NOACs in ACS

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February 24, 2017 – 16:40-16:55 – 15 min. + 5 disc.
- Co-author ESC Guidelines on Atrial Fibrillation 2010-2012
- Steering Committee member, National Coordinator for Italy, and Co-author of APPRAISE-2, ARISTOTLE, AVERROES, ENGAGE-AF, Re-DUAL PCI
- Fees, honoraria and research funding from Sanofi-Aventis, Boehringer Ingelheim, Bayer, BMS/Pfizer, Daiichi-Sankyo, Novartis, Merck
Review

Targeting thrombin long-term after an acute coronary syndrome: Opportunities and challenges

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NOACs in ACS – 2 different scenarios

1. ACS in the setting of AF
2. ACS without AF

EUROPEAN HEART HOUSE

Anti-Thrombotic Therapy – Update 2017
Thursday 23 February – Saturday 25 February, 2017

SESSION 9: COEXISTING ATRIAL FIBRILLATION AND CAD – Chairs: R. De Caterina and S.D. Kristensen

10:50-11:05  Stable coronary artery disease, elective stenting and atrial fibrillation – K. Huber
11:05-11:10  Discussion
11:10-11:25  After an ACS – R. De Caterina
11:25-11:30  Discussion
NOACs in ACS – 2 different scenarios

1. ACS in the setting of AF
2. ACS without AF
NOACs in ACS – 2 different scenarios

1. ACS in the setting of AF
2. ACS without AF
   a. The Rationale
   b. The Implementation
Easy take-home message:

- Nothing really new in the past two years, but stay tuned, because things may quickly change
NOACs in ACS without AF

- The Rationale
- The Implementation
NOACs in ACS without AF

- The Rationale
- The Implementation
Double Antiplatelet Therapy (ASA + CLOPIDOGREL)

- **CURE**
- **PCI-CURE**
- **CREDO**

- For all patients, immediate 300 mg loading dose of clopidogrel is recommended, followed by 75 mg clopidogrel daily (I-A). Clopidogrel should be maintained for 12 months unless there is an excessive risk of bleeding (I-A).
## New P2Y\textsubscript{12} ADP receptor antagonists

<table>
<thead>
<tr>
<th>Drug</th>
<th>Type</th>
<th>Route</th>
<th>Action</th>
<th>Dose</th>
<th>MPI*</th>
<th>Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prasugrel</td>
<td>Hepatic Conv</td>
<td>Oral</td>
<td>Irreversible binding</td>
<td>LD 60 mg - MD 10 mg</td>
<td>70% (&lt;1h)</td>
<td>TRITON</td>
</tr>
<tr>
<td>Cangrelor</td>
<td>Direct Inh.</td>
<td>Parenteral</td>
<td>Competitive binding</td>
<td>4 mcg/kg/min</td>
<td>95% (&lt;5 min)</td>
<td>CHAMPION</td>
</tr>
<tr>
<td>AZD-6140 Ticagrelor</td>
<td>Direct Inh.</td>
<td>Oral</td>
<td>Competitive binding</td>
<td>90 mg x 2</td>
<td>95% (2-4h)</td>
<td>PLATO</td>
</tr>
</tbody>
</table>

*MPI = mean platelet inhibition
A P2Y$_{12}$ inhibitor is recommended, in addition to aspirin, for 12 months unless there are contraindications such as excessive risk of bleeds.

- Ticagrelor (180 mg loading dose, 90 mg twice daily) is recommended, in the absence of contraindications, for all patients at moderate-to-high risk of ischaemic events (e.g. elevated cardiac troponins), regardless of initial treatment strategy and including those pretreated with clopidogrel (which should be discontinued when ticagrelor is started).

- Prasugrel (60 mg loading dose, 10 mg daily dose) is recommended in patients who are proceeding to PCI if no contraindication.

- Clopidogrel (300–600 mg loading dose, 75 mg daily dose) is recommended for patients who cannot receive ticagrelor or prasugrel or who require oral anticoagulation.
Thus, there appear to be differences between the 2 new P2Y$_{12}$ oral inhibitors

<table>
<thead>
<tr>
<th>Prasugrel</th>
<th>Ticagrelor</th>
</tr>
</thead>
<tbody>
<tr>
<td>✓ Only in patients undergoing PCI</td>
<td>✓ Both in patients treated invasively and non-invasively</td>
</tr>
<tr>
<td>✓ Only in clopidogrel-naive patients</td>
<td>✓ Also in clopidogrel pretreated patients</td>
</tr>
<tr>
<td>✓ Not in patients with previous stroke</td>
<td>✓ Not in patients with prior ICH</td>
</tr>
<tr>
<td>✓ Careful in &gt;75 yo with dose adjustment</td>
<td>✓ No dose adjustment in the elderly &gt;75</td>
</tr>
<tr>
<td>✓ Not to be given with pretreatment in NSTEMI</td>
<td>✓ Pretreatment in STEMI not greatly effective, but not harmful</td>
</tr>
<tr>
<td>✓ Irreversible inhibitor</td>
<td>✓ Reversible inhibitor, with faster offset of effect</td>
</tr>
</tbody>
</table>
Why adding an anticoagulant long-term?
Meta-analysis: ASA + warfarin reduced CV outcomes vs ASA alone

N=25,307 patients with ACS:

Studies with target INR 2.0–3.0 (n=10)

- Death/MI/stroke
  - All studies (n=14)
  - OR (fixed) 95% CI
    - Death/MI/stroke: 0.96 (0.90–1.03)
    - All major bleeding events: 0.73 (0.63–0.84)
    - Major extracranial bleeding events: 2.32 (1.63–3.29)
    - Major intracranial bleeding events: 2.37 (1.37–4.10)

- Major intracranial bleeding events: 3.02 (0.61–15.02)

Warfarin + ASA versus ASA alone:

- Reduces death/MI/stroke only when the correct therapeutic dose is applied (INR 2.0–3.0)
- Increases the risk of major bleeding events

ACS, acute coronary syndrome; ASA, acetylsalicylic acid; CI, confidence interval; CV, cardiovascular; INR, international normalized ratio; MI, myocardial infarction; OR, odds ratio.

A new era in anticoagulation

NOACs in ACS without AF

- The Rationale
- The Implementation
APPRAISE-2: Primary efficacy outcome (CV death, MI, stroke)

Hazard ratio with apixaban, 0.95 (95% CI, 0.80–1.11); P=0.50

First graph:
- Probability of cardiovascular death, myocardial infarction, or ischemic stroke
- X-axis: Months since randomization
- Y-axis: Probability

Second graph:
- No. at Risk
  - Apixaban: 3705, 3356, 3048, 2799, 2552, 2312, 2025, 1739, 1525, 1277, 1021, 797, 561, 390, 254, 154
  - Placebo: 3687, 3316, 3014, 2751, 2537, 2272, 2030, 1728, 1495, 1248, 987, 803, 571, 412, 267, 164

ATLAS ACS 2–TIMI 51: Primary efficacy outcome (CV death, MI, stroke)

ATLAS ACS 2–TIMI 51: rivaroxaban 2.5 mg bid significantly reduced CV events and death

The primary efficacy endpoint reduction was driven by reduced mortality

CV death/MI/stroke (primary efficacy endpoint)

- Rivaroxaban 2.5 mg bid
  - HR = 0.84
  - mITT p = 0.02
  - ITT p = 0.007
  - NNT = 63

- Placebo
  - 10.7%
  - 9.1%

CV death

- Rivaroxaban 2.5 mg bid
  - HR = 0.66
  - mITT p = 0.002
  - ITT p = 0.005
  - NNT = 71

- Placebo
  - 4.1%
  - 2.7%

All-cause death

- Rivaroxaban 2.5 mg bid
  - HR = 0.68
  - mITT p = 0.002
  - ITT p = 0.004

- Placebo
  - 4.5%
  - 2.9%

NNT = 63

Cumulative incidence (%)

Both strata. bid, twice daily; CV, cardiovascular; HR, hazard ratio; ITT, intention to treat; MI, myocardial infarction; mITT, modified intention to treat; NNT, number needed to treat.

ATLAS ACS 2–TIMI 51: rivaroxaban 2.5 mg bid did not increase fatal bleeding or fatal ICH vs placebo

*\( p = 0.04 \) vs placebo; \# \( p = 0.005 \) vs placebo; ‡ \( p < 0.001 \) vs placebo. bid, twice daily; CABG, coronary artery bypass graft; ICH, intracranial haemorrhage; NS, not significant; TIMI, Thrombolysis in Myocardial Infarction.

Subgroup analyses for primary efficacy endpoint (mITT/all strata/combined doses)

Overall

Age [yrs] (<55, ≥55, <65, ≥65, <75, ≥75)

Sex (male, female)

Race (white, black, Asian, other)

Weight [kg] (<60, ≥60–<90, ≥90)

Body mass index [kg/m²] (<25, ≥25–<30, ≥30)

CrCl [ml/min] (<30, ≥30–<50, ≥50–≤80, >80)

Index event (STEMI, NSTEMI, UA, NSTEMI + UA)

Prior myocardial infarction (yes, no)

PCI for index event (yes, no)

Elevated cardiac biomarker (yes, no)

Congestive heart failure (yes, no)

Prior ischaemic stroke/TIA (yes, no)

Hypertension (yes, no)

Diabetes (yes, no)

Region (East Europe, Western Europe, North America, South America, Asia, other)

Hazard ratio and 95% confidence interval

Rivaroxaban ← Favours → Placebo

CrCl, creatinine clearance; mITT, modified intention to treat; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; TIA, transient ischaemic attack; UA, unstable angina. FDA briefing information, 23 May 2012.
There is good clinical rationale to exclude patients with prior stroke/TIA

- Patients with prior stroke/TIA do not appear to benefit, consistent results seen with other compounds in this sub-population.

**History of stroke**

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>No History of Stroke</th>
<th>Yes History of Stroke</th>
<th>HR (95% CI)</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRITON TIMI-38 (prasugrel)(^1)</td>
<td>No</td>
<td></td>
<td></td>
<td>0.79 (0.71–0.88)</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td></td>
<td></td>
<td>1.37 (0.89–2.13)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prasugrel better</td>
<td></td>
<td>Clopidogrel better</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATLAS 2 (rivaroxaban 5 mg bid, 15 months)(^2)</td>
<td>No</td>
<td></td>
<td></td>
<td>0.88 (0.75–1.03)</td>
<td>0.22</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td></td>
<td></td>
<td>1.61 (0.63–4.10)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rivaroxaban better</td>
<td></td>
<td>Placebo better</td>
<td></td>
<td></td>
</tr>
<tr>
<td>APPRAISE-2 (apixaban 5 mg bid, 15 months)(^3)</td>
<td>No</td>
<td></td>
<td></td>
<td>0.89 (0.74–1.06)</td>
<td>0.08</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td></td>
<td></td>
<td>1.32 (0.88–1.99)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Apixaban better</td>
<td></td>
<td>Placebo better</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

bid, twice daily; CI, confidence interval; HR, hazard ratio; TIA, transient ischaemic attack.

Rivaroxaban 2.5 mg bid in ATLAS ACS 2–TIMI 51 vs standard antiplatelet therapy showed...

- Greater efficacy, including fewer deaths and reduction in stent thrombosis (not shown)
- An important increase in bleeding, including intracranial haemorrhage (ICH), but without any increase in fatal bleeding or fatal ICH
- Even greater benefits in patients with elevated cardiac biomarkers and without previous stroke/TIA

### Overview on rivaroxaban 2.5 mg bid subgroups compared with overall study population

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Primary composite endpoint (CV death/MI/stroke)</th>
<th>CV death</th>
<th>NCB*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Efficacy: non-bleed CV death, MI, ischaemic stroke events prevented</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Safety: fatal bleeding, symptomatic ICH</td>
</tr>
<tr>
<td>Overall study population</td>
<td>HR 0.84, 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>Exclude 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: +8</td>
</tr>
<tr>
<td>Restrict to elevated biomarkers Exclude 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>

*Excess number of events in 10,000 patient-years. ARR: absolute risk reduction based on 2-year K–M estimates; bid, twice daily; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; ICH, intracranial haemorrhage; MI, myocardial infarction; NCB, net clinical benefit; NNT: number needed to treat; TIA, transient ischaemic attack.

Difficulties in buying this concept

- Triple therapy in ACS is more complicated than DAPT using ticagrelor (or prasugrel)
- Identifying candidate patients is somewhat complicated
- Clopidogrel perceived as «an old drug»
- Is the lower mortality with rivaroxaban real? «One swallow does not make spring»
- Difficulties in accepting the much higher rates of bleeding
**Objective:** Efficacy and safety of rivaroxaban, low-dose rivaroxaban plus ASA or ASA alone for reducing risk of MI, stroke or CV death in patients with CAD or PAD

**Population:** Patients with CAD or PAD

- Rivaroxaban 2.5 mg bid + ASA 100 mg od
- Rivaroxaban 5.0 mg bid + ASA placebo
- ASA 100 mg od + rivaroxaban placebo

N~27,400

1:1:1

30-day washout period

Final follow-up visit

Final washout period visit
News Release

Not intended for U.S. and UK Media

Phase III COMPASS study with Bayer’s Rivaroxaban in Patients with Coronary or Peripheral Artery Disease Shows Overwhelming Efficacy and Meets Primary Endpoint Early

08 Feb 2017
Objective: Safety of rivaroxaban versus ASA in addition to either clopidogrel or ticagrelor therapy in patients with a recent ACS

Population: Patients with an acute coronary syndrome\(^a\),\(^b\)

Acute phase treatment (invasive or not)

Maintenance dose of ASA and P2Y\(_12\)

<table>
<thead>
<tr>
<th>Selection up until 10 days prior to R</th>
<th>Randomization</th>
<th>Treatment phase</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 1</td>
<td>Day 30</td>
<td>Day 90</td>
</tr>
</tbody>
</table>

Clopidogrel 75 mg od + ASA 100 mg od

Clopidogrel 75 mg od + rivaroxaban 2.5 mg bid

Ticagrelor 90 mg bid + ASA 100 mg od

Ticagrelor 90 mg bid + rivaroxaban 2.5 mg bid
Stay tuned!
Thank you!