Catheterization laboratories open 24 hours a day, every day: does stable non-ST-elevation acute coronary syndrome need the offer?

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This editorial refers to ‘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)’, by H. Thiele et al., on page 2035

Non-ST-elevation acute coronary syndrome (NSTE-ACS) represents the majority of ACS. Despite the fact that we pay most attention to ST-elevation-ACS, NSTE-ACS is where logistically the action is, as these patients account for ≈ 3 out of 4 hospital ACS discharges. Recent studies have helped to clarify that a strategy of routine catheterization is superior to a conservative strategy of catheterization only if the patient develops spontaneous or stress-induced ischaemia. Routine angiography and revascularization after NSTE-ACS reduces mortality by 25%, myocardial infarction by 18%, and re-hospitalization for unstable angina by 31% at mid-term follow-up. However, it is still controversial, for initially stabilized patients, whether the catheterization and percutaneous coronary intervention (PCI) need to be done early (i.e. within 24 h) or whether they could be delayed ≥1 day while the patient receives medical therapy and logistic attention. Thus, should we open our laboratories 24 h a day, every day, to catheterize NSTE-ACS patients early, even within the first few hours of hospital admission, analogous to the standard of primary PCI?

Timing of invasive therapy before the LIPSIA-NSTEMI trial

Five trials (ISAR-COOL, ELISA, ABOARD, TIMACS, and OPTIMA) and a meta-analysis have compared early vs. delayed intervention in stable NSTE-ACS before the LIPSIA-NSTEMI trial and form the basis of the recently updated recommendations in both American and European guidelines. Unstable patients with very high risk, i.e. those with refractory angina, heart failure, life-threatening arrhythmias, or haemodynamic instability, have not been included in these trials and should be subject to an immediate (<2 h) invasive strategy similar to the case for ST-elevation ACS.

Table 1 shows the principal characteristics of the five above-mentioned randomized trials comparing an early invasive strategy (0.5–14 h) with a delayed strategy (20.8–86 h). Of note, only the ISAR-COOL study showed the early invasive strategy to be clinically superior to deferral of intervention. The findings of this trial were limited mainly because of the prolonged delay before angiography in the deferred strategy. In this sense, the results were not confirmed in the largest scale multicentre study to date, the TIMACS trial, which showed that early intervention did not differ greatly from delayed intervention in preventing the primary outcome of death, myocardial infarction, and stroke at 6 months, although it did reduce the rate of death, myocardial infarction, or refractory ischaemia. In contrast, the OPTIMA trial found an increased rate of procedure-related myocardial infarction in patients having immediate PCI compared with deferred PCI. Similarly, the pilot ELISA trial showed that a delayed strategy with concomitant pre-treatment with glycoprotein IIb/IIIa inhibitors was associated with less initial enzyme release and improved angiographic outcomes compared with a strategy of early angiography without glycoprotein IIb/IIIa inhibitors. Finally, information more relevant to contemporary practice patterns was provided in the ABOARD trial regarding the procedure-related and the size of myocardial infarction, showing that a strategy of immediate intervention, analogous to the OPTIMA trial and the standard of primary PCI, did not result in a difference in myocardial infarction as defined by a peak troponin level compared with a strategy of intervention deferred to the next working day. Thus, in summary, two trials suggest a benefit of an early invasive strategy (ISAR-COOL and TIMACS), two trials suggest a benefit of a
delayed invasive strategy (ELISA and OPTIMA), and one trial was totally neutral (ABOARD).

In a meta-analysis of the aforementioned trials,8 (except for the OPTIMA trial that was excluded by the authors because randomization to early vs. late PCI was performed after knowing the results of the coronary angiography) early coronary intervention was found to reduce the risk of recurrent ischaemia and shortened hospital stay, but with respect to hard endpoints did not significantly reduce the risk of death, myocardial infarction, or major bleeding.

Data overall are limited to performing subgroup analysis to identify whether we should perform early revascularization in high-risk patients. Subgroup analyses from TIMACS and ISAR-COOL did not indicate any significant difference in the effect of early intervention in patients with ST deviation and elevated troponin and those with normal troponin values at baseline.8 However, the TIMACS trial showed that in patients at high risk (defined by a GRACE score >140) an early invasive strategy was associated with a reduction of 35% in the composite outcome of death, myocardial infarction, or stroke at 6 months.

On this basis, currently updated ESC guidelines recommend in high-risk patients with a GRACE risk score of >140 or with at least one major high-risk criterion an early invasive strategy within 24 h with a recommendation class II level A.11 This implies that angiography within 24 h should be performed on the vast majority of patients admitted with NST-ACS, as the criteria for a high-risk patient are defined by a GRACE score >140 choosing an early invasive strategy within 12–24 h of admission over a delayed invasive strategy with a recommendation class II level A. Neither guidelines indicate any incremental benefit derived by angiography and intervention performed within the first few hours in the early invasive strategy.

### The LIPSIA-NSTEMI trial

The LIPSIA-NSTEMI trial,9 the subject of this editorial, carried out at six tertiary care centres in Germany with 24 h PCI facilities between July 2006 and December 2009, randomized 600 patients with NST-ACS to undergo immediate invasive therapy within 2 h (median time to angiography 1.1 h), early invasive therapy on the next working day with a time window of 10–48 h (median time to angiography 18.3 h), or selectively invasive therapy where patients were initially treated medically (median time to angiography 67.2 h). All patients had the last episode of ischaemic symptoms <24 h previously and had elevated troponin levels. Underlying medical therapy in the three treatment arms included aspirin, clopidogrel with a loading dose of 600 mg or prasugrel with a loading dose of 60 mg, unfractionated heparin, and intravenous tirofiban for 24 h. The primary outcome was the peak creatine kinase (CK)-MB activity during hospitalization, and clinical outcomes were designed as secondary endpoints. The rate of non-final coronary revascularization was double in the selective invasive group (31%) compared with early invasive (17%) or immediate invasive (17%) therapies, mainly due to a decrease rate of coronary angiography. Immediate intervention conferred no advantage with regard to the primary endpoint, nor was there an advantage regarding the pre-specified clinical secondary endpoint of death and myocardial infarction; death, myocardial infarction, and refractory ischaemia; and death, myocardial infarction, refractory ischaemia, and re-hospitalization for unstable angina.

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**Table 1**  Principal characteristics of randomized trials, prior to the LIPSIA-NSTEMI trial, comparing early versus delayed invasive strategies

<table>
<thead>
<tr>
<th>Enrolment period</th>
<th>ISAR-COOL3</th>
<th>ELISA4</th>
<th>ABOARD5</th>
<th>TIMACS6</th>
<th>OPTIMA7</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>Early</td>
<td>Delayed</td>
<td>Early</td>
<td>Delayed</td>
<td>Early</td>
</tr>
<tr>
<td>203</td>
<td>207</td>
<td>109</td>
<td>111</td>
<td>175</td>
<td>177</td>
</tr>
<tr>
<td>Time to angiography, h</td>
<td>2.4</td>
<td>86</td>
<td>6</td>
<td>50</td>
<td>1.16</td>
</tr>
<tr>
<td>Elevated troponin, %</td>
<td>68</td>
<td>66</td>
<td>78</td>
<td>71</td>
<td>75</td>
</tr>
<tr>
<td>Clopidogrel, %</td>
<td>100</td>
<td>100</td>
<td>44</td>
<td>49</td>
<td>97</td>
</tr>
<tr>
<td>GP IIB/IIIa inhibitor, %</td>
<td>100</td>
<td>100</td>
<td>8</td>
<td>100</td>
<td>65</td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>Death or MI at 30 days</td>
<td>Enzymatic infarct size LDHQA4</td>
<td>Peak troponin value during hospitalization</td>
<td>Death, MI, or stroke at 6 months</td>
<td>Death, MI, or unplanned revascularization at 30 days</td>
</tr>
<tr>
<td>Result based on the primary endpoint (early vs. delayed)</td>
<td>5.9% vs. 11.6%; P = 0.04</td>
<td>629 ± 503 vs 432 ± 441 U/L; P = 0.02</td>
<td>2.1 (0.3–7.1) vs. 1.7 (0.3–7.2) ng/mL; P = 0.70</td>
<td>9.6% vs. 11.3%; P = 0.15</td>
<td>60% vs. 39%; P = 0.004</td>
</tr>
</tbody>
</table>

GP, glycoprotein; MI, myocardial infarction.
4LDHQA, infarct size based on enzyme concentrations of lactate dehydrogenase (LDH) as the reference enzyme, in which an area under the curve was calculated from preferably seven, but from at least five measurements.
within 6 months. However, an increased rate of myocardial infarction, the majority procedure related, in patients having immediate invasive therapy compared with early or selective invasive groups was observed (16.5% vs. 10.0% vs. 8.0%; \( P = 0.02 \)). In contrast, immediate invasive therapy was associated with a reduction in the occurrence of refractory ischaemia (0% vs. 6.5% vs. 10.0%; \( P < 0.001 \)).

**Timing of invasive therapy after the LIPSIA-NSTEMI trial**

In our opinion, the LIPSIA-NSTEMI trial confirms more than extends previous findings. As shown in the ABOARD trial, immediate intervention, analogous to the standard of primary PCI, does not halt the infarct size. Furthermore, similar to what was observed in the OPTIMA trial, it could increase the rate of procedure-related myocardial infarction. Immediate and early interventions were shown in the LIPSIA-NSTEMI trial to be superior in terms of lower risk of recurrent ischaemia and shorter hospital stay compared with a selective invasive strategy, as the only available meta-analysis to date had already shown.\(^8\) However, there was no beneficial effect toward improving survival or other pre-specified clinical secondary endpoints, as the TIMACS trial showed. Finally, although no data regarding the GRACE score are available, we must remember that all patients were at high risk according to ESC guidelines, as patients had as an inclusion criterion for the study elevated troponin levels. So the LIPSIA-NSTEMI trial evaluated the benefit of an immediate and early invasive strategy in a cohort of high-risk patients.

We have included the LIPSIA-NSTEMI trial together with the ISAR-COOL, ELISA, ABOARD, TIMACS, and OPTIMA trials in a meta-analysis in order to address further whether observed trends (i.e. death, myocardial infarction, and major bleeding) reach formal statistical significance. As shown in Figure 1, there is again a trend for an early invasive strategy to reduce mortality. Availability of data from ongoing trials (i.e. ELISA-3 and IDEAL NSTEMI) will help to clarify whether this trend will reach significance. In contrast, as for myocardial infarction, the analysis suggests increased risk with the early strategy, which can be explained by the periprocedural elevation of cardiac damage biomarkers, but this association did not reach the level of formal statistical significance. Finally, major bleeding is, for the first time, shown to be significantly reduced by early intervention, suggesting that patients at high risk of bleeding may benefit from an early angiography. Thus, we have yet to start to open our catheterization laboratory 24 h a day, every day, for ‘stable’ NST-ACS in order specifically to target fragile patients.

**Conflict of interest:** none declared.

**References**


Primary aortic sarcoma with multiple metastatic sites

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A 58-year-old male was admitted to our hospital with symptoms of numbness, paraesthesia, and mild weakness of the right forearm. Gadolinium-enhanced magnetic resonance cerebral imaging showed a large mass in the right precentral region with strong contrast enhancement (Panel A). This altered suspicion for metastasis of an unknown primary tumour. Subsequently performed computed tomography (CT) of the thorax demonstrated partial occlusion of the aortic arch by a lobulated intraluminal mass (Panels B and C) as well as total, non-calcified occlusion of the left common carotid artery. Computed tomography scan also revealed a suspicious tumour of the left adrenal gland and left-sided second rib (not shown). To further characterize, the pathology of the aortic arch transoesophageal echocardiography was performed. Hereby an irregularly shaped, partial mobile mass originating from the aortic wall could be visualized in the aortic arch and descending aorta (Panels D and E).

Computed tomography-guided needle biopsy of the second rib was performed. Histologic findings revealed undifferentiated pleomorphic tumour cells showing atypical mitosis figures and hyperchromatic nuclei (Panel F). In summary histologic, CT and echocardiographic findings strongly suggested an undifferentiated aortic intimal sarcoma.

Since the tumour already had multiple satellites curative surgery was not an option. The patient was treated with palliative chemotherapy (ifosfamide and doxorubicine) and received cerebral radiation (30 Gy). He died 3 months later due to fast progress of his metastatic malignancy.

Primary aortic sarcoma is a rare and usually fatal malignant disease typically presenting with neurological symptoms due to early cerebral metastasis or malperfusion signs following central or peripheral vessel occlusion.

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