Dual antiplatelet therapy (DAPT) – update 2016

PD Dr. med
Pedrazzini Giovanni
Co-Head Cardiology Cardiocentro Ticino

Lausanne, 17.06.2016
Historical consideration on DAPT

- **1996 (CAPRIE study)**: superiority of Clopidogrel over ASS in secondary prevention.
- **2001 (CURE and CURE PCI study)**: superiority of Clopidogrel + ASS vs ASS in ACS (12 months regimen);
- **2003 (Credo)**: superiority of 12 months regimen over ASS in stable pts.
- **2004 Late Stent Thrombosis saga** (first generation DES): US consensus over 12 months DAPT in non-ACS pts.
- **2010** first trial (CHARISMA) with prolonged DAPT (> 12 months)
The clinical context

*Role of the dual antiplatelet therapy (DAPT)*
The clinical DAPT context

Emergent

Urgent (6 – 48h)

Elective

STEMI (thrombus burden +++)

NSTEMI (thrombus burden ++)

SIHD (no thrombus)

High mortality

Low mortality

STENT-VESSEL PREPARATION

HOW LONG ?

STENT PROTECTION

HOW SHORT?

PATIENT PROTECTION
ROLE OF THE ANTITHROMBOTIC TREATMENT

M. Roffi et al, NSTEMI ESC Guidelines 2015
## P2Y12 Inhibitors

### Characteristics and Pharmacological Properties of Available Oral and Intravenous P2Y12 Receptor Inhibitors

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Oral Administration</th>
<th>Intravenous Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug class</strong></td>
<td>Clopidogrel (Thienopyridine)</td>
<td>Cangrelor (ATP analogue)</td>
</tr>
<tr>
<td><strong>Reversibility</strong></td>
<td>Irreversible</td>
<td>Reversible</td>
</tr>
<tr>
<td><strong>P2Y12 receptor interaction</strong></td>
<td>Competitive</td>
<td>Competitive</td>
</tr>
<tr>
<td><strong>Bioactivation</strong></td>
<td>Yes (pro-drug, CYP dependent, two steps)</td>
<td>No*</td>
</tr>
<tr>
<td><strong>(Pre-treatment)-dose</strong></td>
<td>300/600 mg LD, 75 mg MD</td>
<td>ATP analogue, i.v. bolus, 4 µg/kg/min i.v. infusion for PCI</td>
</tr>
<tr>
<td><strong>Onset of effect</strong></td>
<td>Delayed: 2–6 h</td>
<td>Immediate: 2 min</td>
</tr>
<tr>
<td><strong>Duration of effect</strong></td>
<td>3–10 days</td>
<td>30–60 min</td>
</tr>
<tr>
<td><strong>Delay to surgery</strong></td>
<td>5 days</td>
<td>No significant delay</td>
</tr>
<tr>
<td><strong>Price</strong></td>
<td>0.50 €/day</td>
<td>350 €/vial</td>
</tr>
</tbody>
</table>

*Note: CYP refers to cytochrome P450 enzymes, which are involved in the metabolism of drugs.
DAPT OPEN QUESTIONS

Emergent

Urgent (6 – 48h)

Elective

STEMI
(thrombus burden +++)

NSTEMI
(thrombus burden ++)

SIHD
(no thrombus)

High mortality

Low mortality

1 - PRELOADING YES or NO

2 - DAPT AFTER STENT: HOW LONG – HOW SHORT (3 – 12 months)

3 - LONG TERM DURATION (>12 Months): YES OR NO
1 - Preloading

Very attractive…but
Pretreatment

D. Sibbing et Al, Eur Heart J 2016;37:1284-1295
Pretreatment

- Reduce periprocedural myocardial infarction
- Reduce early stent trombosis (intra- or post-procedural)
- Reduce reocclusion (if received lytics)
- Reduce risk when waiting for CABG (especially if long delay)
- Reduce need for bail-out GP IIb/IIIa (with associated bleeding risk and costs)

Potential benefits

Disadvantages

- Higher procedural bleeding risk (especially if femoral approach)
- Higher risk of CABG-related bleeding if surgical anatomy is found and emergency (immediate) surgery is required
- Prolongation of hospitalization (expensive, potentially morbid) if CABG is required, the surgeon requests delay for washout of P2Y₁₂ inhibitor, and the patient is too unstable for discharge prior to surgery
- Treatment costs (minimal)

D. Sibbing et Al, Eur Heart J 2016;37:1284-1295
### Pretreatment trials - NSTEMI

<table>
<thead>
<tr>
<th>Study name Date of publication</th>
<th>Population</th>
<th>No. of patients</th>
<th>Pre-treatment (timing)</th>
<th>No pre-treatment</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>CURE 2001</td>
<td>NSTE-ACS</td>
<td>12 562 (PCI, n = 2658)</td>
<td>300 mg LD (median 10 days pre-PCI) then 75 mg MD for 3–12 months</td>
<td>No LD then 75 mg for 4 weeks if PCI Double-blind</td>
<td>30 days 1 year</td>
</tr>
<tr>
<td>CREDO 2002</td>
<td>Stable/NSTE-ACS</td>
<td>2116</td>
<td>300 mg LD 3–24 h pre-PCI (mean 9.8 h) then long-term MD</td>
<td>No pre-treatment 28 days clopidogrel Double-blind</td>
<td>28 days 1 year</td>
</tr>
<tr>
<td>PRAGUE-8 2008</td>
<td>Stable</td>
<td>1028</td>
<td>600 mg LD (&gt;6 h pre-PCI)</td>
<td>600 mg LD in cath-lab before PCI Open label</td>
<td>7 days/hospital discharge</td>
</tr>
<tr>
<td>ARMYDA5 PRELOAD 2010</td>
<td>Stable/NSTE-ACS</td>
<td>409</td>
<td>600 mg LD (4–8 h pre-PCI)</td>
<td>600 mg LD in cath-lab before PCI Open label</td>
<td>30 days</td>
</tr>
<tr>
<td>ACCOAST 2013</td>
<td>NSTE-ACS</td>
<td>4033</td>
<td>Prasugrel 30 mg at admission Then, prasugrel 30 mg in cath-lab if PCI (median 4 h before catheterization)</td>
<td>Placebo at admission Then, prasugrel 60 mg in cath-lab if PCI Double-blind</td>
<td>30 days</td>
</tr>
</tbody>
</table>

Main Randomized controlled trials of pre-treatment in NSTEMI

D. Sibbing et Al, Eur Heart J 2016;37:1284-1295
Pretreatment in NSTEMI

ACCOAST TRIAL, 4033 pts
30 mg PRASUGREL

CONCLUSIONS 1
PRETREATMENT IN ACS NSTEMI

It is advisable to administer a potent and rapidly acting antiplatelet agent (*prasugrel* or *ticagrelor*) once the coronary anatomy is known (and the patient proceeds to immediate PCI).

If prasugrel or ticagrelor are contraindicated, pre-treatment with *clopidogrel* before coronary angiography may be advisable for patients with low bleeding risk and a high likelihood for immediate PCI, especially if radial access is planned.
### Pretreatment trials - STEMI

Main Randomized controlled trails of pre-treatment in **STEMI**

<table>
<thead>
<tr>
<th>Study name Date of publication</th>
<th>Population</th>
<th>No. of patients</th>
<th>Pre-treatment (timing)</th>
<th>No pre-treatment</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCI CLARITY 2005</td>
<td>STEMI/fibrinolysis + PCI</td>
<td>1863</td>
<td>300 mg LD at hospital presentation (median 3 days) then 75 mg MD</td>
<td>Placebo LD and MD Open-label 300 mg LD then 75 mg MD if PCI</td>
<td>30 days 1 year</td>
</tr>
<tr>
<td>CIPAMI 2011</td>
<td>STEMI/primary PCI</td>
<td>337</td>
<td>600 mg (timing unknown)</td>
<td>600 LD in cath-lab Open-label</td>
<td>7 days/hospital discharge</td>
</tr>
<tr>
<td>ATLANTIC 2014</td>
<td>STEMI/primary PCI</td>
<td>1862</td>
<td>Ticagrelor 180 mg LD (median 63 min pre-PCI)</td>
<td>Ticagrelor 180 mg LD (in-hospital) Double-blind</td>
<td>30 days</td>
</tr>
</tbody>
</table>

D. Sibbing et Al, Eur Heart J 2016;37:1284-1295
Pretreatment - STEMI

ATLANTIC TRIAL, 1862 pts
180 mg TICAGRELOR

<table>
<thead>
<tr>
<th>Variable</th>
<th>Prehospital Ticagrelor</th>
<th>In-Hospital Ticagrelor</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
<th>Difference (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic end point</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients who could be evaluated</td>
<td>906</td>
<td>952</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Composite of death, myocardial infarction, stroke, urgent revascularization, or definite stent thrombosis — no. (%)</td>
<td>41 (4.5)</td>
<td>42 (4.4)</td>
<td>1.03 (0.66 to 1.60)</td>
<td>0.91</td>
<td>0.001 (−0.018 to 0.020)</td>
</tr>
<tr>
<td>Composite of death, myocardial infarction, or urgent revascularization — no. (%)</td>
<td>39 (4.3)</td>
<td>34 (3.6)</td>
<td>1.22 (0.76 to 1.94)</td>
<td>0.42</td>
<td>0.007 (−0.010 to 0.025)</td>
</tr>
<tr>
<td>Stent thrombosis — no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Definite at ≤24 hr after index PCI</td>
<td>0</td>
<td>8 (0.8)</td>
<td>—</td>
<td>0.008‡</td>
<td>0.008 (−0.017 to −0.003)§</td>
</tr>
<tr>
<td>Definite at 30 days</td>
<td>2 (0.2)</td>
<td>11 (1.2)</td>
<td>0.19 (0.04 to 0.86)</td>
<td>0.02‡</td>
<td>−0.009 (−0.017 to −0.002)§</td>
</tr>
<tr>
<td>Definite or probable at 30 days¶</td>
<td>21 (2.3)</td>
<td>20 (2.1)</td>
<td>1.11 (0.60 to 2.05)</td>
<td>0.75</td>
<td>0.002 (−0.011 to 0.016)</td>
</tr>
<tr>
<td>Death from any cause — no. (%)</td>
<td>30 (3.3)</td>
<td>19 (2.0)</td>
<td>1.68 (0.94 to 3.01)</td>
<td>0.08</td>
<td>0.013 (−0.001 to 0.028)</td>
</tr>
<tr>
<td>Myocardial infarction — no. (%)</td>
<td>7 (0.8)</td>
<td>10 (1.1)</td>
<td>0.73 (0.28 to 1.94)</td>
<td>0.53</td>
<td>−0.003 (−0.011 to 0.006)</td>
</tr>
<tr>
<td>Stroke — no. (%)</td>
<td>4 (0.4)</td>
<td>2 (0.2)</td>
<td>2.11 (0.39 to 11.53)</td>
<td>0.39</td>
<td>0.002 (−0.004 to 0.009)§</td>
</tr>
<tr>
<td>Transient ischemic attack — no. (%)</td>
<td>0</td>
<td>1 (0.1)</td>
<td>—</td>
<td>NE</td>
<td>−0.001 (−0.006 to 0.003)§</td>
</tr>
<tr>
<td>Urgent coronary revascularization — no. (%)</td>
<td>5 (0.6)</td>
<td>8 (0.8)</td>
<td>0.66 (0.21 to 2.01)</td>
<td>0.46</td>
<td>−0.003 (−0.010 to 0.005)</td>
</tr>
<tr>
<td>Thrombotic bailout with glycoprotein IIb/IIIa inhibitors — no. (%)</td>
<td>78 (8.6)</td>
<td>100 (10.5)</td>
<td>0.80 (0.59 to 1.10)</td>
<td>0.17</td>
<td>−0.019 (−0.046 to 0.008)</td>
</tr>
</tbody>
</table>

Clinical End Points at 30 days

Pretreatment - STEMI

ATLANTIC TRIAL, 1862 pts
180 mg TICAGRELOR

Definite Stent Thrombosis up to 30 days after Ticagrelor

Routine pre-hospital pre-treatment cannot be recommended for patients with STEMI over the in-lab administration of the drug since the two strategies had similar outcomes. It can be advisable to administer potent and rapidly acting antiplatelet agents (*prasugrel* or *ticagrelor*) in the emergency department (ie ambulance) once the diagnosis of STEMI is confirmed and the patient proceeds to primary PCI.
2 - How long...how short

The longer is better...the shorter is safer
<table>
<thead>
<tr>
<th></th>
<th>US</th>
<th>EU</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACS</strong></td>
<td>At least 12 months</td>
<td>Up to 12 months</td>
</tr>
<tr>
<td><strong>Non ACS</strong></td>
<td>12 months</td>
<td>6 months</td>
</tr>
<tr>
<td><strong>BMS</strong></td>
<td>1 – 12 months</td>
<td>1 months</td>
</tr>
<tr>
<td><strong>Secondary prevention</strong></td>
<td>May be considered</td>
<td>For selected patients at high risk</td>
</tr>
<tr>
<td><strong>ASS</strong></td>
<td>Long term</td>
<td>Long term</td>
</tr>
</tbody>
</table>
The Terms of the Equation

- Complexe interaction between **safety** and **efficacy**
- All studies have used DAPT initially, although for variable periods, followed by randomly assigned treatment with DAPT vs SAPT using **ASS as monotheraphy**
- Very complexe interaction between DAPT duration and **DES generation** (from 1st generation to polymer coated free DES)
How short
(stent protection)

As short as possible but not to short
### Abbreviated duration of DAPT (<6 months)

#### TABLE 2: Studies Evaluating Abbreviated Duration of DAPT (<6 Months) After DES

<table>
<thead>
<tr>
<th>Trial (Ref. #)</th>
<th>Year</th>
<th>Study Population (n)</th>
<th>Design</th>
<th>Longest Follow-Up</th>
<th>Primary Endpoint</th>
<th>Mean Age</th>
<th>DM (%)</th>
<th>ACS (%)</th>
<th>1st-Generation DES (%)</th>
<th>2nd-Generation DES (%)</th>
<th>Study Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISAR-SAFE (39)</td>
<td>2014</td>
<td>4,000</td>
<td>6 months vs. 12 months DAPT</td>
<td>12 months</td>
<td>Composite of death, MI, stroke, ST, or TIMI major bleeding at 15 months after PCI</td>
<td>67</td>
<td>25</td>
<td>40</td>
<td>10</td>
<td>72</td>
<td>6 months NI to 12 months</td>
</tr>
<tr>
<td>ITALIC (38)</td>
<td>2014</td>
<td>1,822</td>
<td>6 months vs. 12 months DAPT</td>
<td>12 months</td>
<td>Composite of death, MI, repeat TVR, stroke, or TIMI major bleeding at 12 months after PCI</td>
<td>62</td>
<td>37</td>
<td>24</td>
<td>—</td>
<td>100</td>
<td>6 months NI to 12 months</td>
</tr>
<tr>
<td>SECURITY (37)</td>
<td>2014</td>
<td>1,399</td>
<td>6 months vs. 12 months DAPT</td>
<td>24 months</td>
<td>Composite of cardiac death, MI, stroke, ST, or BARC 3 or 5 bleeding at 12 months after PCI</td>
<td>65</td>
<td>31</td>
<td>38</td>
<td>—</td>
<td>100</td>
<td>6 months NI to 12 months</td>
</tr>
<tr>
<td>OPTIMIZE (36)</td>
<td>2014</td>
<td>3,119</td>
<td>3 months vs. 12 months DAPT</td>
<td>12 months</td>
<td>Composite of death, MI, stroke, or major bleeding at 12 months after PCI</td>
<td>61</td>
<td>35</td>
<td>32</td>
<td>—</td>
<td>100</td>
<td>3 months NI to 12 months</td>
</tr>
<tr>
<td>PRODIGY (34)</td>
<td>2012</td>
<td>1,970</td>
<td>6 months vs. 24 months DAPT</td>
<td>24 months</td>
<td>Composite of death, MI, or cerebrovascular accidents at 24 months after PCI</td>
<td>68</td>
<td>24</td>
<td>75</td>
<td>25</td>
<td>50</td>
<td>6 months NI to 24 months</td>
</tr>
<tr>
<td>RESET (35)</td>
<td>2012</td>
<td>2,117</td>
<td>3 months vs. 12 months DAPT</td>
<td>12 months</td>
<td>Composite of cardiac death, MI, ST, ischemia-driven TVR, or bleeding at 12 months after PCI</td>
<td>62</td>
<td>29</td>
<td>55</td>
<td>21</td>
<td>85</td>
<td>3 months NI to 12 months</td>
</tr>
<tr>
<td>EXCELLENT (33)</td>
<td>2011</td>
<td>1,443</td>
<td>6 months vs. 12 months DAPT</td>
<td>12 months</td>
<td>Composite of cardiac death, MI, or TVR at 12 months after PCI</td>
<td>63</td>
<td>38</td>
<td>51</td>
<td>25</td>
<td>75</td>
<td>6 months NI to 12 months</td>
</tr>
</tbody>
</table>

BARC — Bleeding Academic Research Consortium; DAPT — dual antiplatelet therapy; DM — diabetes mellitus; EXCELLENT — Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting; ISAR-SAFE — Randomized, Double-Blind, Placebo-controlled Trial of 6 vs. 12 Months Clopidogrel Therapy After Implantation of a Drug-Eluting Stent; ITALIC — Is There A Life for DES After Discontinuation of Clopidogrel; MI — myocardial infarction; NI — noninferior; OPTIMIZE — Optimized Duration of Clopidogrel Therapy Following Treatment With the Endeavor Zotarolimus-Eluting Stent in the Real World Clinical Practice; PCI — percutaneous coronary intervention; PRODIGY — PROlonging Dual Antiplatelet Treatment In Patients With Coronary Artery Disease After Graded Stent-induced Intimal Hyperplasia; RESET = A New Strategy Regarding Discontinuation of Dual Antiplatelet; Real Safety and Efficacy of a 3-month Dual Antiplatelet Therapy Following Zotarolimus-eluting Stents Implantation; SECURITY = Second-Generation Drug-Eluting Stent Implantation Followed by 6- Versus 12-Month Dual Antiplatelet Therapy; ST = stent thrombosis; TIMI = Thrombolysis In Myocardial Infarction; TVR = target vessel revascularization; other abbreviations as in Table 1.
### Abbreviated duration of DAPT (<6 months)

<table>
<thead>
<tr>
<th></th>
<th>3 – 6 months</th>
<th>≥ 12 months</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>ST rate (%)</td>
<td>0.5</td>
<td>0.4</td>
<td>0.1</td>
</tr>
<tr>
<td>Pooled MI (%)</td>
<td>1.7</td>
<td>1.5</td>
<td>0.2</td>
</tr>
<tr>
<td>Major bleeding (%)</td>
<td>0.4</td>
<td>0.8</td>
<td>0.4</td>
</tr>
<tr>
<td>Death rate (%)</td>
<td>1.7</td>
<td>1.9</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Net clinical benefit of longer DAPT in studies evaluating a period of DAPT ≤ months
Abbreviated duration of DAPT (<6 months)

Net clinical benefit of longer DAPT in studies evaluating a period of DAPT ≤ months
How long (patient protection)

Who can really benefit?
### Table 3 Main studies evaluating long-term duration of dual antiplatelet therapy in coronary patients

<table>
<thead>
<tr>
<th>Studies</th>
<th>Drug</th>
<th>Duration (months)</th>
<th>Population</th>
<th>Size (n patients)</th>
<th>Primary endpoint</th>
<th>Main result</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHARISMA</td>
<td>Clopidogrel</td>
<td>0 vs. 28</td>
<td>Documented or high-risk CV disease</td>
<td>15 603</td>
<td>CV death, MI, or stroke</td>
<td>Difference: NS</td>
</tr>
<tr>
<td>DES-late</td>
<td>Clopidogrel</td>
<td>12 vs. 24</td>
<td>PCI-Stent</td>
<td>5045</td>
<td>Death, MI, or stroke</td>
<td>Difference: NS</td>
</tr>
<tr>
<td>PRODIGY</td>
<td>Clopidogrel</td>
<td>6 vs. 24</td>
<td>PCI-Stent</td>
<td>1970</td>
<td>Death, MI, or cerebrovascular accidents</td>
<td>6 months non-inferior to 24 months</td>
</tr>
<tr>
<td>ARCTIC-interruption</td>
<td>Clopidogrel or prasugrel</td>
<td>12 vs. 24</td>
<td>PCI-Stent</td>
<td>1259</td>
<td>Death, MI, ST, stroke, or urgent revascularization</td>
<td>Difference: NS</td>
</tr>
<tr>
<td>DAPT</td>
<td>Clopidogrel or prasugrel</td>
<td>12 vs. 30</td>
<td>PCI-Stent</td>
<td>9961</td>
<td>Death, MI, or stroke, Stent thrombosis</td>
<td>30 months superior to 12 months for both primary endpoints</td>
</tr>
<tr>
<td>TRILOGY</td>
<td>Prasugrel (vs. clopidogrel)</td>
<td>17</td>
<td>NSTE-ACS</td>
<td>9326</td>
<td>CV death, MI, or stroke</td>
<td>Difference: NS</td>
</tr>
<tr>
<td>PEGASUS-TIMI 54</td>
<td>Ticagrelor 90 or 60 mg bid (vs. placebo)</td>
<td>33</td>
<td>STEMI or NSTEMI</td>
<td>21 162</td>
<td>CV death, MI, or stroke</td>
<td>Difference: $P = 0.008$ (90 mg dose) and $P = 0.004$ (60 mg dose)</td>
</tr>
<tr>
<td>TRACER</td>
<td>Vorapaxar (vs. placebo)</td>
<td>16</td>
<td>NSTE-ACS</td>
<td>12 944</td>
<td>CV death, MI, or stroke, recurrent ischaemia or urgent revascularization</td>
<td>Difference: NS</td>
</tr>
<tr>
<td>TRA-2P</td>
<td>Vorapaxar (vs. placebo)</td>
<td>30</td>
<td>Prior history of MI, ischemic stroke, or peripheral arterial disease</td>
<td>26 449</td>
<td>CV death, MI, or stroke</td>
<td>Difference: $P &lt; 0.001$</td>
</tr>
</tbody>
</table>

Montalescot, EHJ 2015
Long Term DAPT Duration, > 12 months

DAPT trial
Clopidogrel or Prasugrel, 9961 pts, 30 Months FU, 30% ACS)

<table>
<thead>
<tr>
<th>Major Adverse Cardiovascular and Cerebrovascular Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>12–30 mo Thienopyridine vs. placebo, 4.3% vs. 5.9%; hazard ratio, 0.71; P&lt;0.001</td>
</tr>
<tr>
<td>12–33 mo Thienopyridine vs. placebo, 5.6% vs. 6.5%; hazard ratio, 0.82; P=0.02</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stent Thrombosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>12–30 mo Thienopyridine vs. placebo, 0.4% vs. 1.4%; hazard ratio, 0.29; P&lt;0.001</td>
</tr>
<tr>
<td>12–33 mo Thienopyridine vs. placebo, 0.7% vs. 1.4%; hazard ratio, 0.45; P&lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Minor bleeding (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
</tr>
<tr>
<td>Thienopyridine</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Months since Enrollment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thienopyridine</td>
<td>5020 4917 4840 4778 4702 4611 4554 3029</td>
</tr>
<tr>
<td>Placebo</td>
<td>4941 4799 4715 4635 4542 4476 4412 2997</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Months since Enrollment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thienopyridine</td>
<td>5020 4934 4870 4828 4765 4686 4642 3110</td>
</tr>
<tr>
<td>Placebo</td>
<td>4941 4845 4775 4721 4651 4603 4556 3105</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Major Bleeding (%)</th>
<th>30 months</th>
<th>12 months</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

L. Mauri et al, NEJM 2014; 371: 2155-66
Long Term DAPT Duration, > 12 months

Pegasus trial
21,162 ACS patients, FU 33 months

CV events reduction, interesting profile of 60mg Ticagrelor

<table>
<thead>
<tr>
<th>End Point</th>
<th>Ticagrelor</th>
<th>Placebo</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular death, myocardial infarction, or stroke</td>
<td>7.85</td>
<td>9.04</td>
<td>0.85 (0.75–0.96)</td>
<td>0.008</td>
</tr>
<tr>
<td>Ticagrelor, 90 mg</td>
<td>7.77</td>
<td>9.04</td>
<td>0.84 (0.74–0.95)</td>
<td>0.004</td>
</tr>
<tr>
<td>Ticagrelor pooled</td>
<td>7.81</td>
<td>9.04</td>
<td>0.84 (0.76–0.94)</td>
<td>0.001</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>2.94</td>
<td>3.39</td>
<td>0.87 (0.71–1.06)</td>
<td>0.15</td>
</tr>
<tr>
<td>Ticagrelor, 90 mg</td>
<td>2.86</td>
<td>3.39</td>
<td>0.83 (0.68–1.01)</td>
<td>0.07</td>
</tr>
<tr>
<td>Ticagrelor pooled</td>
<td>2.90</td>
<td>3.39</td>
<td>0.85 (0.71–1.00)</td>
<td>0.06</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>7047</td>
<td>6979</td>
<td>0.81 (0.69–0.95)</td>
<td>0.01</td>
</tr>
<tr>
<td>Ticagrelor, 90 mg</td>
<td>7050</td>
<td>6973</td>
<td>0.84 (0.72–0.98)</td>
<td>0.03</td>
</tr>
<tr>
<td>Ticagrelor pooled</td>
<td>7045</td>
<td>6969</td>
<td>0.83 (0.72–0.95)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Bonaca et al, NEJM 2015, 372. 1791-99
HOW LONG, HOW SHORT: THE COMMON SENSE APPROACH

SAPT only
- No Q-wave
- No prior stent
- No prior CABG
- No coronary angio
- No CT scan
- Negative troponin
- High bleeding risk

3-month DAPT
- Documented obstructive CAD
- Recent/prior bleeding
- Scheduled surgery
- Oral anticoagulation needed

6–12 month DAPT
- Documented obstructive CAD
- Bleeding risk factors (age, gender, anaemia...)

> 12-month DAPT
- Documented obstructive CAD
- No excess bleeding risk
- No bleeding event during 1st year of DAPT

THE COMMON SENSE APPROACH

Montalescot, EHJ 2015
Tailored treatment or SAPT for everybody
GLOBAL LEADERS flowchart

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

Bivalirudin* - supported
BioMatrix Flex™ stent implantation
1:1 Randomization, Open-Label Design

Experimental Treatment Strategy
- ASA
  - 1 month
- Ticagrelor
  - 24 months

Reference Treatment Strategy
- ASA
  - 24 months
- Ticagrelor
  - 12 months
- Clopidogrel
  - only allowed in stable PTS
  - not allowed in stable PTS

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

Scientific Grants to ECRI: Biosensors, AstraZeneca and The Medicines Company

* In countries where available
TOWARD A TAILORED TREATMENT
Is there any room for a tailored treatment?

D. Aradi et al, Eur Heart J. 2015;36:1762-1771
Reality can be so complex that equally valid observations from differing perspectives can appear to be contradictory.
Thank you for your attention
Coronary Stenting and Atrial Fibrillation
How long

CENTRAL ILLUSTRATION  Decision-Making After the Mandatory DAPT Period

Drug-eluting coronary stent implantation

Mandatory period of DAPT

Comprehensive clinical evaluation

**UNFAVORABLE PROFILE**

Clinical considerations:
- Short life expectancy
- Poor socioeconomic status
- Poor expected DAPT adherence
- Poor mental status
- Malignancy
- End stage renal failure
- Smoker

**BLEEDING RISK OUTWEIGHS ISCHEMIC RISK**

Patient presentation:
- Clinically significant bleeding on DAPT
- Advanced age
- Female
- Liver disease
- Peptic ulcer disease
- Chronic oral nonsteroidal anti-inflammatory drug (NSAID) therapy
- Anemia and/or thrombocytopenia
- Uncontrolled hypertension
- Bleeding diathesis
- Prior major bleeding/prior hemorrhagic stroke
- Atrial fibrillation/chronic anticoagulation therapy
- High bleeding risk score

**ISCHEMIC RISK OUTWEIGHS BLEEDING RISK**

Patient presentation:
- Recurrent ischemic event on DAPT
- Stent-related complications
- Acute coronary syndrome
- Male
- Diabetes mellitus
- Left ventricular dysfunction
- Chronic kidney disease
- Peripheral vascular disease
- Prior ischemic stroke
- Clopidogrel nonresponsiveness
- Prior myocardial infarction
- Lesion complexity
- Incomplete stent apposition
- Stent undersizing/underexpansion
- Residual edge dissection
- Stent deployment in necrotic core
- Stent overlap

**STOP DAPT AFTER MANDATORY PERIOD**

**CONTINUE WITH DAPT**


When a mandatory period of DAPT is completed, a careful evaluation of the patient’s ischemic risk and bleeding risk, and of the overall clinical profile should be undertaken. DAPT = dual antiplatelet therapy; NSAID = nonsteroidal anti-inflammatory drug.
Long Term DAPT Duration, Pegasus trial
## How long: Long Term Duration (> 12 months)

### TABLE 5  Ongoing Studies Examining Abbreviated Duration of DAPT

<table>
<thead>
<tr>
<th>Study (Ref. #)</th>
<th>Design</th>
<th>Size</th>
<th>Active (Months)</th>
<th>Control (Months)</th>
<th>Population</th>
<th>Primary EP</th>
<th>Expected Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLOBAL LEADERS</td>
<td>RCT (Biomatrix stent)</td>
<td>16,000</td>
<td>1</td>
<td>12</td>
<td>DES</td>
<td>Composite of all-cause mortality or nonfatal new Q-wave MI up to 2 yrs post-randomization</td>
<td>June 2016</td>
</tr>
<tr>
<td>REDUCE</td>
<td>RCT (COMBO dual therapy stent)</td>
<td>1,500</td>
<td>3</td>
<td>12</td>
<td>ACS</td>
<td>Composite of all-cause mortality, MI, ST, stroke, or bleeding at 12 months</td>
<td>March 2017</td>
</tr>
<tr>
<td>SMART-CHOICE</td>
<td>RCT</td>
<td>5,100</td>
<td>3</td>
<td>12</td>
<td>DES</td>
<td>Composite of death, MI, cerebrovascular events, or bleeding over 3-12 months after the index procedure</td>
<td>February 2020</td>
</tr>
<tr>
<td>SMART-DATE</td>
<td>RCT</td>
<td>3,000</td>
<td>6</td>
<td>12</td>
<td>ACS</td>
<td>Composite of death, MI, CVA, ST, or major bleeding over 6-18 months post-hospitalization</td>
<td>August 2016</td>
</tr>
<tr>
<td>DAPT-STEMI</td>
<td>RCT</td>
<td>1,100</td>
<td>3</td>
<td>12</td>
<td>STEMI</td>
<td>Composite of death, MI, revascularization, CVA, or bleeding at 18 months post-randomization</td>
<td>December 2017</td>
</tr>
<tr>
<td>TWILIGHT</td>
<td>RCT</td>
<td>8,000</td>
<td>3</td>
<td>12</td>
<td>complex PCI with DES</td>
<td>Major bleeding at 15 months post-PCI</td>
<td>March 2017</td>
</tr>
</tbody>
</table>

CVA = cerebrovascular accident; DAPT-STEMI = Prospective, Randomized, Open Label Trial of 6 Months vs. 12 Months Dual Antiplatelet Therapy After Drug-Eluting Stent Implantation In ST-elevation Myocardial Infarction; GLOBAL LEADERS = Comparative Effectiveness of 1 Month of Ticagrelor Plus Aspirin Followed by Ticagrelor Monotherapy Versus a Current-day Intensive Dual Antiplatelet Therapy in All-comers Patients Undergoing Percutaneous Coronary Intervention With Bivalirudin and BioMatrix Family Drug-eluting Stent Use; REDUCE = Randomized Evaluation of Short-term Dual Anti Platelet Therapy in Patients With Acute Coronary Syndrome Treated With the COMBO Dual-therapy stEnt; SMART-CHOICE = Comparison Between P2Y12 Antagonist Monotherapy and Dual Antiplatelet Therapy in Patients Undergoing Implantation of Coronary Drug-Eluting Stents; SMART-DATE = Smart Angioplasty Research Team: Safety of 6-month Duration of Dual Antiplatelet Therapy After Percutaneous Coronary Intervention in Patients With Acute Coronary Syndromes; TWILIGHT = Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention; other abbreviations as in Tables 1 to 3.
OPEN QUESTIONS

Emergent
Thrombus burden +++
High mortality
STEMI

Urgent (6 – 48h)
Thrombus burden +(+)
Low mortality
NSTEMI

elective
No thrombus
SIHD

Preloading
How long > 12 months

+ DAPT

How short < 6 months
How long > 6 months
THANK YOU
for your attention
ROLE OF THE ANTITHROMBOTIC TREATMENT

R. Storey, Eur Heart J 2015;36:1714-1717

M. Roffi et al, NSTEMI ESC Guidelines 2015
The clinical context

Emergent

Urgent (6 – 48h)

Elective

STEMI (thrombus burden +++)

NSTEMI (thrombus burden ++)

SIHD (no thrombus)

High mortality

Low mortality

OPEN QUESTIONS ON DAPT

PRELOADING

HOW SHORT

HOW LONG > 12 MONTHS
OPEN QUESTIONS

Emergent

Thrombus burden
+++ 

High mortality

STEMI

OPEN QUESTIONS

Preloading

How long > 12 months

Urgent (6 – 48h)

Thrombus burden
+(+)

Low mortality

NSTEMI

OPEN QUESTIONS

DAPT

+ 

elective

No thrombus

SIHD

OPEN QUESTIONS

How short < 6 months

How long > 6 months
The common sense approach

Montalescot, EHJ 2015