Update on Dual Antiplatelet Therapy

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Disclosures

• None
Questions

• Which combination of DAPT?

• Optimal Duration of DAPT?

• Warfarin/NOAC Therapy?
Platelet inhibition represents the cornerstone of cardiovascular therapy...

[Diagram showing platelet inhibition with key components such as ADP, Aspirin, TXA₂, COX, P2Y12rec, and inhibitors like Clopidogrel bisulfate, Ticlopidine hydrochloride, Prasugrel hydrochloride, Ticagrelor, Gp 2b/3a Inhibitors, Dipyridamole, Collagen, Thrombin, TXA₂, and COX.]
<table>
<thead>
<tr>
<th></th>
<th>Acetylsalicylic acid (ASA)</th>
<th>Ticlopidine hydrochloride</th>
<th>Clopidogrel bisulfate</th>
<th>Prasugrel hydrochloride</th>
<th>Ticagrelor</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trade Name</strong></td>
<td>Aspirin(^1-3)</td>
<td>Ticlid®(^4)</td>
<td>Plavix®(^5)</td>
<td>Effient®(^6)</td>
<td>Brilinta®(^7)</td>
</tr>
<tr>
<td><strong>Class</strong></td>
<td>Salicylate</td>
<td>(\text{P}<em>2\text{Y}</em>{12}) Receptor Antagonist</td>
<td>(\text{P}<em>2\text{Y}</em>{12}) Receptor Antagonist</td>
<td>(\text{P}<em>2\text{Y}</em>{12}) Receptor Antagonist</td>
<td>(\text{P}<em>2\text{Y}</em>{12}) Receptor Antagonist</td>
</tr>
<tr>
<td><strong>Formulation</strong></td>
<td>Active Drug</td>
<td>Active Drug</td>
<td>Pro-Drug</td>
<td>Pro-Drug</td>
<td>Active Drug</td>
</tr>
<tr>
<td><strong>Maintenance Dose</strong></td>
<td>75-325 mg daily*</td>
<td>250 mg BID</td>
<td>75 mg daily</td>
<td>10 mg daily</td>
<td>90 mg BID</td>
</tr>
<tr>
<td><strong>Reversible</strong></td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Clopidogrel

PCI-CURE

- Placebo: % Death or MI over time
- Clopidogrel: % Death or MI over time
- P = 0.04
- P = 0.047

CREDO

- Placebo: % Death, MI, or stroke over time
- Clopidogrel: % Death, MI, or stroke over time
- P = NS
- P = 0.02

Follow-up (months)
Less Bleeding
Less Cost
Ischemia

Benefit
Risk
Why is DAPT so important?

- Protect the stented vascular segment from the development of stent thrombosis while vascular healing and progressive strut endotheliazation
  - in-hospital mortality rate of 5% to 10%
  - 30-day mortality rate of 10% to 25%

(JAMA. 2005;293:2126-2130)
Stent Implantation

- Endothelial Denudation
- Medial Dissection
- Exposure of sub-intimal components
- Thrombogenecity of metal

- Activation of platelets

- Reaction to stent struts (Macrophages and Giant Cells)

- Production of:
  - Cytokines
  - Mitogens
  - Chemotaxic factors

- Activation of vascular smooth muscle cells

- Proliferation and migration of vascular smooth muscle cells

- Restenosis
Stent thrombosis rates reduced with better technique and DAPT...

Independent Risk Factors for ST

- Clopidogrel stop <30 days
- Undersizing
- Clopidogrel stop 180-365 days
- Clopidogrel stop 30-180 days
- Malignancy
- CAD ≥50% proximal of culprit
- TIMI flow post-PCI <3
- Dissection
- Bifurcation stenting
- LVEF <30%
- PAD
- CAD ≥50% distal of culprit
- No ASA
- any DES
- DM
- Age (per 10 yrs)

HR 95%-CI  P-value
---------------------
36.53 [7.96-167.77] P<0.0001
13.39 [5.27-34.04] P<0.0001
5.87 [1.74-19.80] P=0.0043
4.63 [1.40-15.35] P=0.0122
4.50 [2.14-9.49] P<0.0001
4.40 [2.71-7.16] P<0.0001
3.77 [2.09-6.80] P<0.0001
2.88 [1.67-5.00] P=0.0002
2.27 [1.48-3.47] P=0.0002
2.27 [1.43-3.60] P=0.0005
2.13 [1.01-4.51] P=0.0492
1.98 [1.32-2.95] P=0.0009
1.91 [1.01-3.88] P=0.0487
1.88 [1.21-2.94] P=0.0052
1.66 [1.02-2.70] P=0.0432
0.80 [0.68-0.94] P=0.0072
Interindivual variability in platelet response to clopidogrel after stenting

Michelle O'Donoghue, and Stephen D. Wiviott Circulation. 2006;114:e600-e606
Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel (TRITON-TIMI 38)

13,608 patients with high-risk ACS scheduled for PCI randomized to clopidogrel (300 mg LD and 75 mg MD) or prasugrel (60 mg LD and 10 mg MD) for a median of 12 months

Prasugrel reduces ischemic events with a higher rate of bleeding

ACS=Acute coronary syndrome, ICH=Intracranial hemorrhage, LD=Loading dose, MD=Maintenance dose

Net Clinical Benefit
Bleeding Risk Subgroups

Prior Stroke / TIA

Age > 75

Wgt < 60 kg

Prasugrel

Clopidogrel

HR

Rel Risk

Prior Stroke / TIA: +37%
P_{int} = 0.006

Age > 75: -1%
P_{int} = 0.18

Wgt < 60 kg: +3%
P_{int} = 0.36

Prasugrel Better

Clopidogrel Better
PLATO: Primary Efficacy Endpoint

CV death, MI or stroke

N=18,624

Clopidogrel 11.7%
Ticagrelor 9.8%

p=0.0003

HR 0.84 (95% CI 0.77–0.92)

Wallentin L: NEJM 2009; 361:1045-57
Time to major bleeding – primary safety event

HR 1.04 (95% CI 0.95–1.13), p=0.434

Wallentin L: NEJM 2009; 361:1045-57
## Dyspnea

<table>
<thead>
<tr>
<th></th>
<th>Ticagrelor  (n=6,732)</th>
<th>Clopidogrel (n=6,676)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All patients</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Dyspnea, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any dyspnea event</td>
<td>15.4</td>
<td>10.4</td>
</tr>
<tr>
<td>Requiring discontinuation of study-treatment</td>
<td>0.9</td>
<td>0.3</td>
</tr>
</tbody>
</table>
## Specific P2Y12 Inhibitors: Recommendations

<table>
<thead>
<tr>
<th></th>
<th>Clopidogrel</th>
<th>Prasugrel</th>
<th>Ticagrelor</th>
<th>Cangrelor</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Route</strong></td>
<td>Oral</td>
<td>Oral</td>
<td>Oral</td>
<td>IV</td>
</tr>
<tr>
<td><strong>Onset</strong></td>
<td>120 – 360 min</td>
<td>60 min</td>
<td>30 min</td>
<td>2 min</td>
</tr>
<tr>
<td><strong>Offset</strong></td>
<td>5 days</td>
<td>7 days</td>
<td>5 days</td>
<td>60 min</td>
</tr>
<tr>
<td><strong>Reversible</strong></td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Platelet</strong></td>
<td>20 – 60%</td>
<td>60 – 80%</td>
<td>70 – 95%</td>
<td>95%</td>
</tr>
<tr>
<td><strong>Inhibition</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Dosing for PCI</strong></td>
<td>LD: 600 mg</td>
<td>LD 60 mg</td>
<td>LD 180 mg</td>
<td>LD 3 mcg/kg</td>
</tr>
<tr>
<td></td>
<td>MD 75 mg</td>
<td>MD 10 mg</td>
<td>MD 90 mg BID</td>
<td>MD 4 mcg/kg/min</td>
</tr>
<tr>
<td><strong>Dosing for Bridging</strong></td>
<td></td>
<td></td>
<td></td>
<td>LD none</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MD 0.75</td>
<td>MD 0.75 mcg/kg/min</td>
</tr>
</tbody>
</table>
Duration of therapy still unclear?

- **BMS Era**
  - **CURE (PCI-CURE)** 2001 (1 year)
  - AHA/ACC Guidelines 2001 (9-12 months post PCI)
  - TAXUS® Express² Stent Launch 2004

- **DES Era**
  - **Cypher Stent** Launch 2003
  - ESC PCI Updated Guidelines 2010 (6-12 months post PCI)
  - AHA/ACC/SCAI Updated Guidelines 2005 (TAXUS stent 6 months post PCI) (Cypher stent 3 months post PCI)
  - FDA, ACC/AHA/SCAI Recommendations 2011 (1 year post PCI in pts at low risk of bleeding)
No significant differences in all cause mortality between short term and 12 month dual antiplatelet therapy
Longer Duration: DAPT Trial

- 9961 patients
- international, multicenter, randomized, placebo-controlled trial


Myocardial infarction that was not related to stent thrombosis (P<0.001) accounted for 55% of the treatment benefit.
Long DAPT after drug-eluting stent reduced the risks of stent thrombosis and MACE and cerebrovascular events but...
Development and Validation of a Prediction Rule for Benefit and Harm of Dual Antiplatelet Therapy Beyond 1 Year After Percutaneous Coronary Intervention.

### Clinical Prediction Score

<table>
<thead>
<tr>
<th>Variable</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td></td>
</tr>
<tr>
<td>≥75</td>
<td>-2</td>
</tr>
<tr>
<td>65-&lt;75</td>
<td>-1</td>
</tr>
<tr>
<td>&lt;65</td>
<td>0</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>MI at presentation</td>
<td>1</td>
</tr>
<tr>
<td>Prior PCI or prior MI</td>
<td>1</td>
</tr>
<tr>
<td>Paclitaxel-eluting stent</td>
<td>1</td>
</tr>
<tr>
<td>Stent diameter &lt;3 mm</td>
<td>1</td>
</tr>
<tr>
<td>CHF or LVEF &lt;30%</td>
<td>2</td>
</tr>
<tr>
<td>Vein graft stent</td>
<td>2</td>
</tr>
</tbody>
</table>

Total score range: -2 to 10
Q1 = Score -2 to 0
Q2 = Score 1
Q3 = Score
Q4 = Score > 2

Risk Difference (Continued Thienopyridine – Placebo), 12-30M

Stent Thrombosis
- Q1: -0.07%
- Q2: -0.06%
- Q3: -1.34%
- Q4: -2.18%

Myocardial Infarction
- Q1: -0.73%
- Q2: 0.59%
- Q3: -2.56%
- Q4: -3.48%

GUSTO Moderate/Severe Bleeding
- Q1: 1.97%
- Q2: 1.17%
- Q3: 0.69%
- Q4: 0.03%
<table>
<thead>
<tr>
<th>Clinical condition</th>
<th>STEMI</th>
<th>NSTEMI</th>
<th>Stable CAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive approach</td>
<td>Emergency PCI (&lt;90 min)</td>
<td>Urgent PCI (24–48 h)</td>
<td>Elective PCI</td>
</tr>
<tr>
<td>Goal of DAPT</td>
<td>Lesion preparation</td>
<td>Lesion preparation</td>
<td>–</td>
</tr>
<tr>
<td>• Hours/Minutes before PCI (preloading)</td>
<td>Lesion preparation</td>
<td>Lesion preparation</td>
<td>–</td>
</tr>
<tr>
<td>• Months after PCI</td>
<td>Stent Protection (9–12 months)</td>
<td>Stent Protection (9–12 months)</td>
<td>Stent Protection (3–6 months)</td>
</tr>
<tr>
<td>• Years after PCI</td>
<td>Patient Protection (in selected cases)</td>
<td>Patient Protection (in selected cases)</td>
<td>Patient Protection (in selected cases)</td>
</tr>
</tbody>
</table>
Optimal DAPT duration after PCI differs according to clinical presentation
So how do we decide?
So how do we decide?

Circulation. 2016;133:000–000
What has really changed?