NSTE ACS

Timing of intervention
Timing of intervention in NSTE-ACS

• What do the guidelines tell us?

• Any need for immediate invasive approach?

• No mortality benefit with an early invasive approach?

• Putting trials in perspective
ESC guidelines: Risk stratify your ACS patients!

http://www.outcomes.umassmed.org/grace/acs_risk/acs_risk_content.html

www.escardio.org/ACCA
## Recommendations for revascularization in NSTEMI

<table>
<thead>
<tr>
<th>Specification Level</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
</table>
| An invasive strategy is indicated in patients with:  
  • GRACE score >140 or at least one high-risk criterion.  
  • recurrent symptoms.  
  • inducible ischaemia at stress test. | I | A |
| An early invasive strategy (<24 h) is indicated in patients with GRACE score >140 or multiple other high-risk criteria. | I | A |
| A late invasive strategy (within 72 h) is indicated in patients with GRACE score <140 or absence of multiple other high-risk criteria but with recurrent symptoms or stress-inducible ischaemia. | I | A |
| Patients at very high ischaemic risk (refractory angina, with associated heart failure, arrhythmias or haemodynamic instability) should be considered for emergent coronary angiography (<2 h). | IIa | C |
| An invasive strategy should not be performed in patients:  
  • at low overall risk  
  • at a particular high-risk for invasive diagnosis or intervention. | III | A |
Randomized clinical trials comparing different invasive treatment strategies

<table>
<thead>
<tr>
<th>Trials</th>
<th>FRISC</th>
<th>TRUCS</th>
<th>TIMI 8</th>
<th>VINO</th>
<th>RITA-3</th>
<th>ICTUS</th>
<th>ELISA</th>
<th>ISAR-COOL</th>
<th>OPTIMA</th>
<th>TIMACS</th>
<th>ABOARD</th>
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<tbody>
<tr>
<td>Patients</td>
<td>2456</td>
<td>148</td>
<td>2220</td>
<td>131</td>
<td>1810</td>
<td>1199</td>
<td>220</td>
<td>410</td>
<td>142</td>
<td>3031</td>
<td>352</td>
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<tr>
<td>Time to angio (h)</td>
<td>96/408</td>
<td>48/120</td>
<td>22/79</td>
<td>6.2/1464</td>
<td>48/1020</td>
<td>23/283</td>
<td>6/50</td>
<td>2.4/86</td>
<td>0.5/25</td>
<td>14/50</td>
<td>1.2/21</td>
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<tr>
<td>Mean age (year)</td>
<td>66</td>
<td>62</td>
<td>62</td>
<td>66</td>
<td>62</td>
<td>62</td>
<td>63</td>
<td>70</td>
<td>62</td>
<td>65</td>
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<tr>
<td>Women, %</td>
<td>30</td>
<td>27</td>
<td>34</td>
<td>39</td>
<td>38</td>
<td>27</td>
<td>30</td>
<td>33</td>
<td>32</td>
<td>35</td>
<td>28</td>
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<tr>
<td>Diabetes, %</td>
<td>12</td>
<td>29</td>
<td>28</td>
<td>25</td>
<td>13</td>
<td>14</td>
<td>14</td>
<td>29</td>
<td>20</td>
<td>27</td>
<td>27</td>
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<tr>
<td>Troponin ↑ at inclusion, %</td>
<td>55</td>
<td>NA</td>
<td>54</td>
<td>100</td>
<td>75</td>
<td>67</td>
<td>68</td>
<td>67</td>
<td>46</td>
<td>77</td>
<td>74</td>
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<tr>
<td>Invasive (%)</td>
<td>78/45</td>
<td>100/61</td>
<td>64/45</td>
<td>73/39</td>
<td>57/28</td>
<td>79/54</td>
<td>74/77</td>
<td>78/72</td>
<td>100/99</td>
<td>74/69</td>
<td>91/81</td>
</tr>
<tr>
<td>PCI/CABG (%)</td>
<td>30/27</td>
<td>43/16</td>
<td>36/19</td>
<td>50/27</td>
<td>26/17</td>
<td>51/10</td>
<td>54/15</td>
<td>68/8</td>
<td>99/0</td>
<td>57/28</td>
<td>63/2</td>
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<tr>
<td>Primary outcome</td>
<td>D/MI 6 months</td>
<td>D/MI/H</td>
<td>D/MI/A 6 months</td>
<td>D/MI 12 months</td>
<td>D/MI/A 12 months</td>
<td>Infarct size LDH</td>
<td>D/MI 1 months</td>
<td>D/MI/UR 30 days</td>
<td>D/MI/S 6 months</td>
<td>Troponin release</td>
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<tr>
<td>Endpoint met</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
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</table>
Early (≤24hrs) vs delayed (≥36hrs) coronary angiography in NSTEMI/UAP TIMACS trial

**Death, MI, or stroke**

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Days</th>
<th>Cumulative Hazard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delayed</td>
<td>1438</td>
<td>1328</td>
</tr>
<tr>
<td>Early</td>
<td>1593</td>
<td>1484</td>
</tr>
</tbody>
</table>

Hazard ratio, 0.85 (95% CI, 0.68–1.06)  
P=0.15

**Death, MI, or refractory ischemia**

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Days</th>
<th>Cumulative Hazard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delayed</td>
<td>1438</td>
<td>1303</td>
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<tr>
<td>Early</td>
<td>1593</td>
<td>1485</td>
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</table>

Hazard ratio, 0.72 (95% CI, 0.58–0.89)  
P=0.003

<table>
<thead>
<tr>
<th>Early Intervention (N=1593)</th>
<th>Delayed Intervention (N=1438)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary angiography (%)</td>
<td>97.6</td>
<td>95.7</td>
</tr>
<tr>
<td>Median time (hr)</td>
<td>14</td>
<td>50</td>
</tr>
<tr>
<td>Interquartile range (hr)</td>
<td>3–21</td>
<td>41–81</td>
</tr>
</tbody>
</table>

SR Mehta et al.  
Early (≤24hrs) vs delayed (≥36hrs) coronary angiography in NSTEMI/Unstable AP - TIMACS trial

Death, MI, or stroke hazard in high (GRACE>140) vs low risk (GRACE ≤140) patients

SR Mehta et al.  
High risk situations needing emergency coronary angiography

Ongoing or recurrent ischaemia.

Dynamic spontaneous ST changes (>0.1 mV depression or transient elevation).

Deep ST depression in anterior leads V2–V4 indicating ongoing posterior transmural ischaemia.

Haemodynamic instability.

Major ventricular arrhythmia.
High risk situations needing emergency coronary angiography

Ongoing or recurrent ischaemia.

Dynamic spontaneous ST changes (>0.1 mV depression or transient elevation).

Deep ST depression in anterior leads V2–V4 indicating ongoing posterior transmural ischaemia.

Haemodynamic instability.

Major ventricular arrhythmia.
Do not miss a true posterior acute STEMI!
Do not miss a true posterior acute STEMI!
Timing of intervention in NSTE-ACS

• What do the guidelines tell us?

• Any need for immediate invasive approach?

• No mortality benefit with an early invasive approach?

• Putting trials in perspective
Immediate (<2 hrs) vs. early (10-48 hrs) vs. selective invasive approach (LIPSIA-NSTEMI Trial)

death and non-fatal MI

death, non-fatal MI, & refractory ischaemia
Immediate (<2 hrs) vs. early (10-48 hrs) vs. selective invasive approach (LIPSIA-NSTEMI Trial)

definition of death, non-fatal MI, & refractory ischaemia

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

Catheterization laboratories open 24 hours a day, every day: does stable NSTE ACS need the offer?

...there is again a trend for an early invasive strategy to reduce mortality.

In contrast, as for MI, 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.
Timing of intervention in NSTE-ACS

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• Putting trials in perspective
In patients presenting with NSTE-ACS, early angiography within 48 h does not reduce the incidence of 5-year death or MI, when compared with delayed angiography within 48 to 120 h.
Optimal Timing of Invasive Strategy in NSTE-ACS

ORs for MI early vs. a delayed invasive strategy

Randomized Trials

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Early Strategy</th>
<th>Delayed Strategy</th>
<th>Weight, %</th>
<th>OR D-L, Random (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events, n</td>
<td>Total Patients, n</td>
<td>Events, n</td>
<td>Total Patients, n</td>
</tr>
<tr>
<td>ABOARD</td>
<td>16</td>
<td>175</td>
<td>8</td>
<td>177</td>
</tr>
<tr>
<td>ELISA</td>
<td>7</td>
<td>109</td>
<td>6</td>
<td>111</td>
</tr>
<tr>
<td>ISAR-COOL</td>
<td>12</td>
<td>203</td>
<td>21</td>
<td>207</td>
</tr>
<tr>
<td>LIPSIA-NSTEMI</td>
<td>33</td>
<td>200</td>
<td>13</td>
<td>200</td>
</tr>
<tr>
<td>OPTIMA</td>
<td>44</td>
<td>73</td>
<td>27</td>
<td>69</td>
</tr>
<tr>
<td>TIMACS</td>
<td>76</td>
<td>1593</td>
<td>82</td>
<td>1438</td>
</tr>
<tr>
<td>Zhang et al, 2010 (16)</td>
<td>23</td>
<td>446</td>
<td>40</td>
<td>369</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>211</td>
<td>2799</td>
<td>197</td>
<td>2541</td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 0.44$; chi-square = 32.98; $P < 0.001$; $I^2 = 82\%$
Test for overall effect: $Z = 0.48$ ($P = 0.63$)

Observational Studies

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Early Strategy</th>
<th>Delayed Strategy</th>
<th>Weight, %</th>
<th>OR D-L, Random (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events, n</td>
<td>Total Patients, n</td>
<td>Events, n</td>
<td>Total Patients, n</td>
</tr>
<tr>
<td>ACUITY</td>
<td>382</td>
<td>4997</td>
<td>301</td>
<td>2812</td>
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<tr>
<td>CRUSADE</td>
<td>1366</td>
<td>45 548</td>
<td>313</td>
<td>10 804</td>
</tr>
<tr>
<td>SYNERGY</td>
<td>404</td>
<td>3326</td>
<td>416</td>
<td>3026</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>2152</td>
<td>53 611</td>
<td>1030</td>
<td>16 642</td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 0.03$; chi-square = 14.66; $P < 0.001$; $I^2 = 86\%$
Test for overall effect: $Z = 1.32$ ($P = 0.190$)
To definitively answer the question of a potential survival benefit with early compared with later intervention:

an RCT would require approximately 7807 patients per group (a total of 15 614 patients) to have 80% statistical power

and approximately 10 450 per group (a total of 20 900 patients) to have 90% statistical power

to detect the 30-day mortality decrease estimated in this analysis (OR, 0.80, translating into a 1% absolute difference in favor of early intervention, assuming the absolute mortality rate of 4.7% seen in the late intervention trial groups) with \( \alpha \)-sided of 0.05.
Timing of intervention in NSTE-ACS

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Timing of angiography in NSTEMI and risk of complications

Risk periprocedural MI

Risk major bleeding

A

RR for MI of the earliest strategy

ABOARD  OPTIMA  LIPSIA-NSTEMI  TIMACS

0,25  0,5  1  2  4

Hours to catheterisation

B

RR for Major bleeding of the earliest strategy

ABOARD  ISAR COOL  OPTIMA  TIMACS  LIPSIA-NSTEMI

0,25  0,5  0,75  1  2

Hours to catheterisation

RK Riezebos & FWA Verheugt
Heart 2013, in press
Timing of angiography in NSTEMI and risk of complications

Risk periprocedural MI

Risk recurrent ischemia/MI

RK Riezebos & FWA Verheugt
Heart 2013, in press
Conclusion: Let’s stick to the guidelines!

1. Clinical Evaluation
   - Quality of chest pain.
   - Symptom-orientated physical examination.
   - Short history for the likelihood of CAD.
   - Electrocardiogram (ST elevation?).

2. Diagnosis/Risk Assessment
   - Response to antianginal treatment.
   - Biochemistry/troponin.
   - ECG.
   - Echocardiogram.
   - Calculated risk score (GRACE).
   - Risk criteria.
   - Optional: CT, MRI, scintigraphy.

3. Coronary angiography
   - reperfusion
   - Very high risk

   STEMI → reperfusion → Very high risk
   ACS possible
   No CAD

   Grace > 140
   early < 24 h
   Grace < 140
   urgent < 120 min
   < 72 h
   no/elective

Eur Heart Journal (2011) 32:2999–3054
doi:10.1093/eurheartj/ehr236