Up-date sulle sindromi coronariche acute

“Stratificazione prognostica e terapia medica delle sindromi coronariche acute”

Micaela Conte
The time is heart

Acute Myocardial Infarction in patients presenting with ST-segment elevation
Acute Myocardial Infarction in patients presenting with ST-segment elevation
Recomandation for risk stratification (STEMI-ACS)

Older age, higher Killip class, elevated heart rate, lower systolic blood pressure, anterior location of the infarct are the most important independent predictors of early mortality in clinical trials and registries.

These characteristics contain most of the prognostic information in the clinical data available at the time of the first medical contact.
Recomandation for diagnosis and risk stratification (NSTEMI-ACS)

Diagnosis and short-term risk stratification of NSTEMI should be based on a combination of clinical history, symptoms, ECG, biomarkers and risk score results (I-B)
FRISC II, ICTUS and RITA III trials showed a direct relationship between risk, evaluated by a set of risk indicators including age, diabetes, hypotension, ST depression, and body mass index (BMI), and benefit from an early invasive approach. Troponin elevation and ST depression at baseline appear to be among the most powerful individual predictors of benefit from invasive treatment.

**Table II**  Indicators predicting high thrombotic risk or high-risk for progression to myocardial infarction, which indicate emergent coronary angiography

<table>
<thead>
<tr>
<th>Indicators</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing or recurrent ischaemia.</td>
</tr>
<tr>
<td>Dynamic spontaneous ST changes (&gt;0.1 mV depression or transient elevation).</td>
</tr>
<tr>
<td>Deep ST depression in anterior leads V2–V4 indicating ongoing posterior transmural ischaemia.</td>
</tr>
<tr>
<td>Haemodynamic instability.</td>
</tr>
<tr>
<td>Major ventricular arrhythmia.</td>
</tr>
</tbody>
</table>
ESC Guidelines for NSTE-ACS recommend the GRACE risk score as the preferred classification to apply on admission and at discharge in daily clinical practice.

http://www.outcomes.umassmed.org/grace
TIMI risk score

adverse cardiac outcomes (death, new or recurrent MI, urgent revascularization) at 14 days

(1 point for each):

- Age ≥ 65
- Prior coronary stenosis ≥ 50 %
- ST segment deviation on ECG at presentation
- At least 2 anginal events in prior 24 hours
- Use of ASA in prior 7 days
- At least 3 risk factors for CAD (family history, male, hypertension, hyperlipidemia, DM, smoking, obesity)
- Elevated serum cardiac markers
  - low (0-2; 5-8% risk);
  - intermediate (3-4; 13-20% risk);
  - high (5-7; 26-41% risk).
DUAL ANTIPLATELET THERAPY
ADP = adenosine diphosphate, TXA$_2$ = thromboxane A$_2$, COX = cyclooxygenase.

Efficacy of Antiplatelet Therapy in Reducing Coronary Events after Stenting

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>ASA + Ticlopidine</th>
<th>ASA only</th>
<th>ASA + Warfarin</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hall (1996)¹</td>
<td>226</td>
<td>0.8</td>
<td>3.9</td>
<td>6.2</td>
<td>P=0.1</td>
</tr>
<tr>
<td>ISAR (1997)²</td>
<td>517</td>
<td>1.6</td>
<td></td>
<td>6.2</td>
<td>P=0.01</td>
</tr>
<tr>
<td>STARS (1998)³</td>
<td>1653</td>
<td>0.5</td>
<td>2.7</td>
<td>5.6</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>MATTIS (1998)⁴</td>
<td>350</td>
<td></td>
<td>5.6</td>
<td>11.0</td>
<td>P=0.07</td>
</tr>
<tr>
<td>FANTASTIC (1998)⁵</td>
<td>485</td>
<td></td>
<td>5.7</td>
<td>8.3</td>
<td>P=0.37</td>
</tr>
</tbody>
</table>

The Thienopyridine Family

**Ticlopidine**

(1st generation)

- P2Y₁₂ ADP receptor antagonism: antithrombotic treatment of choice for coronary stenting
- Side effects: neutropenia, thrombocytopenia, rash, diarrhea, etc
- Delayed time frame to achieve full antiplatelet effects

**Clopidogrel**

(2nd generation)

- Better Safety profile - Fewer side effects
- Rapid onset of action with a loading dose
- Better clinical outcomes at 30 days in PCI
  (Bhatt DL et al. J Am Coll Cardiol 2002; 39: 9–14.).

Solution to these problems:
The Target for Clopidogrel is the Platelet P2Y$_{12}$ Receptor
CURE

12,562 pts with ACS were treated with aspirin and randomized to clopidogrel vs. placebo and followed for up to 12 months

Primary endpoint = CV Death, MI, or Stroke

Placebo + Aspirin* (n = 6303)

Clopidogrel + Aspirin* (n = 6259)

11.4%
9.3%

20%↓

P<0.001

* In combination with standard therapy

PCI was performed in 2658 pts (21%): 1 Yr CV Death or MI

A=median time to PCI; B=open label clopidogrel for 30 d after PCI

**CYP2C19 Variants Reduce Clopidogrel Efficacy**

CYP2C19 Reduced-Function Allele Carriers

Non-carriers

HR 1.53
(95% CI 1.07-2.19)
P=0.014

* Carriers ~30% of the population

Clopidogrel: Value and Limitations

Better Safety profile - Fewer side effects

Rapid onset of action with a loading dose

Better clinical outcomes at 30 days in PCI
(Bhatt DL et al. J Am Coll Cardiol 2002; 39: 9–14.).

bleeding risk in CABG

1) Irreversible platelet inhibitor

2) Response variability

full antiplatelet effects not always so rapid

level of inhibition not always so high

clopidogrel resistance
Ideal ADP P2Y12 receptor antagonist

- Rapid onset
- High level of inhibition
- No resistance
- No bleeding
Novel ADP P2Y$_{12}$ receptor antagonist

Prasugrel

Ticagrelor

Cangrelor

Elinogrel
Prasugrel 60 mg LD vs Clopidogrel 300 mg or 600 mg LD: Faster Onset and Higher IPA

Payne CD. TCT 2006
**CYP2C19 Variants Do Not Affect Prasugrel**

- **Non-carriers of a CYP2C19 reduced function allele**
  - Hazard Ratio 0.89
  - (95% CI 0.60-1.31)
  - \( P=0.27 \)

- **Carriers**
  - Hazard Ratio 0.58
  - (95% CI 0.13-2.69)
  - \( P=0.48 \)

- *Carriers ~30% of the population*

Healthy volunteer crossover study
IPA (20 \( \mu \text{M ADP} \)) at 24 hours

Inhibition of platelet aggregation (%)

Response to clopidogrel 300 mg
Response to prasugrel 60 mg

N=64

Brandt J et al. AHJ 2006
TRITON-TIMI-38

13,608 pts with ACS (unstable angina, NSTEMI, acute STEMI, or recent STEMI) undergoing PCI with known coronary anatomy (except for primary PCI pts) were treated with aspirin and randomized to clopidogrel 300 mg load + 75 mg qd vs. prasugrel 60 mg load + 10 mg qd and followed for 6-15 mos (median 12 mos)

Wiviott SD et al. NEJM 2007;357:2001-15
TRITON-TIMI 38: Balancing Efficacy and Safety
Balance of Efficacy and Safety

CV Death / MI / Stroke

Prasugrel: HR 0.81 (0.73-0.90) P=0.0004

Clopidogrel: HR 1.32 (1.03-1.68) P=0.03

NNT = 46
NNH = 167

TIMI Major NonCABG Bleeds

Prasugrel: ↓ 138 events

Clopidogrel: ↑ 35 events

HR 1.32 (1.03-1.68) P=0.03

NNT = 46
NNH = 167
Net Clinical Benefit* Bleeding Risk Subgroups

*Primary Efficacy Endpoint + TIMI Major Bleeding

**Post-hoc analysis**

Prior Stroke / TIA

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>-37</td>
<td>+16</td>
</tr>
</tbody>
</table>

Age

<table>
<thead>
<tr>
<th>&gt;=75</th>
<th>&lt;75</th>
</tr>
</thead>
<tbody>
<tr>
<td>-1</td>
<td>-16</td>
</tr>
</tbody>
</table>

Wgt

<table>
<thead>
<tr>
<th>&lt; 60 kg</th>
<th>&gt;=60 kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>+3</td>
<td>-14</td>
</tr>
</tbody>
</table>

Overall

<table>
<thead>
<tr>
<th>0.5</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prasugrel Better</td>
<td>Clopidogrel Better</td>
<td></td>
</tr>
</tbody>
</table>

Risk (%)

-13

$P_{int} = 0.006$

$P_{int} = 0.18$

$P_{int} = 0.36$
Novel ADP P2Y$_{12}$ receptor antagonist

Prasugrel

Ticagrelor

Cangrelor

Elinogrel
Ticagrelor (AZD6140)

- A non-thienopyridine, in the chemical class CPTP (CycloPentylTriazoloPyrimidine)
- First oral reversible ADP P2Y₁₂ receptor antagonist
- Direct acting via the P2Y₁₂ receptor - metabolism not required for activity
- More potent platelet inhibitor than clopidogrel
DISPERSE: Faster, Greater and More Consistent IPA with AZD6140 vs clopidogrel

Husted SE et al Eur Heart J 2006; 27: 1038-1047
K-M estimate of time to first primary efficacy event (composite of CV death, MI or stroke)

No. at risk

<table>
<thead>
<tr>
<th></th>
<th>Clopidogrel</th>
<th>Ticagrelor</th>
</tr>
</thead>
<tbody>
<tr>
<td>9,333</td>
<td>8,628</td>
<td>8,460</td>
</tr>
<tr>
<td>8,460</td>
<td>8,219</td>
<td>6,743</td>
</tr>
<tr>
<td>6,743</td>
<td>5,161</td>
<td>4,147</td>
</tr>
<tr>
<td>5,161</td>
<td>4,147</td>
<td></td>
</tr>
</tbody>
</table>

K-M = Kaplan-Meier; HR = hazard ratio; CI = confidence interval
Time to major bleeding
– primary safety event

PLATO Trial of AZD 6140

K-M estimated rate (% per year)

<table>
<thead>
<tr>
<th>Days from first IP dose</th>
<th>Ticagrelor</th>
<th>Clopidogrel</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>120</td>
<td></td>
<td></td>
</tr>
<tr>
<td>180</td>
<td></td>
<td></td>
</tr>
<tr>
<td>240</td>
<td></td>
<td></td>
</tr>
<tr>
<td>300</td>
<td></td>
<td></td>
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<tr>
<td>360</td>
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</tr>
</tbody>
</table>

HR 1.04 (95% CI 0.95–1.13), p=0.434

No. at risk

<table>
<thead>
<tr>
<th>Drug</th>
<th>0</th>
<th>60</th>
<th>120</th>
<th>180</th>
<th>240</th>
<th>300</th>
<th>360</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ticagrelor</td>
<td>9,235</td>
<td>7,246</td>
<td>6,826</td>
<td>6,545</td>
<td>5,129</td>
<td>3,783</td>
<td>3,433</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>9,186</td>
<td>7,305</td>
<td>6,930</td>
<td>6,670</td>
<td>5,209</td>
<td>3,841</td>
<td>3,479</td>
</tr>
</tbody>
</table>
Triton vs Plato: Is there a winner?

- Prasugrel and ticagrelor both showed favorable efficacy and safety profiles in their respective trials and only a head-to-head comparison will be able to define the winner.

- Subgroup analysis will allow to define the best niche for each drug.

- Prasugrel. Particularly efficacious in reducing stent thrombosis, MI, uTVR and great benefit in diabetics and STEMI. Considerations: safety in prior TIA/stroke, CABG/surgery.

- Ticagrelor. Particularly efficacious in reducing mortality (off-target effects), attractive for upstream use even if CABG is required, OK for patients with prior TIA/stroke.
Antithrombotic therapy in STEMI-ACS

<table>
<thead>
<tr>
<th>STEMI</th>
<th>Antiplatelet therapy</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ASA</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>Clopidogrel&lt;sup&gt;f&lt;/sup&gt; (with 600 mg loading dose as soon as possible)</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>Prasugrel&lt;sup&gt;d&lt;/sup&gt;</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>Ticagrelor&lt;sup&gt;d&lt;/sup&gt;</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>+ GPIIb–IIa antagonists (in patients with evidence of high intracoronary thrombus burden)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Abciximab</td>
<td>IIa</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>Eptifibatide</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>Tirofiban</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>Upstream GPIIb–IIa antagonists</td>
<td>III</td>
<td>B</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Anticoagulation</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Bivalirudin (monotherapy)</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>UFH</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>III</td>
<td>B</td>
</tr>
</tbody>
</table>
## Antithrombotic therapy in NSTEMI-ACS

<table>
<thead>
<tr>
<th>NSTE-ACS</th>
<th>Antiplatelet therapy</th>
<th>Anticoagulation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>ASA</strong></td>
<td><strong>Very high-risk of ischaemia</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Clopidogrel (with 600 mg loading dose as soon as possible)</strong></td>
<td><strong>UFH (+GPIIb–IIIa antagonists) or</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Clopidogrel (for 9–12 months after PCI)</strong></td>
<td><strong>Bivalirudin (monotherapy)</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Prasugrel(^d)</strong></td>
<td><strong>Bivalirudin</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Ticagrelor(^d)</strong></td>
<td><strong>UFH</strong></td>
</tr>
<tr>
<td></td>
<td><strong>+ GPIIb–IIIa antagonists</strong> (in patients with evidence of high intracoronary thrombus burden)**</td>
<td><strong>Bivalirudin</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Fondaparinux</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Enoxaparin</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Abciximab (with DAPT)</strong></td>
<td><strong>Low-risk of ischaemia</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Fondaparinux</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Enoxaparin</strong></td>
</tr>
</tbody>
</table>

### Anticoagulation

- **Very high-risk of ischaemia**
  - UFH (+GPIIb–IIIa antagonists) or
  - Bivalirudin (monotherapy)

- **Medium-to-high-risk of ischaemia**
  - UFH
  - Bivalirudin

- **Low-risk of ischaemia**
  - Fondaparinux
  - Enoxaparin

### Anticoagulation

- **Abciximab (with DAPT)**
- **Tirofiban, Eptifibatide**
- **Upstream GPIIb–IIIa antagonists**

- **UFH**
- **Bivalirudin**
- **Fondaparinux**
- **Enoxaparin**
Thank you