Clopidogrel vs New Antiplatelet Therapy (Prasugrel)

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Seoul, April 30, 2010
Dual Antiplatelet Therapy for Stenting

In addition, drastic reduction in bleeding!!!
A Patient with Stent Thrombosis and Clopidogrel Resistance
A Patient with Stent Thrombosis and Clopidogrel Resistance

Stent Thrombosis Patient

Control Individual

Beckerath et al, Thromb Haemost 2005
A Patient with Stent Thrombosis and Failed Metabolization of Clopidogrel

A

Clopidogrel

B

Active Metabolite

Beckerath et al, Thromb Haemost 2005
Prasugrel
A New Alternative to Clopidogrel

Cardiovascular Death, MI, or Ischemic Stroke by CYP2C19 Genotype

A. Carriers of One or Two CYP2C19 Reduced-Function Alleles versus Non-Carriers

<table>
<thead>
<tr>
<th>Study</th>
<th>HR</th>
<th>Lower Limit</th>
<th>Upper Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLARITY-TIMI 28</td>
<td>1.556</td>
<td>0.614</td>
<td>3.943</td>
</tr>
<tr>
<td>EXCELSIOR</td>
<td>1.631</td>
<td>0.518</td>
<td>5.138</td>
</tr>
<tr>
<td>TRITON-TIMI 38</td>
<td>1.528</td>
<td>1.066</td>
<td>2.191</td>
</tr>
<tr>
<td>AFUJ</td>
<td>6.380</td>
<td>2.321</td>
<td>12.473</td>
</tr>
<tr>
<td>FAST-MI</td>
<td>0.790</td>
<td>0.569</td>
<td>1.056</td>
</tr>
<tr>
<td>RECLOE</td>
<td>2.320</td>
<td>1.120</td>
<td>4.806</td>
</tr>
<tr>
<td>ISAR</td>
<td>1.230</td>
<td>0.693</td>
<td>1.695</td>
</tr>
<tr>
<td>CLEAR-PLATELETS</td>
<td>3.946</td>
<td>1.112</td>
<td>14.022</td>
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<tr>
<td>INTIMOUNTAIN</td>
<td>1.290</td>
<td>0.966</td>
<td>1.723</td>
</tr>
</tbody>
</table>

Hazard Ratio and 95% CI

Overall HR 1.57
95% CI 1.13-2.15
P=0.006

Stent Thrombosis by CYP2C19 Genotype

A. Carriers of One or Two CYP2C19 Reduced-Function Alleles versus Non-Carriers

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<tr>
<td>EXCELSIOR</td>
<td>0.567</td>
<td>0.063</td>
<td>5.090</td>
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<tr>
<td>TRITON-TIMI 38</td>
<td>3.056</td>
<td>1.190</td>
<td>8.003</td>
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<tr>
<td>AFUJ</td>
<td>6.040</td>
<td>1.752</td>
<td>20.823</td>
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<tr>
<td>RECLOE</td>
<td>2.550</td>
<td>1.140</td>
<td>5.702</td>
</tr>
<tr>
<td>ISAR</td>
<td>2.450</td>
<td>1.081</td>
<td>5.664</td>
</tr>
<tr>
<td>CLEAR-PLATELETS</td>
<td>4.777</td>
<td>0.433</td>
<td>52.690</td>
</tr>
</tbody>
</table>

Hazard Ratio and 95% CI

Overall HR 2.81
95% CI 1.81-4.37
P<0.00001

Mega et al, AHA 2009
Prasugrel
A New Alternative to Clopidogrel

Schomig A. NEJM 2009
Prasugrel vs. Clopidogrel Platelet Inhibition

**Principle**

TIMI 44, Circ 2007

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**Prasugrel**

PRINCIPLE-TIMI 44, Circ 2007

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**Graph**

- **Y-axis**: IPA (%)
- **X-axis**: Hours (0-24)
- **Data Points**:
  - Prasugrel 60 mg:
    - 0 hours: 4.9
    - 4 hours: 20.3
    - 8 hours: 31.8
    - 24 hours: 69.3
  - Clopidogrel 600 mg:
    - 0 hours: 30.8
    - 4 hours: 64.5
    - 8 hours: 74.8
    - 24 hours: 32.5

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**Significance**

***P<0.0001**
Prasugrel vs. Clopidogrel
TRITON-TIMI 38

ACS (STEMI or UA/NSTEMI) & Planned PCI

ASA

13,608 patients

Double-blind

CLOPIDOGREL
300 mg LD/ 75 mg MD

PRASUGREL
60 mg LD/ 10 mg MD

Median duration of therapy - 12 months

1° endpoint: CV death, MI, Stroke
2° endpoints: CV death, MI, Stroke, Rehosp-Rec Isch
CV death, MI, UTVR
Stent Thrombosis (ARC definite/prob.)

Safety endpoints: TIMI major bleeds, Life-threatening bleeds

Key Substudies: Pharmacokinetic, Genomic
TRITON-TIMI 38 Primary Endpoint

Cardiovascular Death, Nonfatal Myocardial Infarction, Nonfatal Stroke

Primary Endpoint (%)

Intent To Treat = 13,608; Lost to Follow-Up = 14 (0.1%)

Days After Randomization

Clopidogrel

HR 0.77
(0.67 - 0.88)
p < 0.001

Prasugrel

HR 0.80
(0.71 - 0.90)
p < 0.001

HR 0.81
(0.73 - 0.90)
p < 0.001

NNT = 46

12.1
(781)

9.9
(643)
TRITON-TIMI 38
Primary Endpoint

Cardiovascular Death, Nonfatal Myocardial Infarction, Nonfatal Stroke

Days after Randomization

Primary Endpoint (%)

Prasugrel

Clopidogrel

Prasugrel

Clopidogrel

HR 0.82
(0.71 - 0.96)

p = 0.01

HR 0.80
(0.70 - 0.93)

p = 0.003
TRITON-TIMI 38
Periprocedural and Spontaneous MI

Peri-procedural MI (%)
- Clopidogrel 6.1%
- Prasugrel 4.8%
- 22% RRR
  p = 0.0009

Spontaneous MI (%)
- Clopidogrel 4.0%
- Prasugrel 2.9%
- 29% RRR
  p = 0.0004

Days from randomization

Morrow et al, Circ 2009
TRITON-TIMI 38
Early and Late MI

Morrow et al, Circ 2009

Clopidogrel 5.2
Prasugrel 4.3

HR = 0.81 (0.70-0.95)
P = 0.008

Clopidogrel 4.8
Prasugrel 3.4

HR = 0.69 (0.58-0.83)
P < 0.0001

Morrow et al, Circ 2009
TRITON-TIMI 38
Stent Thrombosis

Wiviott et al, Lancet 2008

HR 0.48 (0.36-0.64); P<0.0001

1 year: 1.06 vs. 2.15%
HR 0.48 (0.36-0.65); P<0.0001
TRITON-TIMI 38
Early and Late Stent Thrombosis

Wiviott et al, Lancet 2008
TRITON-TIMI 38
Safety Endpoint

TIMI Major Bleeding (%)

Prasugrel 2.4%
Clopidogrel 1.8%

HR 1.32
(1.03-1.68)
P=0.03

TRITON-TIMI 38, NEJM 2007
TRITON-TIMI 38
Safety Endpoint

Non—CABG TIMI Major Bleeding LTE 90

All Patients

Non—CABG TIMI Major Bleeding GT 90

All Patients
TRITON-TIMI 38
Net Clinical Benefit

Endpoint (%) vs Days

ITT= 13,608

Prasugrel

Clopidogrel

HR 0.87
CI 95%
0.79-0.95
P=0.004

109 events

13.9
12.2

Events per 1000 pts

MI

Major Bleed (non CABG)

P=0.004
### Table 4. The Balance of Efficacy and Safety in Selected Subgroups.*

<table>
<thead>
<tr>
<th>End Point</th>
<th>Prasugrel</th>
<th>Clopidogrel</th>
<th>Hazard Ratio for Prasugrel (95% CI)</th>
<th>P Value</th>
<th>P Value for Interaction†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt;75 yr, body weight ≥60 kg, and no history of stroke or TIA</td>
<td>433/5421 (8.3)</td>
<td>569/5383 (11.0)</td>
<td>0.74 (0.66–0.84)</td>
<td>&lt;0.001</td>
<td>0.008</td>
</tr>
<tr>
<td>Death from cardiovascular causes, nonfatal MI, or nonfatal stroke (primary efficacy end point)</td>
<td>91/5390 (2.0)</td>
<td>73/5337 (1.5)</td>
<td>1.24 (0.91–1.69)</td>
<td><em>0.17</em></td>
<td>0.64</td>
</tr>
<tr>
<td>Non–CABG-related TIMI major bleeding</td>
<td>522/5421 (10.2)</td>
<td>641/5383 (12.5)</td>
<td>0.80 (0.71–0.89)</td>
<td>&lt;0.001</td>
<td>0.006</td>
</tr>
</tbody>
</table>
TRITON-TIMI 38
STEMI Subset

All ACS/PCI patients
N=13,608

UA/NSTEMI patients
N=10,074

STEMI patients
N=3,534

Primary PCI
N=2,438 (69%)

Clopidogrel
N=1,235

Prasugrel
N=1,203

Secondary PCI
N=1,094 (31%)

Clopidogrel
N=530

Prasugrel
N=564

Montalescot et al, Lancet 2009
TRITON-TIMI 38
STEMI Subset

Primary endpoint: CV death, nonfatal MI, nonfatal stroke

- Clopidogrel
  - 9.5%
  - HR 0.68
    - (0.54-0.87)
    - P=0.002
  - RRR 21%
  - NNT 42

- Prasugrel
  - 6.5%
  - HR 0.79
    - (0.65-0.97)
    - P=0.02

Age adjusted HR 0.81 (0.66-0.99)

Montalescot et al, Lancet 2009
TRITON-TIMI 38
STEMI Subset

Stent thrombosis – ALL STEMI patients

Age adjusted HR = 0.59, CI 95% 0.37-0.96

RRR 42%
NNT = 83

HR 0.49
(0.28-0.84)
P=0.008

HR 0.58
(0.36-0.93)
P=0.02

Montalescot et al, Lancet 2009
Main safety endpoint (TIMI major non-CABG bleedings)

All STEMI patients

- Clopidogrel
- Prasugrel

HR 1.11 (0.70-1.77)  
P=0.65

Montalescot et al, Lancet 2009
TRITON-TIMI 38
Diabetic Subset

Primary endpoint: CV death, nonfatal MI, nonfatal stroke

Wiviott et al, Circ 2008
TRITON-TIMI 38 Diabetic Subset

Stent Thrombosis

Wiviott et al, Circ 2008
TRITON-TIMI 38
Diabetic Subset

TIMI Major Bleeding

Wiviott et al, Circ 2008
In the majority of patients with ACS undergoing PCI, prasugrel is a superior alternative to clopidogrel.

The role of prasugrel in patients with stable CAD undergoing PCI waits for evaluation.
Platelet Function Testing After Clopidogrel Hyporesponsiveness and Thrombosis

n=1608 pts

Cumulative incidence of definite ST (%)

Days after randomization

Cumulative incidence of death or definite ST (%)

Days after randomization

P<0.0001

Sibbing et al, JACC 2009
Successful PCI with DES without major complication and NO GPIIb/IIIa use

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Post-PCI VerifyNow P2Y12 Assay (PRU)

- **Non-Responder**: PRU > 208
  - **A**: N = 1075
    - "Prasugrel arm"
      - Prasugrel 60 mg LD
      - Prasugrel 10 mg MD
      + Clopidogrel placebo
  - **B**: N = 1075
    - "Clopidogrel arm"
      - Placebo LD
      - Clopidogrel 75 mg MD
      + Prasugrel placebo

- **Responder**: PRU ≤ 208
  - N = 2,150 → 33%
  - Non-interventional study (Registry)

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Clinical Follow-up and blinded VerifyNow Assessment at 90 days, 180 days

Primary Endpoint: 6 month CV Death and MI