Antithrombotic therapy in acute coronary syndrome

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PANHELLENIC CONGRESS OF CARDIOLOGY
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A prototype patient...

female, 51y, active smoker
Chest pain for 2 hrs
ST elevation II, III, aVF

... but what is the optimal post-PCI antithrombotic regimen?
Dual antiplatelet therapy (DAPT) – gold standard in invasively managed ACS

Intensified DAPT with Aspirin plus Ticagrelor or Prasugrel for 12 months

Valgimigli et al, Eur Heart J 2017
Ibanez et al, Eur Heart J 2018;39:119-177

TRITON trial

PLATO trial

... but, ACS patients are heterogeneous in terms of ischemic and bleeding risk

- Female, 66 y
- Anterior STEMI
- History of hemorrhagic shock due to GIT bleed
- On dialysis for 6 years

What to do if ischemic risk predominates?

- Female, 66 y
- Anterior STEMI
- Permanent atrial fibrillation

- Female, 66 y
- Anterior STEMI
- with cardiogenic shock
- History of inferior MI
Intensified early antithrombotic therapy combining DAPT plus FX inhibitor

>15,000 ACS patients
(STEMI 50.3%; NSTEMI 25.6%)

Ibanez et al, Eur Heart J 2018

In low bleeding-risk patients who receive aspirin and clopidogrel, low-dose rivaroxaban (2.5 mg twice daily) may be considered.

Ibanez et al, Eur Heart J 2018
Prolonged DAPT (>12 months) after ACS – is there a net benefit?

36 months DAPT after AMI - DAPT trial, AMI cohort

Thienopyridine vs. placebo, 3.9% vs. 6.8%; hazard ratio 0.56, p<0.001

No significant reduction in mortality!

Mauri et al., N. Engl. J. Med. 2014; Yeh et al., JACC 2015; Garratt et al., Circulation 2015
In high ischaemic-risk patients that tolerated DAPT without bleeding, treatment with ticagrelor 60 mg twice a day on top of aspirin for longer than 12 months may be considered for up to 3 years.
Intensified chronic antithrombotic treatment by combining ASS plus FX inhibitor

- 313 deaths (3.4%)
- 378 deaths (4.1%)
- Hazard ratio 0.82; P = 0.01
- Major bleeding: 1.70; P<0.001

Compass trial

Eikelboom et al., N Engl J Med 2017
Connolly et al., Lancet 2018

Absolute risk reduction 1.3%, NNT 76

Connolly et al., Lancet 2018
Eikelboom et al., N Engl J Med 2017
High „number needed to treat“ in COMPASS

Imagine your next 1,000 patients …

>98% treated to no purpose.

KEY
- Good outcome
- Bad outcome
- Better with treatment

944
13
43

Calculated using http://www.nntonline.net/visualrx/
# Patients with potential benefit from escalation in COMPASS

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Rivaroxaban 2.5 mg bid + aspirin n/N (%)</th>
<th>Aspirin alone n/N (%)</th>
<th>HR (95% CI)</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All participants</td>
<td>379/9152 (4.1)</td>
<td>496/9126 (5.4)</td>
<td></td>
<td>0.76 (0.66–0.86)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.20</td>
</tr>
<tr>
<td>&lt;65 years</td>
<td>79/2150 (3.7)</td>
<td>126/2184 (5.8)</td>
<td></td>
<td>0.63 (0.48–0.84)</td>
<td></td>
</tr>
<tr>
<td>65–75 years</td>
<td>179/5078 (3.5)</td>
<td>238/5045 (4.7)</td>
<td></td>
<td>0.74 (0.61–0.90)</td>
<td></td>
</tr>
<tr>
<td>≥75 years</td>
<td>121/1924 (6.3)</td>
<td>132/1897 (7)</td>
<td></td>
<td>0.89 (0.69–1.14)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.75</td>
</tr>
<tr>
<td>Male</td>
<td>300/7093 (4.2)</td>
<td>393/7137 (5.5)</td>
<td></td>
<td>0.76 (0.66–0.89)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>79/2059 (3.8)</td>
<td>103/1989 (5.2)</td>
<td></td>
<td>0.72 (0.54–0.97)</td>
<td></td>
</tr>
<tr>
<td>Body weight</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.64</td>
</tr>
<tr>
<td>≤60 kg</td>
<td>41/901 (4.6)</td>
<td>45/836 (5.4)</td>
<td></td>
<td>0.83 (0.55–1.27)</td>
<td></td>
</tr>
<tr>
<td>&gt;60 kg</td>
<td>335/8241 (4.1)</td>
<td>448/8285 (5.4)</td>
<td></td>
<td>0.75 (0.65–0.86)</td>
<td></td>
</tr>
<tr>
<td>Estimated GFR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.95</td>
</tr>
<tr>
<td>&lt;60 mL/min</td>
<td>132/2054 (6.4)</td>
<td>177/2114 (8.4)</td>
<td></td>
<td>0.75 (0.60–0.94)</td>
<td></td>
</tr>
<tr>
<td>≥60 mL/min</td>
<td>247/7094 (3.5)</td>
<td>319/7012 (4.5)</td>
<td></td>
<td>0.76 (0.64–0.90)</td>
<td></td>
</tr>
<tr>
<td>CAD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.47</td>
</tr>
<tr>
<td>Yes</td>
<td>347/8313 (4.2)</td>
<td>460/8261 (5.6)</td>
<td></td>
<td>0.74 (0.65–0.86)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>32/839 (3.8)</td>
<td>36/865 (4.2)</td>
<td></td>
<td>0.89 (0.55–1.43)</td>
<td></td>
</tr>
<tr>
<td>PAD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.61</td>
</tr>
<tr>
<td>Yes</td>
<td>126/2492 (5.1)</td>
<td>174/2504 (6.9)</td>
<td></td>
<td>0.72 (0.57–0.90)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>253/6660 (3.8)</td>
<td>322/6622 (4.9)</td>
<td></td>
<td>0.77 (0.66–0.91)</td>
<td></td>
</tr>
</tbody>
</table>

- Favours rivaroxaban 2.5 mg bid + aspirin
- Favours aspirin alone
Patients with potential benefit from escalation in COMPASS

**MACE**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Incidence (%)</th>
<th>ARR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>7.0</td>
<td>1.9</td>
</tr>
<tr>
<td>No diabetes</td>
<td>5.1</td>
<td></td>
</tr>
</tbody>
</table>

HR = 0.72
(95% CI 0.58–0.88)

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<thead>
<tr>
<th>Condition</th>
<th>Incidence (%)</th>
<th>ARR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>4.8</td>
<td>1.2</td>
</tr>
<tr>
<td>No diabetes</td>
<td>3.6</td>
<td></td>
</tr>
</tbody>
</table>

HR = 0.77
(95% CI 0.64–0.93)

**Major bleeding**

(mod. ISTH definition)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Incidence (%)</th>
<th>ARI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>2.0</td>
<td>1.3</td>
</tr>
<tr>
<td>No diabetes</td>
<td>3.3</td>
<td></td>
</tr>
</tbody>
</table>

HR = 1.65
(95%-CI 1.20–2.27)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Incidence (%)</th>
<th>ARI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>1.9</td>
<td>1.2</td>
</tr>
<tr>
<td>No diabetes</td>
<td>3.1</td>
<td></td>
</tr>
</tbody>
</table>

HR = 1.67
(95%-CI 1.30–2.15)

ASS (n = 8.313)  Rivaroxaban 2.5 mg 2x tägl. plus ASS (n = 8.261)

Connolly SJ et al, Lancet 2018
Tailoring of DAPT after an ACS – do Risk Scores help?

<table>
<thead>
<tr>
<th>PRECISE-DAPT score$^{18}$</th>
<th>DAPT score$^{15}$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time of use</strong></td>
<td><strong>At the time of coronary stenting</strong></td>
</tr>
<tr>
<td><strong>DAPT duration strategies assessed</strong></td>
<td>Short DAPT (3–6 months) vs. Standard/long DAPT (12–24 months)</td>
</tr>
<tr>
<td><strong>Score calculation</strong></td>
<td><strong>Score range</strong></td>
</tr>
<tr>
<td>HB</td>
<td>0 to 100 points</td>
</tr>
<tr>
<td>WBC</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>≤50</td>
<td>No</td>
</tr>
<tr>
<td>≥50</td>
<td>Yes</td>
</tr>
<tr>
<td>≤10-5</td>
<td></td>
</tr>
<tr>
<td>≥11-5</td>
<td></td>
</tr>
<tr>
<td>≥12</td>
<td></td>
</tr>
<tr>
<td>≥20</td>
<td></td>
</tr>
<tr>
<td>CrCl</td>
<td></td>
</tr>
<tr>
<td>≥100</td>
<td></td>
</tr>
<tr>
<td>80</td>
<td></td>
</tr>
<tr>
<td>≥20</td>
<td></td>
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<tr>
<td>80</td>
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<tr>
<td>≥100</td>
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</tr>
<tr>
<td>60</td>
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<td>≥80</td>
<td></td>
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<tr>
<td>40</td>
<td></td>
</tr>
<tr>
<td>≥60</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td></td>
</tr>
<tr>
<td>≥20</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td></td>
</tr>
<tr>
<td>≤10</td>
<td></td>
</tr>
<tr>
<td></td>
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</tbody>
</table>

What options do we have in ACS patients with predominating bleeding risk

- Female, 66 y
- Anterior STEMI
- Permanent atrial fibrillation
- PRECISE DAPT 18

- Female, 66 y
- Anterior STEMI
- History of hemorrhagic shock due to GIT bleed
- On dialysis for 6 years
- PRECISE DAPT 28

- Female, 66 y
- Anterior STEMI
- with cardiogenic shock
- History of inferior MI
What options do we have in ACS patients with predominating bleeding risk

bleeding risk > ischemic risk

DAPT < 12 months
(OPTIMIZE, ZEUS, LEADERS FREE)

In patients with ACS who are at high risk of bleeding (e.g. PRECISE-DAPT ≥25), discontinuation of P2Y12 inhibitor therapy after 6 months should be considered

What options do we have in ACS patients with predominating bleeding risk

bleeding risk > ischemic risk

DAPT < 12 months
(OPTIMIZE, ZEUS, LEADERS FREE)

Deescalation of DAPT
Potent P2Y12 Inhibitor ➔ Clopidogrel
(TOPIC, TROPICAL ACS)
Potent platelet inhibition – major benefit early after PCI

Do we really need potent platelet inhibition for 12 months... ... or may less be more in some ACS patients?

Antman et al., JACC 2008
Uniform DAPT deescalation – the TOPIC trial

ACS patients with successful PCI

1 month potent P2Y12 inhibition (Prasugrel/Ticagrelor)

1:1

R*

11 months potent DAPT (n=323)

11 months clopidogrel (n=322)

Unchanged DAPT

Switched DAPT

°1 EP: CV Death, Urgent Revascularization, Stroke, Bleeding (BARC ≥2)

Bleeding (BARC ≥2)

...but: small trial, no data on MI and stent thrombosis

Cuisset et al., Eur Heart J. 2017 38:3070-3078
Individualized DAPT deescalation – the TROPICAL ACS trial

Biomarker positive ACS patients with successful PCI (n=2610)

Control group

- 14 days prasugrel

Guided de-escalation group

- 7 days prasugrel
- 7 days clopidogrel

PFT (Multiplate analyser) @ 2 weeks after discharge

- Low Responders (HPR*)
- Good Responders (no HPR*)

- 11 ½ months prasugrel
- 11 ½ months clopidogrel

Uniform antiplatelet therapy with prasugrel

PFT guided DAPT de-escalation

*HPR: High platelet reactivity

Sibbing et al., Thromb Haemost. 2017
Individualized DAPT deescalation – the TROPICAL ACS trial

Sibbing et al., Lancet 2017

1 EP: CVD, MI, stroke, BARC ≥2

Control group

Guided de-escalation group

HR 0.81 (0.62-1.06) p=0.0004 for non-inferiority (p=0.1202 for superiority)

0.82 (0.59–1.13) p=0.23

No. at risk

Control 1306 1238 1220 1190 1132 1124 924
De-escalation 1304 1234 1213 1189 1129 1124 942

Bleeding

BARC ≥2

Control 79 (6%)
Deescalation 64 (5%)
Individualized DAPT deescalation – the TROPICAL ACS trial

Clopidogrel Response versus Prasugrel

Primary Endpoint

Ischemic Endpoint

Hein et al., ESC 2018
Individualized DAPT deescalation – the TROPICAL ACS trial

De-escalation of P2Y\textsubscript{12} inhibitor treatment (e.g. with a switch from prasugrel or ticagrelor to clopidogrel) guided by platelet function testing may be considered as an alternative DAPT strategy, especially for ACS patients deemed unsuitable for 12-month potent platelet inhibition.\textsuperscript{717}
Conclusions

- Potent P2Y12 inhibitors for 12 months remain the standard in ACS management.
- In ACS patients with predominating ischemic risk and low bleeding risk prolonged or intensified antithrombotic regimens may be considered (PEGASUS, COMPASS).
- In ACS patients with predominating bleeding risk reduced DAPT durations (<12 months) or PFA-guided switch from potent P2Y12 Inhibitor to clopidogrel (TROPICAL-ACS) may be considered in order to deescalate antithrombotic management.
- Against the background of different treatment options, an individualized assessment of bleeding and ischemic risk should guide our decisions.
DAPT in ACS – PRECISE DAPT SCORE

...however, no prospective data
Individualized DAPT deescalation – the TROPICAL ACS trial

Interaction of Treatment Effects with Age
(guided de-escalation vs. standard prasugrel treatment)

Supremum HR p-value = 0.0268
Patients with potential benefit from escalation

In high ischaemic-risk patients that tolerated DAPT without bleeding, treatment with ticagrelor 60 mg twice a day on top of aspirin for longer than 12 months may be considered for up to 3 years.

Ibanez et al, Eur Heart J 2018;39:119-177

Potential candidates:

Low bleeding risk plus…
...history of stent thrombosis
...diabetics
...1st generations DES
...last vessel PCI
...multiple stenting
...complex lesions
...diffuse multivessel CAD

Sibbing et al., Lancet 2014, 384:1553-1555