**Anti-platelet therapy - What is in the pipeline?**

Prof. Dr. Andreas Zirlik  
Cardio Luxor 2015

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**Disclosures for Andreas Zirlik, MD**

In compliance with CME policy, the following disclosures to the session audience are declared:

<table>
<thead>
<tr>
<th>Research support/P.I.</th>
<th>Astellas, Astra Zeneca, ResMed, Novartis, Medtronic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Travel support</td>
<td>Daichi Sankyo, Astellas, Lilly, Medtronic, Pfizer, Sanofi Aventis, Novartis, Bayer Health Care</td>
</tr>
<tr>
<td>Consultant</td>
<td>Bayer, Boehringer Ingelheim, Rigel, Cardiorentis, Medscape</td>
</tr>
<tr>
<td>Major stockholder</td>
<td>No relevant conflicts of interest to declare</td>
</tr>
<tr>
<td>Honoraria for lectures</td>
<td>Bayer Health Care, Astra Zeneca, Medtronic, ResMed, Boehringer Ingelheim, Rigel, Sanofi Aventis, Pfizer, Janssen-Cilag</td>
</tr>
</tbody>
</table>
How good are we in treating ACS?

<table>
<thead>
<tr>
<th></th>
<th>1999/2000 (n=1.645)</th>
<th>2007/1.4.2008 (n=1.889)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time between onset of symptoms and hospital admission ≤ 2 h</td>
<td>48,7%</td>
<td>42,2%</td>
<td>&lt;0,001</td>
</tr>
<tr>
<td>STEMI (vs. NSTEMI)</td>
<td>76,4%</td>
<td>49,5%</td>
<td>&lt;0,001</td>
</tr>
<tr>
<td>Admission by ambulance</td>
<td>44,1%</td>
<td>49,6%</td>
<td>&lt;0,001</td>
</tr>
<tr>
<td>Primary PCI</td>
<td>18,4%</td>
<td>79,9%</td>
<td>&lt;0,001</td>
</tr>
<tr>
<td>Thrombolysis</td>
<td>40,6%</td>
<td>1,1%</td>
<td>&lt;0,001</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>12,2%</td>
<td>6,2%</td>
<td>&lt;0,001</td>
</tr>
</tbody>
</table>


GRACE: Which factors impact 6-month mortality after ACS?

![Mean Effect of each guideline-conforme therapy](image)

Mean Effect of each guideline-conforme therapy

- No Therapy
- Revascularisation
- Statin
- +Platelet inhibition (Thienopyridin)
- +GPIb/IIa
- +Rehabilitation
- +Beta-blocker
- +ACE-I
- +ASS

ns = non significant

Mod. nach: Chew DP et al Heart. 2010; 96 (15): 1201-6
Platelet activation – a key event in ACS

modified from Ahrens I & Bode C. Curr Opin Investig Drugs 2009;10:902-11

Platelet receptors as targets

modified from Ahrens I & Bode C. Curr Opin Investig Drugs 2009;10:902-11
Platelet receptors as targets

Inhibitors of the Coagulation Cascade
- anti-Xa (Rivaroxaban)
- anti-IX (Pegnivacogin)
- anti-II (Bivalirudin)

Inhibitors of the GPIIb/IIIa (Integrin \(\alpha_{IIb}\beta_3\))
- Thrombin
- ADP
- Collagen
- Serotonin
- Thromboxane A\(_2\)
- Epinephrin
- Thrombin
- GPVI
- GpIa
- vWF
- EPI-R
- TBXA\(_2\)-R
- 5HT\(_2\)-A
- GPIb/Illa (Integrin \(\alpha_{IIb}\beta_3\))
- Fibrinogen
- Fibrin

Abciximab
Eptifibatide
Tirofiban
Platelet receptors as targets

P\(_2\)Y\(_{12}\) inhibitors: mortality and bleeding in ACS

- CV-Death, MI or Stroke
- TIMI major Bleeding*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>CV-Death, MI or Stroke</th>
<th>TIMI major Bleeding*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ohne</td>
<td>20%</td>
<td>0,8</td>
</tr>
<tr>
<td>ASS(^{1,2})</td>
<td>15,0</td>
<td>1,3</td>
</tr>
<tr>
<td>ASS + Clopidogrel(^3)</td>
<td>15%</td>
<td>2,4*</td>
</tr>
<tr>
<td>ASS + Prasugrel(^4)</td>
<td>14%</td>
<td>2,4*</td>
</tr>
<tr>
<td>ASS + Ticagrelor(^4)</td>
<td>17%</td>
<td>2,2*</td>
</tr>
</tbody>
</table>

*non-CABG-associated TIMI major bleeding: symptomatic ICH or Hb-drop>5 g/dl or Hct-drop≥15%

Champion Phoenix – Cangrelor in PCI

- Direct reversible platelet P2Y₁₂ receptor antagonist
- Fast onset, fast offset, i.v.
- T₁/₂ = 3 to 6 minutes
- Offset = 60 minutes

CHAMPION PHOENIX
N = 10,900 MITT
SA/ NSTEMI-ACS/ STEMI
Patients requiring PCI
P2Y₁₂ inhibitor naïve

N=11145, urgent or elective PCI, Clopidogrel loading 300/600mg vs. Cangrelor 300ug/kg
i.v. + 4ug/kg Infusion 48h, 1°: death, MI, revasc, stent thrombosis after 48h
Platelet receptors as targets

- GPIIb/IIIa (Integrin \( \alpha_{IIb}\beta_3 \))
- ADP
- Collagen
- Thromboxane A\(_2\)
- Epinephrin
- Thrombin
- GpIa
- GpVI
- EPI-R
- TBX-A-R
- 5HT\(_2\)-A
- GPVI Inhibitors

Inhibitors of the Coagulation Cascade:
- anti-Xa (Rivaroxaban)
- anti-IX (Pegnivacogin)
- anti-II (Bivalirudin)
- Fibrinogen
- Fibrin

Thrombin receptor blockade: Vorapaxar

- Vorapaxar is an oral, potent, and selective antagonist of PAR-1
- Metabolism by CYP3A4 enzymes
- No meaningful renal clearance
- Long half-life (T1/2 > 100 hrs)
TRA2P: Vorapaxar in secondary prophylaxis

TRA 2° P: previous MI, (stroke), or PAD, N=26 400, Vorapaxar* 2.5mg vs. Placebo*

1° efficacy EP: CV death, MI, stroke

1° safety EP: major bleeding

FDA Approval 2014

**Platelet receptors as targets**

- **GPVI Inhibitors**
- **Clopidogrel**
- **Prasugrel**
- **Ticagrelor**
- **Eptifibatide**
- **Tirofiban**
- **Fibrinogen**
- **Platelet receptors as targets**
  - GPIIb/IIIa
  - ADP
  - Collagen
  - Serotonin
  - Thromboxane A2
  - Epinephrin
  - Thrombin
  - GpIa
  - GpVI
  - EPI-R
  - TBX2-R
  - 5HT2-A
  - Platelet receptors as targets
    - GPIIb/IIIa (Integrin $\alpha_{IIb}\beta_3$)
    - Fibrinogen
    - Fibrin

**Glycoprotein VI – a promising novel preclinical candidate**

- Only expressed on platelets and megakaryocytes
- Recruits platelets to sites of injury
- Hardly any effect on general hemostasis
- Presumed selectivity, targeted therapy

Rationale for dual pathway inhibition

Real-time in vivo imaging of an arterial thrombosis in mice following laser-induced injury

 Addition of Warfarin reduces events after ACS

Meta-analysis: ACS secondary prevention Warfarin + ASA vs. ASA
(10 Trials, n=5 938)

<table>
<thead>
<tr>
<th>Event</th>
<th>Rate Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>0.96 (0.77-1.20)</td>
</tr>
<tr>
<td>MI</td>
<td>0.56 (0.48-0.69)</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>0.46 (0.27-0.77)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>2.48 (1.67-3.68)</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>2.65 (2.14-3.29)</td>
</tr>
</tbody>
</table>

Rationale for dual pathway inhibition

A C S T R E A T M E N T
ATLAS II: Rivaroxaban on top of ASS/Clopidogrel

Pat. with recent ACS, Randomization Rivaroxaban 2x2.5mg/d vs. 2x5mg/d vs. Placebo, n=15526
1° EP: CV death, MI, stroke

Efficacy & Safety

ATLAS ACS 2-TIMI 51: Efficacy

Rivaroxaban 2x2,5mg/d (all on ASS + Thienopyridin)
### ESC Guidelines 2010 / 2011/2012

#### Classes of recommendation & levels of evidence

<table>
<thead>
<tr>
<th></th>
<th>NSTEMI-ACS</th>
<th>STEMI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>class</td>
<td>level</td>
</tr>
<tr>
<td>Ticagrelor*</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Prasugrel*</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Clopidogrel (for 9-12 months post PCI)</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Clopidogrel (with 600 mg loading dose as soon as possible)</td>
<td>I</td>
<td>C</td>
</tr>
</tbody>
</table>

Recommended duration of dual antiplatelet therapy after ACS: 1 year in all patients, irrespective of revascularization strategy.

### New STEMI Recommendations

<table>
<thead>
<tr>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIb</td>
<td>B</td>
</tr>
</tbody>
</table>

In selected patients who receive aspirin and clopidogrel, low dose rivaroxaban (2.5 mg twice daily) may be considered if the patient is at low bleeding risk.

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### Which patients profit most from RIVAROXABAN in ACS?

#### Subgroup

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Primary Composite Endpoint [CV death/MI/Stroke]</th>
<th>CV death</th>
<th>Net Clinical Benefit **</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall ATLAS ACS 2 TIMI Study Population</td>
<td>HR 0.64, CI: 0.72–0.97 (ARR: 1.6%), NNT: 63</td>
<td>HR 0.66, CI: 0.51–0.86 (ARR: 1.4%), NNT: 71</td>
<td>Efficacy: -125, Safety: +10</td>
</tr>
<tr>
<td>Excluding Prior Stroke/TIA</td>
<td>HR 0.81, CI: 0.69–0.94 (ARR: 1.8%), NNT: 56</td>
<td>HR 0.63, CI: 0.48–0.82 (ARR: 1.5%), NNT: 67</td>
<td>Efficacy: -143, Safety: +6</td>
</tr>
<tr>
<td>Targeted population with Elevated Biomarkers, Excluding prior Stroke/TIA</td>
<td>HR 0.80, CI: 0.68–0.94 (ARR: 2.1%), NNT: 48</td>
<td>HR 0.55, CI: 0.41–0.74 (ARR: 2.0%), NNT: 50</td>
<td>Efficacy: -159, Safety: +3</td>
</tr>
</tbody>
</table>

ARR = absolute risk reduction based on 2-year KM estimates; NNT = number needed to treat

** Excess number of events in 10,000 patient years
Rationale for dual pathway inhibition


Rationale for dual pathway inhibition

**RADAR: Pegnivacogin in ACS**

RADAR Phase II Study for REG1 system (Pegnivacogin as anticoagulant + Animaversen as complementary antidot):
NSTEMI with planned PCI <24h, 3:1 Pegnivacogin 1mg/kg + 25, 50, 75, 100% Animaversen vs. Heparin i.v. n=640

30d Total & Major* Acuity Bleeding

30d MACE

* ICH, intraocular, retroperitoneal, bleed requiring intervention/surgery, hematoma ≥ 5 cm, Hgb ≥ 3 g/dL with an overt source or ≥ 4 g/dL without overt source of bleeding, blood product transfusion.

Eur Heart J 2013;34:2481-9
**CAD requiring PCI**

Open Label Randomization

**PCI**

- Pegnivacogin 1mg/kg N ~ 6600
- Bivalirudin N ~ 6600

Anivamersen Reversal
Immediate Sheath Removal
Sheath removal per local standard (0-4 hrs)

Death, myocardial infarction, urgent target lesion revascularization and stroke at 3-days

- 30-day clinical FU
- 6-month mortality FU

* “all comers” PCI excluding STEMI primary PCI
* Approximately 6600 patients with recent NSTEMI

Enrollment was stopped in August 2014 after 3 patients experienced allergic-like reactions.

* “all comers” PCI excluding STEMI primary PCI
* Approximately 6600 patients with recent NSTEMI
**Take home messages:**

- Advances in antiplatelet therapy significantly **reduced mortality** in ACS over last decades.
- Further **increase in IPA by single targets** my provoke overt bleeding.
- The future of antithrombotic therapy likely comprises a **dual pathway inhibition**.
- The gold standard of Aspirin needs to be challenged and **combinations of a novel antiplatelet with NOACs or PAR1 inhibitors** need to be interrogated.
- More **targeted and reversible antithrombotic strategies** (e.g. GPVI, aptamer technology) may be useful.

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**ACS**

**RADAR Phase II**

RADAR Phase II Studie zum REG1 System (Pegnivacogin als Antikoagulanz + Animaversen als komplementäres Antidot):

NSTEMI mit geplanter PCI <24h bei femoralem Zugang, 3:1 Pegnivacogin 1mg/kg + 25, 50, 75, 100% Animaversen vs. Heparin i.v. n=640

**30d Total & Major* Acuity Bleeding**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Total Bleeding</th>
<th>Major Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>REG1</td>
<td>65.6</td>
<td>10.8</td>
</tr>
<tr>
<td>Heparin</td>
<td>65.6</td>
<td>10.8</td>
</tr>
<tr>
<td>REG1-35%</td>
<td>63.6</td>
<td>10.6</td>
</tr>
<tr>
<td>REG1-50%</td>
<td>63.6</td>
<td>10.6</td>
</tr>
<tr>
<td>REG1-75%</td>
<td>63.6</td>
<td>10.6</td>
</tr>
<tr>
<td>REG1-100%</td>
<td>63.6</td>
<td>10.6</td>
</tr>
<tr>
<td>Heparin</td>
<td>65.6</td>
<td>10.8</td>
</tr>
</tbody>
</table>

**30d MACE**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>MACE</th>
</tr>
</thead>
<tbody>
<tr>
<td>REG1</td>
<td>3.0</td>
</tr>
<tr>
<td>Heparin</td>
<td>5.7</td>
</tr>
</tbody>
</table>

Enrollment was stopped after 3 patients experienced allergic-like reactions.

*ICH, intraocular, retroperitoneal, bleed requiring intervention/surgery, hematoma ≥ 5 cm, Hgb ≥ 3 g/dL with an overt source or ≥ 4 g/dL without overt source of bleeding, blood product transfusion.