Prasugrel: Son of Clopidogrel or Distant Cousin?

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Disclosures

I have no actual or potential conflict of interest in relation to this presentation.

Objectives

1. Understand the apparent lower difference in interpatient variability in the inhibition of platelet aggregation with prasugrel versus clopidogrel.
2. Highlight the potential weaknesses in the Triton-TIMI 38 Trial.
History of Antiplatelet Medications

- Aspirin: August 10, 1897
  - First Chemically pure, commercially viable form of acetylsalicylic acid produced by Felix Hoffmann of Bayer Company
- Dipyridamole: 1959 by the Karl Thomae Company
- Ticlopidine (Ticlid®): FDA approved 1991
- Clopidogrel (Plavix®): FDA approved 1997
- Prasugrel (Effient®): FDA approved 2/2009

Prasugrel vs. Clopidogrel Commonalities

<table>
<thead>
<tr>
<th></th>
<th>Clopidogrel</th>
<th>Prasugrel</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral Thienopyridine</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Irreversible platelet P2Y12 receptor antagonist</td>
<td>Yes</td>
<td>Yes</td>
<td>Last for the lifetime of the platelet (5-10 days)</td>
</tr>
<tr>
<td>Prodrug</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>In vitro activity of active metabolites</td>
<td>Equal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In vivo metabolism by esterases</td>
<td>Yes</td>
<td>Yes</td>
<td>85% of an oral clopidogrel dose is converted to inactive metabolites</td>
</tr>
<tr>
<td>In vivo metabolism by Cytochrome P450 system</td>
<td>Yes</td>
<td>Yes</td>
<td>85% of an oral clopidogrel dose is converted to inactive metabolites</td>
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</table>

Platelet Activation

**Prasugrel vs. Clopidogrel**

**Differences**

<table>
<thead>
<tr>
<th></th>
<th>Clopidogrel</th>
<th>Prasugrel</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Equipotent Doses</strong></td>
<td>175mg-180mg</td>
<td>10mg</td>
</tr>
<tr>
<td><strong>Time to reach 20% IPA</strong></td>
<td>90 minutes (300mg dose)</td>
<td>30 minutes (60mg dose)</td>
</tr>
<tr>
<td><strong>Time to Peak Effect</strong></td>
<td>~ 4 hours</td>
<td>~ 1 hour</td>
</tr>
<tr>
<td><strong>In vivo metabolism by esterases</strong></td>
<td>85% of dose converted to inactive metabolite</td>
<td>Intermediate metabolite</td>
</tr>
<tr>
<td><strong>In vivo metabolism by Cytochrome P450 system</strong></td>
<td>CYPs: (1A2, 2B6, 2C19) Then (3A, 2B6, 2C9, 2C19)</td>
<td>Mainly CYP3A4/5 &amp; CYP2B6</td>
</tr>
</tbody>
</table>

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**Metabolic pathways of Prasugrel and Clopidogrel**

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**JUMBO–TIMI 26 Trial**

- Phase 2 dose-ranging, randomized, double-dummy, parallel group safety study
- Looked at bleeding complications & major adverse cardiac events (MACE)

*CS-747 = prasugrel* 
Circulation 2005;111:3366-3373
JUMBO-TIMI 26 Trial

<table>
<thead>
<tr>
<th>Event</th>
<th>Prasugrel, n (%)</th>
<th>Clopidogrel, n (%)</th>
<th>P</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-STEMI TIMI major-revent</td>
<td>11 (0.7)</td>
<td>10 (0.8)</td>
<td>0.900</td>
<td>1.43 (0.89-2.30)</td>
</tr>
<tr>
<td>Non-STEMI TIMI major</td>
<td>3 (0.2)</td>
<td>1 (0.6)</td>
<td>0.544</td>
<td>0.36 (0.10-1.24)</td>
</tr>
<tr>
<td>Non-STEMI TIMI major revented</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MACE</td>
<td>47 (3.2)</td>
<td>28 (2.6)</td>
<td>0.290</td>
<td>0.54 (0.34-0.87)</td>
</tr>
<tr>
<td>Death</td>
<td>1 (0.1)</td>
<td>0</td>
<td>0.270</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>3 (0.2)</td>
<td>0</td>
<td>0.270</td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>35 (2.3)</td>
<td>25 (2.4)</td>
<td>0.191</td>
<td>0.82 (0.48-1.39)</td>
</tr>
<tr>
<td>Recurrent ischemia</td>
<td>6 (0.4)</td>
<td>7 (0.5)</td>
<td>0.391</td>
<td>0.86 (0.46-1.61)</td>
</tr>
<tr>
<td>Severe ischemia</td>
<td>6 (0.4)</td>
<td>11 (1.0)</td>
<td>0.096</td>
<td>0.52 (0.23-1.19)</td>
</tr>
<tr>
<td>CVST</td>
<td>4 (0.3)</td>
<td>1 (0.1)</td>
<td>0.026</td>
<td>0.32 (0.07-1.46)</td>
</tr>
<tr>
<td>Death/MI</td>
<td>41 (2.7)</td>
<td>27 (2.5)</td>
<td>0.141</td>
<td>0.89 (0.48-1.65)</td>
</tr>
<tr>
<td>Death/CVST/CVD</td>
<td>41 (2.7)</td>
<td>29 (2.7)</td>
<td>0.181</td>
<td>0.89 (0.48-1.65)</td>
</tr>
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Circulation 2005;111:3366-3373

PRINCIPLE–TIMI 44 Trial

- Prasugrel vs. High-Dose Clopidogrel in Patients with Planned Percutaneous Coronary Intervention (PCI)
- Multi-center, randomized, double-blind, double dummy, active comparator controlled phase 2 study with a crossover design

Circulation 2007;116:2923-2932

PRINCIPLE–TIMI 44 Trial
End Points

- Pharmacodynamic
  - Loading phase: Inhibition of platelet aggregation (IPA) at 6 hours
  - Maintenance phase: IPA on days 14 & 29
- Clinical
  - Non CABG surgery related TIMI major or minor bleeds
  - MACE
    - Cardiovascular death, myocardial infarction, and stroke

Circulation 2007;116:2923-2932
PRINCIPLE–TIMI 44 Trial Results

Bleeding Events
- TIMI MAJOR
  - None
- Any bleeding event*
  - Prasugrel arm 19 subjects (18.6%)
  - Clopidogrel arm 14 subjects (14.1%)*

*P=NS

TRITON – TIMI 38 Trial

ACS (STEMI or UA/NSTEMI) and planned PCI

ASA

n = 13,608

Double-blind

Clopidogrel
300 mg LD/75 mg MD

Prasugrel
60 mg LD/10 mg MD

Duration of therapy: 6–15 months

1st endpoint: CV death, Nonfatal MI, Nonfatal Stroke
2nd endpoint: Stent thrombosis
Safety endpoints: Non-CABG TIMI major bleeding, life-threatening bleeding

Am Heart J 2008;152(4):627-35
TRITON – TIMI 38 Trial
Primary Efficacy End Point


TRITON – TIMI 38 Trial
Secondary End Point
Stent Thrombosis


TRITON – TIMI 38 Trial
Subgroups: Primary End Point
CV death, Nonfatal MI, Nonfatal Stroke

TRITON – TIMI 38 Trial
Region: Primary End Point
CV death, Nonfatal MI, Nonfatal Stroke

Cardiovascular and Renal Drugs Advisory Committee Briefing Document: Effient (Prasugrel)

TRITON-TIMI 38 Trial
Potential Pitfalls

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<tr>
<th>Non-Equivalent Doses</th>
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Time to reach 20% IPA
- 90 minutes (300mg dose)
- 30 minutes (60mg dose)

Time to Peak Effect
- ~ 4 hours (300mg)
- ~ 2 hours (60mg)
- ~ 1 hour

CYP450 genotypes:
- Reduced function CYP2C19 & CYP2C9
- Decreases active metabolite exposure
- No effect on pharmacokinetic or pharmacodynamic parameters


TRITON-TIMI 38 Trial
Potential Pitfalls
Timing of Loading Dose

Loading dose given after the PCI in 56% of patients

TRITON-TIMI 38 Trial
Potential Pitfalls

- “The efficacy benefit of prasugrel in the TRITON-TIMI 38 is driven by nonfatal myocardial infarction (with 475 events in the prasugrel group vs. 620 events in the clopidogrel group).”
- Each death from cardiovascular causes prevented by prasugrel is offset by an additional fatal bleed


Future Trial


Lansoprazole Interaction with Clopidogrel and Prasugrel

- Prasugrel
  - IPA unaffected
  - Increasing gastric Ph may decrease solubility slightly
- Clopidogrel
  - Cytochrome P450 2C19 inhibition may decrease active metabolite formation

### MACE rates by PPI: Concomitant Use With Clopidogrel

<table>
<thead>
<tr>
<th>PPI</th>
<th>MACE Rate (%)</th>
<th>Hazard Ratio</th>
<th>p value</th>
</tr>
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<tr>
<td>Omeprazole</td>
<td>25.1</td>
<td>1.39</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Esomeprazole</td>
<td>24.9</td>
<td>1.57</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Pantoprazole</td>
<td>29.2</td>
<td>1.61</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Lansoprazole</td>
<td>24.3</td>
<td>1.39</td>
<td>&lt;0.0004</td>
</tr>
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Questions?