Dual Antiplatelet Therapy

Stephen Monroe, MD FACC
Chattanooga Heart Institute
Scope of Talk

- Identify the antiplatelet drugs and their mechanisms of action
- Review dual antiplatelet therapy in:
  - The medical management of stable cardiovascular disease
  - Acute coronary syndromes
  - After coronary stent implantation
    - Bare metal stenting
    - Drug eluting stenting
The Players

Aspirin
Aspirin
Acetylsalicylic Acid
C_9H_8O_4

Clopidogrel

Prasugrel

Ticagrelor
## Antiplatelet Therapy: Common Oral Agents

<table>
<thead>
<tr>
<th></th>
<th>Acetylsalicylic acid (ASA)</th>
<th>Clopidogrel bisulfate</th>
<th>Prasugrel hydrochloride</th>
<th>Ticagrelor</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trade Name</strong></td>
<td>Aspirin&lt;sup&gt;1-3&lt;/sup&gt;</td>
<td>Plavix®&lt;sup&gt;5&lt;/sup&gt;</td>
<td>Effient®&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Brilinta®&lt;sup&gt;7&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Class</strong></td>
<td>Salicylate</td>
<td><strong>P&lt;sub&gt;2&lt;/sub&gt;Y&lt;sub&gt;12&lt;/sub&gt; Receptor Antagonist</strong></td>
<td><strong>P&lt;sub&gt;2&lt;/sub&gt;Y&lt;sub&gt;12&lt;/sub&gt; Receptor Antagonist</strong></td>
<td><strong>P&lt;sub&gt;2&lt;/sub&gt;Y&lt;sub&gt;12&lt;/sub&gt; Receptor Antagonist</strong></td>
</tr>
<tr>
<td><strong>Formulation</strong></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>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>Yes</td>
</tr>
</tbody>
</table>

*81 mg is the low dose aspirin option in the United States

Sources:
Aspirin

- Irreversible inhibition of cyclooxygenase 1 (COX 1) preventing formation of thromboxane A₂ (inhibition for the life of the platelet)
Aspirin

- Measurable platelet inhibition in less than 60 minutes
- Plasma half life of 20 minutes
- Platelets cannot generate new COX
  - Duration is for the life of the platelet
- Platelet COX activity recovers by 10% per day via platelet turnover
- If as little as 20% of platelets have normal COX activity, hemostasis may be normal
  - A single dose of 100mg of aspirin abolishes the production of $\text{TXA}_2$
P2Y_{12}-receptor inhibitors: Clopidogrel

- Pro-drug
- Two step process in liver
- 85% hydrolyzed into inactive metabolite
- 600mg loading dose yields 40-60% ADP platelet inhibition in 2-6 hours
- Irreversible platelet inhibition
- Hold 5 days prior to surgery
P2Y$_{12}$-receptor inhibitors: Prasugrel

- Single step hepatic conversion
- 50% platelet inhibition within 1 hour of loading dose
- Irreversible platelet inhibition
- Hold 7 days prior to surgery
- Not indicated in age > 75
- Contraindicated with history of prior TIA or stroke
P2Y$_{12}$-receptor inhibitors: Ticagrelor

- Direct P2Y$_{12}$ antagonist
- Major metabolite is as active as drug
- Platelet inhibition within 1 hour of dosing
- Half life of 6-13 hours
- Reversible
- 3-5 days for normalization of platelet mediated hemostasis
- Hold 5 days prior to surgery
P2Y$_{12}$ Receptor Inhibitors
Medical management of stable cardiovascular disease

ASPIRIN AND CLOPIDOGREL
Aspirin and Clopidogrel

- CURE, a randomized trial of acute MI, showed that clopidogrel adds to the benefit of aspirin on CVD events but increased major bleeding.

- COMMIT/CCS-2, a randomized trial of acute coronary syndromes in China, showed that clopidogrel adds to the benefit of aspirin on CVD and total mortality without an increase in major bleeding.

- CHARISMA trial demonstrated no differences in the rates of MI, stroke, or death in 15,603 patients with multiple cardiovascular risk factors. Severe bleeding was similar; moderate bleeding increased in the clopidogrel arm.
Aspirin and Clopidogrel

CHARISMA: Dual Therapy Vs. ASA Monotherapy In Symptomatic* Patients
Meta-analysis: CURE, CREDO, CLARITY, COMMIT, and CHARISMA

- clopidogrel plus aspirin results in a small reduction in all-cause mortality in patients with prior ST-elevation myocardial infarction.

- clopidogrel plus aspirin results in a modest reduction in myocardial infarction and stroke in patients with cardiovascular disease.

- major bleeding is increased, however there is no excess of fatal bleeds or hemorrhagic strokes.
Aspirin and Ticagrelor

**Trial Schema**

- **Stable pts with history of MI 1-3 yrs prior + ≥1 additional atherothrombosis risk factor**
  - *Age ≥65 yrs, diabetes, 2nd prior MI, multivessel CAD, or chronic non-end stage renal dysfunction*

- **N ~ 21,000**

- **Randomize Double Blind**
  - **Ticagrelor**
    - 90 mg bid
  - **Ticagrelor**
    - 60 mg bid
  - **Placebo**

- **Follow-up Visits**
  - Q4 mos for 1st yr, then Q6 mos
  - Min 12 mos and median 26 mos follow-up
  - Event-driven trial

- **Primary Efficacy Endpoint:** CV Death, MI, or Stroke
- **Primary Safety Endpoint:** TIMI Major Bleeding
Primary Endpoint

N = 21,162
Median follow-up 33 months

CV Death, MI, or Stroke (%)

- Placebo (9.0%)
- Ticagrelor 90 (7.8%)
- Ticagrelor 60 (7.8%)

Ticagrelor 90 mg
HR 0.85 (95% CI 0.75 – 0.96)
P=0.008

Ticagrelor 60 mg
HR 0.84 (95% CI 0.74 – 0.95)
P=0.004

An Academic Research Organization of
Brigham and Women’s Hospital and Harvard Medical School
**Bleeding**

Ticagrelor 90 mg
Ticagrelor 60 mg
Placebo

P<0.001

P=NS

3-Year KM Event Rate (%)

TIMI Major
TIMI Minor
Fatal bleeding or ICH
ICH
Fatal Bleeding

2.6 2.3 1.1
1.3 1.2 0.4
0.6 0.7 0.6
0.6 0.5
0.1 0.3 0.3
# Other Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Ticagrelor 90 mg bid (N=6988)</th>
<th>Ticagrelor 60 mg bid (N=6958)</th>
<th>Placebo (N=6996)</th>
<th>Ticagrelor 90 vs Placebo p-value</th>
<th>Ticagrelor 60 vs Placebo p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-yr KM rate (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea AE</td>
<td>18.9</td>
<td>15.8</td>
<td>6.4</td>
<td>P&lt;0.001</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Leading to study drug d/c</td>
<td>6.5</td>
<td>4.6</td>
<td>0.8</td>
<td>P&lt;0.001</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Severe</td>
<td>1.2</td>
<td>0.6</td>
<td>0.2</td>
<td>P&lt;0.001</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Bradyarrhythmia</td>
<td>2.0</td>
<td>2.3</td>
<td>2.0</td>
<td>P=0.31</td>
<td>P=0.10</td>
</tr>
<tr>
<td>Gout</td>
<td>2.3</td>
<td>2.0</td>
<td>1.5</td>
<td>P&lt;0.001</td>
<td>P=0.01</td>
</tr>
</tbody>
</table>
Summary

- Adding ticagrelor to low-dose aspirin in stable patients with a history of MI reduced the risk of CV death, MI or stroke

- The benefit of ticagrelor was consistent
  - For both fatal & non-fatal components of primary endpoint
  - Over the duration of treatment
  - Among major clinical subgroups

- Ticagrelor increased the risk of TIMI major bleeding, but not fatal bleeding or ICH

- The two doses of ticagrelor had similar overall efficacy, but bleeding and other side effects tended to be less frequent with 60 mg bid dose
• ACC Guidelines

• In patients receiving a stent (BMS or DES) during PCI for ACS,

• P2Y12 inhibitor therapy should be given for at least 12 months.

• Options include clopidogrel 75 mg daily (570), prasugrel 10 mg daily (567), and ticagrelor 90 mg twice daily (568). (Level of Evidence: B)
▪ In patients receiving DES for a non-ACS indication, clopidogrel 75 mg daily should be given for at least 12 months if patients are not at high risk of bleeding. *(Level of Evidence: B)*

▪ In patients receiving BMS for a non-ACS indication, clopidogrel should be given for a minimum of 1 month and ideally up to 12 months (unless the patient is at increased risk of bleeding; then it should be given for a minimum of 2 weeks). *(Level of Evidence: B)*
Acute Coronary Syndromes
TRITON – TIMI 38

Protocol Design

ACS (STEMI or UA/NSTEMI) & Planned PCI

ASA → Double-blind

N = 13,000

PRASUGREL

CLOPIDOGREL

Median duration of therapy - 12 months

1° endpoint: CV death, MI, Stroke
2° endpoints: CV death, MI, Stroke, Re-ischemia, CV death, MI, UTVR
Balance of Efficacy and Safety

- CV Death/MI/Stroke:
  - Clopidogrel: 12.1 events, HR 0.81 (0.73-0.90), p=0.0004, NNT=46
  - Prasugrel: 9.9 events

- TIMI Major Non-CABG Bleeds:
  - Clopidogrel: 1.8 events, HR 1.32 (1.03-1.68), p=0.03, NNH=167
  - Prasugrel: 2.4 events

Net Clinical Benefit
Bleeding Risk Subgroups

Post-hoc analysis

<table>
<thead>
<tr>
<th>Prior Stroke / TIA</th>
<th>Risk (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>+ 54</td>
</tr>
<tr>
<td>No</td>
<td>-16</td>
</tr>
</tbody>
</table>

Risk Subgroups

- **Age**
  - >=75: P_{int} = 0.006, -1
  - < 75: P_{int} = 0.18, -16

- **Wgt**
  - < 60 kg: P_{int} = 0.36, -14
  - >= 60 kg: +3

Overall:

- P_{int} = 0.36, -13

Prasugrel versus clopidogrel for patients with unstable angina/non-ST-segment elevation myocardial infarction who are medically managed after angiographic triage.

Primary Efficacy Endpoint and TIMI Major Bleeding Through 30 Months
(Age < 75 years, N = 7243)

HR (95% CI): 0.91 (0.79, 1.05)  
P = 0.21

16.0% Primary Efficacy Endpoint
13.9%

1.31 (0.81, 2.11)  
P = 0.27

2.1% TIMI Major Bleeding
1.5%

dead from cardiovascular causes, myocardial infarction, or stroke
**Trilogy ACS**

### Primary Efficacy Endpoint to 30 Months (Age < 75 years)

#### Angio
- **N=3085**
- **10.7% vs 14.9%**
  - **P = 0.031**
  - **HR (95% CI): 0.77 (0.61, 0.98)**

#### No Angio
- **N=4158**
- **16.3% vs 16.7%**
  - **P = 0.954**
  - **HR (95% CI): 1.01 (0.84, 1.20)**

**P interaction = 0.08**
Overall, in the TRILOGY ACS Trial prasugrel did not reduce cardiovascular events among patients managed medically for ACS.

When treated with prasugrel compared to clopidogrel, patients triaged to medical therapy following angiography tended to have:

- lower rates of the combined endpoint of CVD/MI/CVA
- Lower rates of MI, CVA alone, and recurrent ischemic events
- higher rates of bleeding.
DAPT Study

Study Design

Randomization*

12-Month Observational Period:
Open-Label
Thienopyridine +
Aspirin Required

Thienopyridine + Aspirin

Placebo + Aspirin

3-Month Observational Period:
Off
Thienopyridine, On
Aspirin

Time in months after index stent procedure (not to scale)

Enrolled: Subjects treated with FDA-approved DES or BMS. Subjects on oral anticoagulant therapy or with life expectancy < 3 years excluded.

Randomized: Free from MI, stroke, repeat revascularization, and moderate or severe bleeding, and adherent with thienopyridine (80% to 120% of doses taken and no interruption > 14 days).

Mauri L, et al. AHA 2014
DAPT Study
DAPT Study

Co-primary Effectiveness End point

Cumulative Incidence of Death, Myocardial Infarction or Stroke

Months After Enrollment

Thienopyrodine
Placebo
Long-term dual antiplatelet therapy for secondary prevention of cardiovascular events in the subgroup of patients with previous myocardial infarction: a collaborative meta-analysis of randomized trials

European Heart Journal
Primary Endpoint – CV Death, MI, or Stroke

<table>
<thead>
<tr>
<th>Study</th>
<th>Events</th>
<th>Total</th>
<th>Events</th>
<th>Total</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHARISMA</td>
<td>125</td>
<td>1903</td>
<td>162</td>
<td>1943</td>
<td>0.77 (0.61 - 0.98)</td>
</tr>
<tr>
<td>PRODIGY</td>
<td>63</td>
<td>732</td>
<td>69</td>
<td>733</td>
<td>0.91 (0.65 - 1.28)</td>
</tr>
<tr>
<td>ARCTIC-Int’n</td>
<td>3</td>
<td>156</td>
<td>4</td>
<td>167</td>
<td>0.79 (0.18 - 3.51)</td>
</tr>
<tr>
<td>DAPT</td>
<td>59</td>
<td>1805</td>
<td>108</td>
<td>1771</td>
<td>0.52 (0.38 - 0.72)</td>
</tr>
<tr>
<td>DES-LATE</td>
<td>56</td>
<td>1512</td>
<td>66</td>
<td>1551</td>
<td>0.85 (0.60 - 1.21)</td>
</tr>
<tr>
<td>PEGASUS</td>
<td>980</td>
<td>14095</td>
<td>578</td>
<td>7067</td>
<td>0.84 (0.76 - 0.94)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>1286</td>
<td>20203</td>
<td>987</td>
<td>13232</td>
<td>0.78 (0.67 - 0.90)</td>
</tr>
</tbody>
</table>

P = 0.001

$Prima{ri}\nendopoi{t}–CV\ death,\ MI,\ or\ stroke$
### Major Bleeding

#### Extended DAPT vs Aspirin Alone

<table>
<thead>
<tr>
<th>Study</th>
<th>Events</th>
<th>Total</th>
<th>Events</th>
<th>Total</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHARISMA</td>
<td>45</td>
<td>1903</td>
<td>39</td>
<td>1943</td>
<td>1.17 (0.76 - 1.79)</td>
</tr>
<tr>
<td>PRODIGY</td>
<td>9</td>
<td>732</td>
<td>6</td>
<td>733</td>
<td>1.50 (0.53 - 4.20)</td>
</tr>
<tr>
<td>ARCTIC-Int’n</td>
<td>2</td>
<td>156</td>
<td>0</td>
<td>167</td>
<td>5.35 (0.26 - 110.6)</td>
</tr>
<tr>
<td>DAPT</td>
<td>34</td>
<td>1805</td>
<td>14</td>
<td>1771</td>
<td>2.38 (1.27 - 4.43)</td>
</tr>
<tr>
<td>DES-LATE</td>
<td>39</td>
<td>1512</td>
<td>31</td>
<td>1551</td>
<td>1.27 (0.79 - 2.03)</td>
</tr>
<tr>
<td>PEGASUS</td>
<td>242</td>
<td>13946</td>
<td>54</td>
<td>6996</td>
<td>2.50 (1.86 - 3.36)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>371</td>
<td>20054</td>
<td>144</td>
<td>13161</td>
<td>1.73 (1.19 - 2.50)</td>
</tr>
</tbody>
</table>

**P = 0.004**

---

Summary

- Compared with aspirin alone, extended DAPT >1 year among stabilized high-risk patients with previous MI:
  - Decreased the risk of MACE, MI, stroke alone & CV death alone
  - Increased risk of major bleeding, but not fatal bleeding or ICH
  - No excess of non-CV causes of death
- Effect of extended DAPT consistent irrespective of:
  - DAPT regimen, time from MI, ST-elevation, or PCI status
- Who were high-risk pts at low risk of bleeding that derived benefit from extended DAPT?
  - **High Risk:** ~1-3 years after an MI with additional CV risk factors
  - **Low Bleeding Risk:** Excluded patients with anticoagulation, recent bleeding, recent surgery, or any history of ICH
  - **Caution:** Very few patients studied had prior stroke/TIA

Final thoughts

▪ Patients with stable coronary artery disease (no ACS):
  ▪ Bare metal stent patients should receive DAPT for 1 month and up to 12 months if no secondary risks/contraindications
  ▪ DES stent patients should receive DAPT for 12 months

▪ All ACS patients should receive dual antiplatelet therapy for at least one year. This is irrespective of PCI or no PCI, bare metal stent or drug eluting stent.

▪ Continued DAPT therapy beyond one year is reasonable in patients:
  ▪ With low bleeding risk
  ▪ History of ischemic heart disease, especially those with prior MI
Answer: ‘but I walk the dog 30 minutes daily’