Study, reference</th>
<th>ELISA(^3)</th>
<th>ISAR-COOL(^4)</th>
<th>OPTIMA(^5)</th>
<th>TIMACS(^2)</th>
<th>ABOARD(^6)</th>
<th>Zhang et al(^7)</th>
<th>LIPSIA-NSTEMI(^8)</th>
<th>ELISA-3(^9)</th>
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<td></td>
<td>Early</td>
<td>Delayed</td>
<td>Early</td>
<td>Delayed</td>
<td>Early</td>
<td>Delayed</td>
<td>Early</td>
<td>Delayed</td>
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<td>Patients, No.</td>
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<td>111</td>
<td>203</td>
<td>207</td>
<td>73</td>
<td>69</td>
<td>1593</td>
<td>1438</td>
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<tr>
<td>Primary outcome Follow-up</td>
<td>Biochemical infarct size</td>
<td>30-day death or MI</td>
<td>30-day death, MI, revasc.</td>
<td>6-month death, MI, stroke</td>
<td>Biochemical infarct size</td>
<td>6-month death, MI, stroke</td>
<td>Biochemical infarct size</td>
<td>30-day death, MI, re-ischemia</td>
</tr>
<tr>
<td>Early, months</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>IH</td>
<td>IH</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>MI, n (%)</td>
<td>7 (6.4)</td>
<td>6 (5.4)</td>
<td>12 (5.9)</td>
<td>21 (10)</td>
<td>24 (33)</td>
<td>17 (25)</td>
<td>57 (3.6)</td>
<td>59 (4.1)</td>
</tr>
<tr>
<td>Death, n (%)</td>
<td>3 (2.8)</td>
<td>5 (4.5)</td>
<td>0</td>
<td>3 (1.4)</td>
<td>0</td>
<td>0</td>
<td>46 (2.9)</td>
<td>47 (3.3)</td>
</tr>
<tr>
<td>Intermediate, months</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>MI, n (%)</td>
<td>8 (7.3)</td>
<td>7 (6.3)</td>
<td>16 (7.9)</td>
<td>27 (13)</td>
<td>24 (33)</td>
<td>19 (28)</td>
<td>76 (4.8)</td>
<td>82 (5.7)</td>
</tr>
<tr>
<td>Death, n (%)</td>
<td>3 (2.8)</td>
<td>6 (5.4)</td>
<td>11 (5.4)</td>
<td>10 (4.8)</td>
<td>1 (1.4)</td>
<td>0</td>
<td>76 (4.8)</td>
<td>85 (5.9)</td>
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</table>

IH, inhospital; MI, myocardial infarction; re-ischemia, recurrent ischemia; revasc, revascularization. Other abbreviations as in previous Tables.
of 20-40 hours. Six trials reported on myocardial infarction at intermediate follow-up (6-12 months; Table 3). Intermediate myocardial infarction was also associated with timing of intervention (P=0.039) and trended towards a similar U-shaped pattern (P=0.10 for nonlinearity; Figure 2B). Between-study heterogeneity resulted in wide confidence intervals.

**DISCUSSION**

To the best of our knowledge, we are the first to demonstrate a U-shaped relationship between timing of intervention and outcome in NSTE-ACS trials, although existence of such an association has also been hypothesized by others recently. Importantly, the excess myocardial

![Figure 2A](image1)

**Figure 2A.** Association between median time from randomization to intervention and the incidence of myocardial infarction at **A.** early follow-up (8 trials; n=5904; P=0.038; P=0.033 for nonlinearity) and **B.** intermediate follow-up (6 trials; n=5018; P=0.039; P=0.10 for nonlinearity). The size of the circles reflect the sample size of the study group. Dashed lines represent the 95% confidence interval. Trial acronyms are listed in Table 1.

![Figure 2B](image2)
infarction seen on both sides of the curve is likely to represent different pathophysiological mechanisms. We speculate that very early intervention inherently lacks adequate pharmacological pretreatment with anticoagulant and antiplatelet agents resulting in an increased risk of periprocedural myocardial infarction due to atherosclerotic plaque instability and distal embolization. However, definitive clinical evidence for this theory is still lacking in the absence of a large trial comparing urgent and early intervention. Moreover, we recognize that periprocedural myocardial infarction can be hard to distinguish from the presenting acute coronary syndrome and its prognostic significance is subject of ongoing debate. Nonetheless, a recent report systematically analyzing cardiac biomarker trends in 10,199 NSTE-ACS patients found periprocedural myocardial infarction (if distinguishable) to be a powerful independent predictor of 1-year mortality. Prolonged delay of intervention, on the other hand, increases the risk of spontaneous myocardial infarction despite pharmacological pretreatment. This is evidenced by the results of the ISAR-COOL trial where the higher 30-day death or myocardial infarction rate in the delayed intervention group (median 86 hours) was mainly the consequence of events occurring before catheterization. The time window between 20 and 40 hours seems to be relatively favorable in our analysis. However, in this regard it is important to understand the results of the largest study in this field to date, the Timing of Intervention in Acute Coronary Syndromes (TIMACS) trial. This trial found no difference between an early intervention (median 14 hours) and a delayed intervention (median 50 hours) with regard to its primary endpoint death, myocardial infarction, or stroke at 6 months. However, a prespecified subgroup analysis showed that patients at high baseline risk (Global Registry of Acute Coronary Events [GRACE] risk score >140) derived significant benefit from an early intervention (hazard ratio 0.65; 95% confidence interval 0.48-0.89; P-interaction=0.01). Therefore, we feel that timing of intervention may only be safely extended to 48 hours in patients with low or intermediate baseline risk. In this study, we clearly show a time-dependent benefit for the use of myocardial revascularization therapy in patients with NSTE-ACS that is different as compared with ST-elevation myocardial infarction (STEMI). This finding has several important implications. Clinicians should be aware that both a STEMI-like approach assuming that “time is muscle” as well as a prolonged “cooling-off” strategy are potentially harmful in NSTE-ACS patients selected for an invasive strategy. Furthermore,
future trials, observational studies, and – in particular – meta-analyses should take this non-linear relationship into account in their analyses.

Limitations
Some limitations of our study should be considered. First, although timing of intervention was randomly assigned to patients in the individual trials, our current analysis is based on aggregate data and warrants further prospective confirmation. Second, analysis of mortality patterns on a continuous scale was not feasible due to the combination of a low event rate and substantial between-study heterogeneity. Similarly, heterogeneous definitions did not allow us to study composite clinical endpoints. Finally, our results and conclusions do not apply to NSTE-ACS patients with hemodynamic or electrical instability, since this patient population was excluded from the trials. These patients should still be considered for urgent intervention.¹

Conclusions
In patients with NSTE-ACS treated using an invasive strategy, the relationship between specific timing of intervention and the occurrence of myocardial infarction is U-shaped. The risk of myocardial infarction is lowest when intervention is timed between 20 and 40 hours. Earlier intervention may increase the risk of periprocedural myocardial infarction, while delayed intervention may result in excess spontaneous myocardial infarction.

Acknowledgments
The authors would like to thank Hongtao Yuan, MD for translating one of the included trials.
Timing of Intervention and Outcome in Non-ST-Elevation Acute Coronary Syndromes

Part 2 – Symptom onset to treatment

REFERENCES


