DOUBLE or TRIPLE ANTI-TROMBLOTIC THERAPY in ACS

Maarten L Simoons
Thoraxcenter - Erasmus MC
Rotterdam - The Netherlands
RECENT DEVELOPMENTS

Better anti-platelet agents:

*Prasugrel* and *Ticagrelor* to replace Clopidogrel in patients treated with aspirin

New anticoagulants:

*Voraxapar*: thrombin receptor antagonist
*Apixaban, Rivaroxaban*: factor Xa inhibitors administered on top of Aspirin and Clopidogrel
RECENT DEVELOPMENTS

Better anti-platelet agents:

*Prasugrel* and *Ticagrelor* to replace Clopidogrel in patients treated with aspirin.

New anticoagulants:

*Voraxapar*: thrombin receptor antagonist

*Apixaban, Rivaroxaban*: factor Xa inhibitors administered on top of Aspirin and Clopidogrel

*Dose selection - Double- or triple therapy?*
DOSE SELECTION - PHASE 2

To evaluate the effect on bleeding (safety) vs. placebo of different doses of Voraxapar / Apixaban / Rivaroxaban in patients with recent ACS on Aspirin (+ Clopidogrel) Double / Triple therapy.

To assess (preliminary) efficacy

To determine the optimal dose for phase 3

Treatment up to 6 months after ACS event
**ATLAS-ACS BLEEDING RATES**

Clinical significant bleeding %
Requiring medical attention, Lancet 2009

ASA

ASA + Clopidogrel

<table>
<thead>
<tr>
<th>Plac</th>
<th>5</th>
<th>10</th>
<th>20</th>
<th>plac</th>
<th>5</th>
<th>10</th>
<th>15</th>
<th>20</th>
</tr>
</thead>
<tbody>
<tr>
<td>252</td>
<td>154</td>
<td>195</td>
<td>157</td>
<td>901</td>
<td>153</td>
<td>851</td>
<td>353</td>
<td>446</td>
</tr>
</tbody>
</table>

Rivaroxaban

Plac | 5 | 10 | 15 | 20 |
---|---|----|----|----|
14,3

1,7 2,1 4,3 10 3,4 8,7 9,7 9,8 14,3
ATLAS-ACS ISCHEMIC OUTCOME

Death, MI, stroke, SRI %
Lancet 2009

<table>
<thead>
<tr>
<th>Plac</th>
<th>5</th>
<th>10</th>
<th>20</th>
<th>Place</th>
<th>5</th>
<th>10</th>
<th>15</th>
<th>20</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA</td>
<td>13.9</td>
<td>6.6</td>
<td>8.7</td>
<td>8</td>
<td>5.1</td>
<td>4</td>
<td>3.4</td>
<td>6.5</td>
</tr>
<tr>
<td>ASA + Clopidogrel</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Rivaroxaban
Phase 3
↓
↓
TRACER: Voraxapar vs placebo
Protease-activated-receptor antagonist inhibits thrombin induced platelet aggregation
12,944 patients, 1 day after ACS

ATLAS-ACS: Rivaroxaban 2 doses vs placebo
Factor Xa inhibitor
15,526 patients, 5 days (3 – 6) after ACS

APPRAISE-2: Apixaban vs placebo
Factor Xa inhibitor
7392 high risk patients, 6 days (4 – 7) after ACS
### TRACER ATLAS-ACS APPRAISE-2

<table>
<thead>
<tr>
<th>Patients</th>
<th>Voraxapar 12,944</th>
<th>Rivarox. 15,526</th>
<th>Apixaban 7392</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>64</td>
<td>62</td>
<td>67</td>
</tr>
<tr>
<td>Female (%)</td>
<td>28</td>
<td>25</td>
<td>32</td>
</tr>
<tr>
<td>Previous MI (%)</td>
<td>29</td>
<td>27</td>
<td>25</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>31</td>
<td>32</td>
<td>48</td>
</tr>
<tr>
<td>STEMI (%)</td>
<td>-</td>
<td>50</td>
<td>40</td>
</tr>
<tr>
<td>ASA (%)</td>
<td>99</td>
<td>99</td>
<td>97</td>
</tr>
<tr>
<td>Thienopyr. (%)</td>
<td>92</td>
<td>93</td>
<td>81</td>
</tr>
<tr>
<td>CABG/PCI (%)</td>
<td>68</td>
<td>60</td>
<td>45</td>
</tr>
</tbody>
</table>
## TRACER ATLAS-ACS APPRAISE-2

<table>
<thead>
<tr>
<th></th>
<th>Voraxapar</th>
<th>Rivarox.</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>12,944</td>
<td>15,526</td>
<td>7392</td>
</tr>
<tr>
<td>Death</td>
<td>3.6</td>
<td>4.1</td>
<td>6.6</td>
</tr>
<tr>
<td>CV death</td>
<td>3.2</td>
<td>3.8</td>
<td>5.0</td>
</tr>
<tr>
<td>MI</td>
<td>7.9</td>
<td>6.0</td>
<td>9.2</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.0</td>
<td>0.9</td>
<td>1.6</td>
</tr>
<tr>
<td>IC bleeding</td>
<td>0.1</td>
<td>0.2</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Events / 100 pts / yr, placebo group
Different final results

APPRAISE-2 / TRACER stopped upon recommendation DSMB because of bleeding excess, with sufficient endpoints (TRACER) and without indication of benefit (APPRAISE-2)

ATLAS-ACS continued, Significant reduction of CV death, MI, stroke at 13 m (mean), with increasing separation of event curves after the first year
TRACER  VORAXAPAR after ACS

12,944 NonSTEMI, 1 day after admission
Median follow-up 502 d  2 yr event rates

p=0.07 (ns)  ns  0.02  ns  <0.001

TRACER  Tricoci et al.  NEJMed 2011
### APPRAISE-2

**APIXABAN after ACS**

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Placebo (n=7392)</th>
<th>Apixaban (n=7392)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV-death</td>
<td>14.0</td>
<td>13.2</td>
<td>ns</td>
</tr>
<tr>
<td>MI</td>
<td>9.2</td>
<td>8.6</td>
<td>ns</td>
</tr>
<tr>
<td>Stroke</td>
<td>6.6</td>
<td>7.1</td>
<td>ns</td>
</tr>
</tbody>
</table>

Median follow-up: 8 months

Events per 100 pts per yr:

- CV-death: 1.7
- MI: 1.8
- Stroke: 1.7
- Major bleed: 0.9

**APPRAISE-2** Alexander et al. *NEJM*ed 2011
ATLAS-ACS  RIVAROXABAN after ACS

15,526 STEMI / NonSTEMI, 5 d after admission
median follow-up 13 m  2 yr event rates

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo</th>
<th>Rivaroxaban</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV-death</td>
<td>10.7</td>
<td>9.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MI</td>
<td>4.5</td>
<td>2.9</td>
<td>0.01</td>
</tr>
<tr>
<td>Stroke</td>
<td>4.4</td>
<td>4.4</td>
<td>ns</td>
</tr>
<tr>
<td>Death</td>
<td>6.6</td>
<td>6.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Major bleed</td>
<td>1.2</td>
<td>1.4</td>
<td>0.01</td>
</tr>
<tr>
<td>MI</td>
<td>6.1</td>
<td>6.1</td>
<td>ns</td>
</tr>
<tr>
<td>Stroke</td>
<td>4.9</td>
<td>4.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Major bleed</td>
<td>1.7</td>
<td>1.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MI</td>
<td>1.8</td>
<td>1.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.6</td>
<td>0.6</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

ATLAS-ACS Mega et al.  NEJMed 2011
TRACER - ATLAS-ACS - APPRAISE-2

CV-death, MI, stroke (2 year follow-up)

P = ns 0.007 0.01 ns

Voraxapar 16.4 14.7
2.5

Rivarox 10.7 9.1
2 x 2.5

Rivarox 10.7 8.8
2 x 5

Apixaban 28.0 26.4
2 x 5
rate/100/2yr
Death (2 year follow-up)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Rate/100/2yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voraxapar 2.5</td>
<td>6.1</td>
</tr>
<tr>
<td>Rivarox 2 x 2.5</td>
<td>4.5</td>
</tr>
<tr>
<td>Rivarox 2 x 5</td>
<td>4.5</td>
</tr>
<tr>
<td>Apixaban 2 x 5</td>
<td>13.2</td>
</tr>
</tbody>
</table>

P = ns

0.004

ns

ns
TRACER - ATLAS-ACS - APPRAISE-2

MI (2 year follow-up)

P = 0.02
ns
0.008
ns

12.5
11.1
8.6
6.1
8.6
4.9
18.4
17.2

Voraxapar
2.5
Rivarox
2 x 2.5
Rivarox
2 x 5
Apixaban
2 x 5
rate/100/2yr
TRACER - ATLAS-ACS - APPRAISE-2

Stroke (2 year follow-up)

P = ns  ns  ns  ns

Voraxapar 2.5

Rivarox 2 x 2.5

Rivarox 2 x 5

Apixaban 2 x 5 rate/100/2yr

2.1 1.9

1.2 1.4

1.2 1.7

3.6 3.4
**TRACER - ATLAS-ACS - APPRAISE-2**

TIMI major bleed, non CABG (2 year follow-up)

<table>
<thead>
<tr>
<th>medication</th>
<th>2 x 2.5</th>
<th>2 x 5</th>
<th>rate/100/2yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voraxapar</td>
<td>2.5</td>
<td>4.0</td>
<td></td>
</tr>
<tr>
<td>Rivarox</td>
<td>0.6</td>
<td>1.8</td>
<td></td>
</tr>
<tr>
<td>Rivarox</td>
<td>0.6</td>
<td>2.4</td>
<td></td>
</tr>
<tr>
<td>Apixaban</td>
<td>1.8</td>
<td>4.8</td>
<td></td>
</tr>
</tbody>
</table>

P < 0.001  < 0.001  < 0.001  0.001
# BLEEDING DEFINITIONS

<table>
<thead>
<tr>
<th></th>
<th>GUSTO severe</th>
<th>TIMI major</th>
<th>TIMI minor</th>
<th>ISHT major</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatal</td>
<td>+</td>
<td>+</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Intra cranial</td>
<td>+</td>
<td>+</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Critical organ</td>
<td>+</td>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Non-overt (Hb↓)</td>
<td></td>
<td>&gt; 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overt (Hb↓ mg%)</td>
<td>&gt; 5</td>
<td>&gt; 3</td>
<td>&gt; 2</td>
<td></td>
</tr>
<tr>
<td>With intervention</td>
<td>+*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transfusion</td>
<td></td>
<td></td>
<td></td>
<td>&gt; 2</td>
</tr>
</tbody>
</table>

*+* hemodynamic compromise
Clinically significant bleed (2 year follow-up)

- **Voraxapar 2.5**: 14.6 vs. 20.2
- **Rivarox 2 x 2.5**: 7.5 vs. 12.9
- **Rivarox 2 x 5**: 7.5 vs. 16.2
- **Apixaban 2 x 5 rate/100/2yr**: 9.2 vs. 24.8

P < 0.001 < 0.001 < 0.001 0.001
Overall conclusion

Triple therapy
(ASA + clopidogrel + TR-Antag / Xa inhibition)
in patients with / after ACS (1 d / 1 wk – 2 yr)

- reduces myocardial infarction
- at the cost of bleeding
- no consistent effect on stroke or mortality
**Similar (un) safety**

Increased bleeding rates:

**Intra Cranial Bleeds:**

<table>
<thead>
<tr>
<th>Drug</th>
<th>HR (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VORAXAPAR</td>
<td>HR = 3.4</td>
</tr>
<tr>
<td>APIXABAN</td>
<td>HR = 4.1 (5mg)</td>
</tr>
<tr>
<td>RIVAROXABAN</td>
<td>HR = 3.7 (5mg)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>TIMI-major bleeds, non-CABG:</td>
<td></td>
</tr>
<tr>
<td>VORAXAPAR</td>
<td>HR = 1.9</td>
</tr>
<tr>
<td>APIXABAN</td>
<td>HR = 2.6 (5mg)</td>
</tr>
<tr>
<td>RIVAROXABAN</td>
<td>HR = 4.5 (5mg)</td>
</tr>
</tbody>
</table>

**TRACER - ATLAS-ACS - APPRAISE-2**
Different final results

APPRAISE-2 / TRACER stopped upon recommendation DSMB because of bleeding excess, with sufficient endpoints (TRACER) and without indication of benefit (APPRAISE-2)

ATLAS-ACS continued,
Significant reduction of CV death, MI, stroke at 13 m (mean), with increasing separation of event curves after the first year:
HR 0.85, p=0.03 (5mg) HR 0.84, p=0.02 (2.5mg)
Reduction of death with 2.5mg, explanation ??
APIXABAN - RIVAROXABAN
decreased risk of death, MI, ischemic stroke
Overall conclusion:
Triple therapy (ASA + clopidogrel + Xa inhibition) reduces thrombotic events, in *patients at low risk* after ACS (1 wk – 2 yr), as in ATLAS-ACS, but not in higher risk patients as in APPRAISE-2.

*Age ≥ 65 years, ↑ markers + ST deviation, diabetes mellitus, Prior MI, ischemic stroke, TIA, asymptomatic carotid stenosis, PAD, prior symptomatic CHF or LVEF <40%, non-revascularised multi-vessel CAD, mild / moderate renal insuff. (CrCl <90 ml/min)*
ATLAS-ACS   RIVAROXABAN after ACS

10,227 STEMI / NonSTEMI, 5 d after admission
median follow-up 13 m    2.5mg  2 yr event rates

p=0.007  0.004  ns  ns  <0.001

CV-death MI stroke

Mega et al. NEJMed 2011
CV-death, MI, stroke

TIMI major bleed

ATLAS-ACS - TRITON - PLATO

ATLAS 2 yr  TRITON 1 yr  PLATO 1 yr

10.7 riva  12.1 pras  11.7 tica

1.8 2.4

0.6 1.8

1.8 2.4

3.8 4.5
Final conclusion:
Triple therapy (ASA + clopidogrel + Xa inhibition) reduces thrombotic events, at the cost of bleeding in patients after ACS.

Reduction of CV-death, MI, Stroke and increase of bleeding with triple therapy similar to ASA + prasugrel (TRITON) or + ticagrelor (PLATO).

ASA + prasugrel / ticagrelor, the best choice.