The Great debate: thrombocardiology post-COMPASS

Anticoagulation should replace antiplatelets in CAD prevention - CON

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What have happened?

- Mixed clinical presentation at time of stent implantation
- Acute coronary syndrome at presentation
- DAPT initiated in patients with prior MI
- DAPT for primary prevention

Size of the circles → sample size
Circle perimeters → type of investigated population

- 1996)
- 1998)
- 1998)
- 2000)
- 2005)
- 2005)
- 2010)
- 2012)
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ASA in SCAD
<table>
<thead>
<tr>
<th>Clinical setting</th>
<th>European Society of Cardiology</th>
<th>ACC/AHA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SCAD</strong></td>
<td>Low-dose aspirin daily is recommended in all SCAD patients (class I LOE A)</td>
<td><strong>Treatment with aspirin</strong> 75 to 162 mg daily should be continued indefinitely in the absence of CI in patients with SIHD (class I LOE A)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Treatment with aspirin</strong> 75 to 162 mg daily and clopidogrel 75 mg daily might be reasonable in certain high-risk patients with SIHD (class IIb LOE B)</td>
</tr>
</tbody>
</table>
| **PCI**          | ASA is indicated before elective stenting (class I LOE B)  
Life-long single antiplatelet therapy, usually ASA, is recommended (class I LOE A) | Patients already on daily aspirin therapy should take 81 mg to 325 mg before PCI (class I LOE B)  
Patients not on aspirin therapy should be given nonenteric aspirin 325 mg before PCI (class I LOE B) |
| **Secondary prevention** | In the chronic phase (>12 months) after MI, aspirin is recommended (class I LOE A) | **Aspirin 75–162 mg daily** is recommended in all patients with coronary artery disease unless contraindicated (class I LOE A) |

Abbreviations: ACS, acute coronary syndromes; CAD, coronary artery disease; DAPT, dual antiplatelet therapy; LOE, level of evidence; NSTE-ACS, non-ST-segment elevation acute coronary syndromes; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; SCAD, stable coronary artery disease; SIHD, stable ischemic heart disease; STEMI, ST-segment elevation myocardial infarction; TIA, transient ischemic attack.
DAPT in SCAD
DAPT beyond one year after ACS

N=33 435 patients from 6 RCT followed over a mean 31 months

Algorithm for the use of antithrombotic drugs in patients undergoing percutaneous coronary intervention (2)

Antithrombotic Treatment in Patients Undergoing Percutaneous Coronary Intervention

**Treatment Indication**
- **Stable Coronary Artery Disease**

**(Pre-) Treatment DAPT**

**Anticoagulation for PCI**
- **UFH** or **Enoxaparin**

**Time**
- 1 month
- 3 months
- 6 months
- 12 months
- 30 months
- 36 months

**DAPT Duration**
- 6 months DAPT
- 1 month DAPT
- 3 months DAPT
- >6 months DAPT

**High Bleeding Risk**
- No
- Yes

**Algorithm for the use of antithrombotic drugs in patients undergoing percutaneous coronary intervention (2)**

**Antiplatelet drugs:**
- **A** Aspirin
- **C** Clopidogrel
- **P** Prasugrel
- **T** Ticagrelor
Adding anti-Xa blockade to DAPT
Synergy between anti-Xa and APT

Phase-2 strategy trials

**TIMI-46**
- Clinically significant bleeding (%)
  - Placebo: 3.3%
  - Rivaroxaban: 0.55% (95% CI 0.41–0.74), p < 0.001
- Major, Minor, or Bleeding Requiring Medical Attention (%)
  - Placebo: 6.1%
  - Rivaroxaban: 2.5 mg bid

**ATLAS-TIMI 51**
- CV death, MI or stroke
  - HR = 0.80 (95% CI 0.68–0.94), p = 0.007
  - Rivaroxaban 2.5 mg bid: 2-year Kaplan-Meier estimate (%)
- CV death
  - HR = 0.55 (95% CI 0.41–0.74), p < 0.001
  - Rivaroxaban 2.5 mg bid

**GEMINI**
- Cumulative event rate (%)
  - Rivaroxaban plus P2Y12 inhibitor: 1.09 (95% CI 0.80–1.50), p = 0.584
  - ASA plus P2Y12 inhibitor
  - Total 2-year Kaplan-Meier estimate (%)

**PIONEER**
- TIMI Major, TIMI Minor, or Bleeding Requiring Medical Attention (%)
  - VKA + DAPT: 26.7%
  - Rivaroxaban + DAPT: 18.0%
  - Rivaroxaban 15 + P2Y12: 16.8%
  - Rivaroxaban 2.5 + DAPT

- VKA + DAPT vs. Rivaroxaban + DAPT
  - HR = 0.59 (95% CI 0.47–0.76), p < 0.000013
  - ARR = 9.9
  - NNT = 11

- Rivaroxaban 15 + P2Y12 vs. DAPT
  - HR = 0.63 (95% CI 0.50–0.80), p < 0.00018
  - ARR = 8.7
  - NNT = 12
Safety issues

Fatal bleeding events
- Placebo
- 2.5 mg rivaroxaban
- 5.0 mg rivaroxaban

ICH
- Placebo
- 2.5 mg rivaroxaban
- 5.0 mg rivaroxaban

Rivaroxaban vs placebo
- Fatal bleeding events: $p=\text{NS}$
- ICH: $p=0.009$
- Fatal ICH: $p=\text{NS}$

2018 Myocardial Revascularization

Recommendations for post-interventional and maintenance treatment in patients with MI undergoing percutaneous coronary intervention

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class\textsuperscript{a}</th>
<th>Level\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>In ACS patients with no prior stroke/TIA, and at high ischaemic risk as well as low bleeding risk, receiving aspirin and clopidogrel, low-dose rivaroxaban (2.5 mg b.i.d. for approximately 1 year) may be considered after discontinuation of parenteral anticoagulation.\textsuperscript{720}</td>
<td>IIb</td>
<td>B</td>
</tr>
</tbody>
</table>

Transition into practice
An ideal case?

- 38 year-old male with anterior NSTEMI (06/2012)
- Discharge on aspirin and prasugrel after LAD stenting (Double Vessel Disease)
- Active smoker/heredity/no comorbidities & Physical activity 6 hrs/week
Question #1
Would you add anti-Xa before discharge?

1. YES
2. NO
Question #1 → Probably Not

- No labelling
- No reimbursement
- Unpredictable risk of Intra-cranial Hemorrhage
- Established alternatives with less safety hazards
After one year?
Risk stratification

- Asymptomatic and no ischemia/MI scare (stress MRI)
- Occasional smoker/LDL at 1.2g/L

DAPT Score = 2

PRECISE-DAPT = 6
Question #2

1. Stop the $\text{P}2\text{Y}_{12}$ inhibitor
2. Maintain the same DAPT regimen
3. De-escalation from prasugrel to clopidogrel
4. Switch from $\text{P}2\text{Y}_{12}$ inh to low dose Anti-Xa
Safety/Efficacy issues with dual therapy
The WARIS-2 Study (n=3630)

Episodes of major, nonfatal bleeding
0.62% vs 0.17% year (P<0.001).

Drug adherence Issues

COMPASS

Stroke/MI/Cardiovascular death

- Rivaroxaban 2.5 mg bid + aspirin vs aspirin:
  - HR = 0.74 (95% CI 0.65–0.86) \( p < 0.0001 \)

- Rivaroxaban 5 mg bid vs aspirin:
  - HR = 0.89 (95% CI 0.78–1.02) \( p = 0.09 \)

Rivaroxaban + Aspirin:
- \( \downarrow \) of MACCE by 26% vs aspirin

Lack of efficacy of anti-Xa alone

<table>
<thead>
<tr>
<th>Crude incidence over mean follow-up of 23 months</th>
<th>Rivaroxaban 5 mg bid n (%) N=8250</th>
<th>Aspirin n (%) N=8261</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI, Stroke or CV death*</td>
<td>411 (5)</td>
<td>460 (6)</td>
<td>0.89 (0.78–1.02)</td>
<td>0.094</td>
</tr>
<tr>
<td>CV death</td>
<td>175 (2)</td>
<td>184 (2)</td>
<td>0.95 (0.77–1.17)</td>
<td>0.63</td>
</tr>
<tr>
<td>Non CV death</td>
<td>141 (2)</td>
<td>155 (2)</td>
<td>0.91 (0.73–1.15)</td>
<td>0.43</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>176 (2)</td>
<td>195 (2)</td>
<td>0.90 (0.74–1.11)</td>
<td>0.18</td>
</tr>
<tr>
<td>Ischemic Stroke</td>
<td>79 (1)</td>
<td>120 (2)</td>
<td>0.66 (0.50–0.87)</td>
<td>0.0037</td>
</tr>
<tr>
<td>Haemorrhagic Stroke</td>
<td>27 (&lt;1)</td>
<td>10 (&lt;1)</td>
<td>2.70 (1.31–5.59)</td>
<td>&lt;0.0051</td>
</tr>
<tr>
<td>Stent thrombosis</td>
<td>50 (1)</td>
<td>46 (1)</td>
<td>1.09 (0.73–1.62)</td>
<td>0.68</td>
</tr>
</tbody>
</table>

Lack of efficacy on ischemic endpoint
Significant increase in intracranial bleeding

### SAFETY ISSUE WITH THE LOW DOSE+ASA

#### Crude incidence over mean follow-up of 23 months

<table>
<thead>
<tr>
<th>Event</th>
<th>Rivaroxaban 2.5 mg bid + aspirin n (%)</th>
<th>Aspirin n (%)</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding (modified ISTH)</td>
<td>263 (3)</td>
<td>158 (2)</td>
<td>1.66 (1.37–2.03)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Fatal</td>
<td>14 (0.2)</td>
<td>9 (0.1)</td>
<td>1.55 (0.67–3.58)</td>
<td>0.30</td>
</tr>
<tr>
<td>ICH</td>
<td>19 (0.2)</td>
<td>19 (0.2)</td>
<td>0.99 (0.52–1.87)</td>
<td>0.98</td>
</tr>
<tr>
<td>Critical organ</td>
<td>36 (0.4)</td>
<td>25 (1)</td>
<td>1.42 (0.85–2.36)</td>
<td>0.18</td>
</tr>
<tr>
<td>Other</td>
<td>194 (2)</td>
<td>105 (1)</td>
<td>1.85 (1.46–2.34)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ISTH major bleeding</td>
<td>186 (2)</td>
<td>105 (1)</td>
<td>1.77 (1.39–2.24)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Pre-specified net clinical benefit (CV death, stroke, MI, fatal bleeding, or critical organ bleeding)</td>
<td>392 (5)</td>
<td>494 (6)</td>
<td>0.78 (0.69–0.90)</td>
<td>0.0003</td>
</tr>
</tbody>
</table>

**Significant increase major bleeding → Almost doubled+++**

**Plus a trend towards more fatal bleeds**

PENDING ISSUES

• Early termination → overstimulation of the Tx effect?

• Bleedings requiring blood transfusion/hospitalisation → NCB?

• Add-on therapy → Treatment adherence and cost-issues?
What should I tell my patient?
Question #2  \(\rightarrow\) DAPT

1. Strong evidence for maintaining DAPT in his situation

2. De-escalation of P2Y_{12} inhibition $\rightarrow$ not an option $\rightarrow$ LOW SCORES

3. Dual therapy with Anti-Xa $\rightarrow$ Higher risk of bleed than with DAPT
# NNT and NNH in SCAD trials

<table>
<thead>
<tr>
<th></th>
<th>DAPT(^1)</th>
<th>PEGASUS(^2,*)</th>
<th>COMPASS(^3**)</th>
<th>COMPASS(^3***)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NNT</strong> (death/MI/Stroke)</td>
<td>64</td>
<td>79</td>
<td>72</td>
<td>72</td>
</tr>
<tr>
<td><strong>NNH</strong> (TIMI/ISTH major)</td>
<td>111</td>
<td>114</td>
<td>80</td>
<td>59</td>
</tr>
</tbody>
</table>

*Cohorte ticagrélor 60 mg  
**Cohort rivaroxaban 2.5mg bid plus aspirin  
***Considering blood transfusion

Independent correlates of MACE

OR plot for multivariate Cox Model using repeated measurements for multiple recurrences

- Pursuit of active smoking: 6.33 (4.88-8.21)
- Multivessel disease: 1.35 (1.03-1.77)
- Inflammatory disease: 1.81 (1.30-2.50)
- Subsaharian african: 1.87 (1.16-3.02)
- Asian: 3.18 (1.86-5.44)

The natural history of premature coronary artery disease over 20 years: the AFIJI registry (ESC 2018 POSTER XX)
Epilogue
How did I treat my patient?

• Prasugrel was switched to clopidogrel in 02/2013

• Clopidogrel was stopped in 02/2014 (on PCP request)

• March 2018 → Acute occlusion of the PL from RCA
Conclusions

• Aspirin $\rightarrow$ The SOC for SCAD

• DAPT $\rightarrow$ May be used when the bleeding risk is low

• Dual Therapy with anti-Xa may be an OPTION but:
  • Only in addition to Aspirin
  • Without possible titration of the treatment intensity
  • Without possible early initiation after PCI
  • With a lower net clinical benefit than DAPT

• Higher risk patient would not have change my decision
Rebuttal

- Failure of aspirin+rivaroxaban 2.5mg bid versus APT?
- Non-inferiority of ticagrelor versus ticagrelor plus aspirin?
The multiple facet of aspirin

Coronary Atherothrombosis
- Evidence from >50 RCTs and meta-analyses

Venous Thromboembolism
- Evidence from several RCTs and meta-analyses

Colorectal Cancer
- Evidence from observational studies and meta-analyses

Cognitive Impairment
- Limited evidence from observational studies
  Currently being tested in the ASPIRE primary prevention trial
GLOBAL LEADERS

All-comers PCI population
(ACS and stable CAD patients)
(N=16,000)

Bivalirudin*-supported
BioMatrix family stent implantation
1:1 Randomisation, open-label design

Experimental treatment strategy
- ASA
  - 1 month
- Ticagrelor
  - 24 months

Reference treatment strategy
- ASA
  - 24 months
- Ticagrelor
  - 12 months
- Clopidogrel
  - OR
    - NOT ALLOWED IN STABLE PATIENTS
  - ONLY ALLOWED IN STABLE PATIENTS

Primary endpoint (effectiveness)
Experimental treatment strategy superior to reference treatment strategy on cumulative 2-year composite of all-cause mortality and new Q-wave MI

IMPORTANT: In the Reference treatment strategy arm, ticagrelor is not allowed in stable patients, and clopidogrel must be given in combination with ASA. However, patients already on stable maintenance treatment with ticagrelor (or prasugrel) can continue with ticagrelor treatment (for 12 months post index PCI).
Objective: Efficacy and safety of rivaroxaban for reducing the risk of MI, stroke or death in HF with CAD
Conclusions

- Aspirin → The standard of care for SCAD

- DAPT → When the bleeding risk is low

- Ticagrelor alone may be an alternative to DAPT?

- Dual Therapy is NOT needed as an alternative to APT

The presentation can be downloaded at action-cœur.org
SAPAT (stable angina)

<table>
<thead>
<tr>
<th></th>
<th>All (n = 2035)</th>
<th>Aspirin + sotalol (n = 1009)</th>
<th>Placebo + sotalol (n = 1026)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (%)</td>
<td>52</td>
<td>51</td>
<td>53</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>67</td>
<td>67 (8)</td>
<td>67 (8)</td>
</tr>
<tr>
<td>Heart rate (min)</td>
<td>65</td>
<td>65 (14)</td>
<td>64 (9)</td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td>152/86</td>
<td>152 (19)/85 (9)</td>
<td>153 (19)/86 (9)</td>
</tr>
<tr>
<td>Serum potassium (mmol/l)</td>
<td>4.3</td>
<td>4.3 (0.3)</td>
<td>4.3 (0.3)</td>
</tr>
<tr>
<td>Serum cholesterol (mmol/l)</td>
<td>6.8</td>
<td>6.7 (1.3)</td>
<td>6.8 (1.5)</td>
</tr>
<tr>
<td>Serum triglycerides (mmol/l)</td>
<td>1.9</td>
<td>1.9 (1.2)</td>
<td>1.9 (1.2)</td>
</tr>
<tr>
<td>Duration of angina (yr)</td>
<td>4.7</td>
<td>4.6 (5.0)</td>
<td>4.7 (5.0)</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>16</td>
<td>17</td>
<td>16</td>
</tr>
<tr>
<td>Heredity for cardiovascular disease (%)</td>
<td>34</td>
<td>34</td>
<td>33</td>
</tr>
<tr>
<td>Treated:</td>
<td></td>
<td></td>
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<tr>
<td>for hypertension (%)</td>
<td>41</td>
<td>43</td>
<td>40</td>
</tr>
<tr>
<td>with calcium channel blockers (%)</td>
<td>9</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>with diuretics (%)</td>
<td>26</td>
<td>27</td>
<td>25</td>
</tr>
<tr>
<td>for type II diabetes (%)</td>
<td>7</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Sotalol, median dose (mg)</td>
<td>160</td>
<td>160 (80–160)</td>
<td>160 (80–160)</td>
</tr>
</tbody>
</table>

Mean (SD) unless otherwise indicated: for sotalol dose interquartile range is given.


34% (81 vs 124 patients) reduction in MI & sudden death; 95% CI 24-49%; p=0.003