Prasugrel (LY640315; CS-747) as an anti-thrombotic therapy in patients with acute coronary syndromes (ACS)

NDA 22-307
EFFIENT™ (prasugrel)
Prasugrel
Introduction and Overview

J. Anthony Ware, M.D.
Vice President Lilly Research Laboratories
Global Brand Development Platform Leader
Cardiovascular, Diabetes, and Acute Care
Eli Lilly and Company
Proposed Indication

Acute Coronary Syndromes (ACS)

EFFIENT (prasugrel) is indicated for the reduction of cardiovascular events in patients with ACS as follows

- Unstable angina (UA) or non-ST-segment elevation myocardial infarction (NSTEMI) when managed with percutaneous coronary intervention (PCI)
- ST-segment elevation myocardial infarction (STEMI) when managed with primary or delayed PCI

EFFIENT has been shown to reduce the rate of a combined endpoint of cardiovascular (CV) death, nonfatal myocardial infarction, or nonfatal stroke, and to prevent stent thrombosis
The TIMI Group and the Sponsors conducted a clinical testing program in response to needs expressed by the cardiovascular community.

- Extensive program
  - 13,608 patients in the pivotal clinical trial (TRITON-TIMI 38)
  - Nearly 9000 people have received at least 1 dose of prasugrel
Relevant to U.S. clinical practice: Nearly one third of the patients in TRITON-TIMI 38 were from the U.S.

Provides information important to practitioners
- Critically ill patients with an unmet need
- Head-to-head comparison with the standard of care
- Meaningful endpoints - cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, stent thrombosis
Prasugrel Clinical Development Program (3)

- The entire clinical program was developed in close consultation with the FDA, who concurred with the design and statistical analysis plan for TRITON-TIMI 38
- The database and adjudication procedures were of very high quality and we and our colleagues at TIMI are confident in their integrity
- The comprehensive efficacy, safety, and benefit-risk analyses of our extensive database are compelling and this application was granted a priority review by the FDA
Central Hypothesis of Prasugrel Research Program

♦ A new thienopyridine (prasugrel) with a faster, higher and more consistent (ie, with fewer poor responders) inhibition of platelet function will produce important clinical benefits for the ACS patient
## External Consultants

<table>
<thead>
<tr>
<th>Name</th>
<th>Title and Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eugene Braunwald, MD</td>
<td>Hersey Distinguished Professor of Theory and Practice of Medicine, Harvard Medical School Chair, TIMI Study Group, Brigham and Women's Hospital</td>
</tr>
<tr>
<td>Elliott M. Antman, MD</td>
<td>Professor of Medicine, Harvard Medical School Senior Investigator, TIMI Study Group Director of Samuel A. Levine Cardiac Unit, Brigham and Women’s Hospital</td>
</tr>
<tr>
<td>Jeffrey S. Barrett, PhD, FCP</td>
<td>Research Associate Professor, Pediatrics University of Pennsylvania, School of Medicine Director, Laboratory for Applied PK/PD, The Children’s Hospital of Philadelphia</td>
</tr>
<tr>
<td>Robert F. Ozols, MD, PhD</td>
<td>Senior Vice President Medical Science Division Fox Chase Cancer Center</td>
</tr>
<tr>
<td>Philip S. Schein, MD</td>
<td>Visiting Professor in Cancer Pharmacology Oxford University</td>
</tr>
<tr>
<td>Topic</td>
<td>Presenter</td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td>Unmet Medical Need</td>
<td>Eugene Braunwald, MD</td>
</tr>
<tr>
<td>Dosing Considerations</td>
<td>Jeffrey Riesmeyer, MD</td>
</tr>
<tr>
<td>Benefit-Risk (TRITON-TIMI 38)</td>
<td>Elliott M. Antman, MD</td>
</tr>
<tr>
<td>Special Topics</td>
<td>William Macias, MD, PhD</td>
</tr>
<tr>
<td>Closing Remarks</td>
<td>Eugene Braunwald, MD</td>
</tr>
</tbody>
</table>
Summary Points

1. A substantial unmet need exists in ACS patients because of shortcomings in current standard of care

2. Prasugrel is superior to clopidogrel in preventing cardiovascular events, including stent thrombosis

3. No credible evidence exists that prasugrel is carcinogenic or promotes the growth of tumors

4. The benefit-risk profile for prasugrel is favorable and we have developed a plan to effectively manage the risk of bleeding in the appropriate patients
Acute Coronary Syndromes: Unmet Medical Need

Eugene Braunwald, MD
Hersey Distinguished Professor of Theory and Practice of Medicine, Harvard Medical School Chairman, TIMI Study Group, Brigham and Women's Hospital
Hospitalizations in the US Due to ACS

Acute Coronary Syndromes*

1.57 Million Hospital Admissions - ACS

- UA/NSTEMI†
  - 1.24 million Admissions per year

- STEMI
  - 0.33 million Admissions per year

*Primary and secondary diagnoses.  †About 0.57 million NSTEMI and 0.67 million UA.

Evolution of ACS Therapies

Adapted from White HD et al. Lancet 2008; 372: 570–84

Aspirin
Heparin
Low molecular weight heparin
IIb/IIIa receptor antagonist
CLOPIDOGREL
Atorvastatin
Fondaparinux
Bivalirudin
Integrated strategy

Early invasive management

Year

3148.01

Adapted from White HD et al. Lancet 2008; 372: 570–84
Limitations of clopidogrel

- Modest antiplatelet effect with high interpatient variability
- Delayed onset of action
- In multiple small clinical studies, lesser pharmacologic response to clopidogrel may increase risk for myocardial infarction (MI) and coronary stent thrombosis
Variable and Unpredictable Response to Clopidogrel

24 hrs after 300 mg Clopidogrel
N = 96, Elective PCI

“Resistance” = 31%

Patients (%)

≤ -30 (-30,-20) (-20,-10) (-10,0) (0,10) (10,20) (20,30) (30,40) (40,50) (50,60) >60

Δ Platelet aggregation before and after Clopidogrel (%)

“Resistance” = ≤ 10% Δ platelet aggregation


2015.01
Clopidogrel Response Variability and Increased Risk of Ischemic Events
Primary PCI for STEMI (N = 60)

Clinical Relevance
of Clopidogrel Response Variability
Post-Stent Ischemic Events and Periprocedural Infarction

<table>
<thead>
<tr>
<th>N</th>
<th>Functional Parameter</th>
<th>Clinical Relevance</th>
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<tbody>
<tr>
<td>60</td>
<td>↑ platelet aggregation (4th quartile)</td>
<td>Post-primary PCI ischemic events (6 months)</td>
</tr>
<tr>
<td>192</td>
<td>↑ periprocedural platelet aggregation</td>
<td>Post-PCI ischemic events (6 months)</td>
</tr>
<tr>
<td>120</td>
<td>↑ periprocedural platelet aggregation</td>
<td>Myonecrosis and inflammation marker release</td>
</tr>
<tr>
<td>106</td>
<td>↑ platelet aggregation</td>
<td>Post-PCI ischemic events (30 days)</td>
</tr>
<tr>
<td>150</td>
<td>↑ clopidogrel/aspirin-resistant patients</td>
<td>Post PCI-myonecrosis</td>
</tr>
<tr>
<td>292</td>
<td>↑ platelet aggregation</td>
<td>Post-PCI ischemic events (30 days)</td>
</tr>
<tr>
<td>802</td>
<td>↑ platelet aggregation (3rd &amp; 4th quartiles)</td>
<td>Post-PCI ischemic events (30 days)</td>
</tr>
<tr>
<td>379</td>
<td>↓ platelet inhibition</td>
<td>Post-PCI ischemic events (3 months)</td>
</tr>
<tr>
<td>100</td>
<td>↑ platelet aggregation</td>
<td>Post-PCI ischemic events (12 months)</td>
</tr>
</tbody>
</table>

Matezky et al. Circulation 2004
Gurbel et al. JACC 2005
Gurbel et al. Circulation 2005
Lev et al. JACC 2006
Cuisset et al. JACC 2006
Hocholzer et al. JACC 2006
Geisler et al. Eur Heart J 2006
Bliden et al. JACC 2007

Angiolillo DJ et al. 2007.
## Recent Trials Reporting Clinical Outcomes at 1 Yr for Patients with ACS Undergoing PCI

<table>
<thead>
<tr>
<th>Study</th>
<th>Total N</th>
<th>D/MI/TVR</th>
<th>Death</th>
<th>MI</th>
<th>TVR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACUITY</strong>*</td>
<td>7789a</td>
<td>1465(18.8)</td>
<td>247 (3.2)</td>
<td>682 (8.8)</td>
<td>928(11.9)b</td>
</tr>
<tr>
<td><strong>ISAR-REACT 2</strong>*</td>
<td>2022</td>
<td>515(25.5)</td>
<td>94 (4.6)</td>
<td>202 (10.0)</td>
<td>301(14.9)c</td>
</tr>
</tbody>
</table>

* Clopidogrel plus ASA  
  a Subset of patients in the ACUITY trial who underwent PCI  
  b Unplanned revascularization for ischemia.  
  c Target vessel revascularization = CABG or repeat PCI for symptoms or ischemia.

White HD et al. *JACC* 2008; 52: 807-814  
Continued Ischemic Events

ACS Managed with PCI

*Dual Antiplatelet Therapy*

High Risk Clinical Features

Genetic Polymorphisms Drug-Drug Interactions

Continued Ischemic Events
Evolution of ACS Therapies

Adapted from White HD et al. Lancet 2008; 372: 570–84
Clinical Pharmacology and Dose Selection

Jeffrey S. Riesmeyer, MD
Medical Fellow I
Prasugrel Product Team
Eli Lilly and Company
Metabolism is a Key Difference Between Prasugrel and Clopidogrel

- Prodrugs - metabolized *in vivo* to active metabolites
- Irreversibly bind to the platelet \( P2Y_{12} \) receptor
  - Inhibit ADP-induced platelet activation and aggregation
  - Inhibition persists for the life of the platelet
- *In vitro*, at equimolar concentrations, active metabolites show similar levels of platelet inhibition
- Prasugrel has a more efficient metabolic pathway compared to clopidogrel
More Efficient and Less Variable Activation of Prasugrel Compared to Clopidogrel

Clopidogrel

- Inactive Metabolite (85%)
- CYP1A2, 2B6, 2C19
- Intermediate
- Active Metabolite
- CYP3A, 2B6, 2C9, 2C19

CYP2C19 variants and inhibitors affect the PK and PD of clopidogrel

Prasugrel

- Active Metabolite
- CYP1A2, 2B6, 2C19

CYP3A, 2B6, 2C9, 2C19

Intermediate

Gut hCE2

Prasugrel has no clinically relevant interactions with CYP2C19 variants or inhibitors

Gut and Liver
Higher Active Metabolite Concentrations of Prasugrel After Loading Dose

- $C_{\text{max}}$ and $T_{\text{max}}$ influence onset of platelet inhibition
  - Relevant for loading dose but not maintenance dose
- AUC influences extent of platelet inhibition
  - Relevant for loading and maintenance dose
Prasugrel 60 mg LD Achieves More Effective Platelet Inhibition than Clopidogrel

*; p < 0.001 vs. clop 300 mg/75 mg 600 mg/75 mg;
†; p < 0.05 vs. clop 300 mg/75 mg;
‡; p < 0.001 vs. clop 300 mg/75 mg
Prasugrel 60 mg LD with 10 mg MD Demonstrates Superior Response Compared to Clopidogrel

Jernberg et al., Eur Heart J 2006; 27:1166-1173
Predictable Relationship between Prasugrel Active Metabolite PK and PD

AUC (μM*hour)

MPA (%)

5-mg

10-mg

15-mg

Prasugrel 90% MD Prediction Interval

3134.01
Summary of Prasugrel Clinical Pharmacology

- Prasugrel metabolism more efficient and less variable compared to clopidogrel
- Prasugrel 60 mg LD more effective platelet inhibition than clopidogrel
- Prasugrel 10 mg MD superior PD response rate compared to clopidogrel
- Predictable PK/PD relationship allows targeted PK
- No clinically relevant impact of
  - Drug-drug interactions
  - CYP genetic variants
TRITON-TIMI 38

Dr. Elliott Antman
Professor of Medicine, Harvard Medical School,
Senior Investigator, TIMI Study Group,
Director of Samuel A. Levine Cardiac Unit
Brigham and Women's Hospital, Boston, MA
TRITON-TIMI 38 Study Design

ACS (STEMI or UA/NSTEMI) & Planned PCI

ASA ↓ N = 13,608
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
Balance of Efficacy and Safety: All ACS

Wiviott SD et al. NEJM 2007; 357: 2001-2015

CV death / MI / stroke

- Prasugrel: 9.9% (HR 0.81, 0.73 - 0.90, P = 0.0004, NNT = 46)
- Clopidogrel: 12.1% (HR 1.32, 1.03 - 1.68, P = 0.03)

TIMI major Non-CABG bleeds

- Prasugrel: 2.4% (HR 1.32, 1.03 - 1.68, P = 0.03)
- Clopidogrel: 1.8% (HR 0.81, 0.73 - 0.90, P = 0.0004, NNH = 167)

Total events

- Prasugrel: 138 events
- Clopidogrel: 35 events
### TRITON Endpoint Testing

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>UA/NSTEMI</th>
<th>All ACS</th>
<th>STEMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVD / MI / stroke 30 days</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>CVD / MI / stroke 90 days</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>CVD / MI / UTVR 30 days</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>CVD / MI / UTVR 90 days</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>All cause death / MI / stroke at study end</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>CVD / MI / rehospitalization for CIE at study end</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Definite or probable stent thrombosis at study end</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

* p-values ranged from 0.023 to 0.0000003
Timing of Benefit (Prospectively Defined) Landmark Analysis - 3 days

- **Prasugrel**
  - Loading Dose: HR 0.83 (95% CI, 0.71 - 0.96) P = 0.01
  - Maintenance Dose: HR 0.80 (95% CI, 0.70 - 0.93) P = 0.003

- **Clopidogrel**
  - Primary Endpoint (%): 5.6% (3 days)

Recurrence of Primary Composite Endpoint

Hazard ratio: 0.65 (95% CI 0.46 - 0.92)  
P = 0.016

CV Death, Nonfatal MI, or Nonfatal Stroke (%)

Days From 1st Event to 2nd Event or Last Follow-up

墨U S et al. EHU 2008; 29: 2473-2479
Total Primary Endpoint Events Prevented With Prasugrel

- 1st event:
  - Clopidogrel: 781
  - Prasugrel: 643
  - P = 0.0004

- Additional events:
  - Clopidogrel: 896 - 781 = 115
  - Prasugrel: 701 - 643 = 58

- Total events:
  - Clopidogrel: 781 + 115 = 896
  - Prasugrel: 643 + 58 = 701

P < 0.001

Murphy SA et al. *EHJ* 2008; 29: 2473-2479
Components of Endpoints

<table>
<thead>
<tr>
<th>Event</th>
<th>Pras (%)</th>
<th>Clop (%)</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death, MI, stroke</td>
<td>9.9</td>
<td>12.1</td>
<td>0.81</td>
</tr>
<tr>
<td>CV death</td>
<td>2.1</td>
<td>2.4</td>
<td>0.89</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>7.3</td>
<td>9.5</td>
<td>0.76</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>1.0</td>
<td>1.0</td>
<td>1.02</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>3.0</td>
<td>3.2</td>
<td>0.95</td>
</tr>
<tr>
<td>uTVR</td>
<td>2.5</td>
<td>3.7</td>
<td>0.66</td>
</tr>
<tr>
<td>Stent thrombosis</td>
<td>1.1</td>
<td>2.4</td>
<td>0.48</td>
</tr>
</tbody>
</table>

Process for Adjudication of MI

Investigator Reported MI Endpoint
HR 0.67 (0.55-0.82) P<0.001

Triggers for Biomarker Elevations

CEC Blinded Adjudication MI

HR 0.76 (0.67 - 0.85)
P < 0.0001
Myocardial Infarction (0 - 450 days)*

- Clopidogrel: 9.7%
- Prasugrel: 7.4%

HR 0.76 (95% CI, 0.67 - 0.85)  
P < 0.0001

*Fatal and nonfatal MIs

Myocardial Infarction* Landmark Analysis - 3 Days

Prasugrel 4.3%
Clopidogrel 5.2%

Loading Dose

Prasugrel 3.4%
Clopidogrel 4.8%

Maintenance Dose

HR 0.81
(95% CI, 0.70 - 0.95)
P = 0.008

HR 0.69
(95% CI, 0.58 - 0.83)
P < 0.0001

*Fatal and nonfatal MIs

Antman et al. JACC 2008; 51(S21):2028-2033.
Efficacy Analysis (Universal MI Classification)

- HRR: 29% ↓, 18% ↓, 24% ↓
- p-value: 0.0015, 0.53, < 0.0001

Cumulative Incidence (%)

- Clopidogrel
- Prasugrel

- Type 1 Spont.: 3.4% Clopidogrel, 2.5% Prasugrel
- Type 2 Secondary: 0.4% Clopidogrel, 0.3% Prasugrel
- Type 3 SCD: 0%
- Type 4a Peri-PCI: 4.7% Clopidogrel, 4.0% Prasugrel
- Type 4b Stent Thrombosis: 1.7% Clopidogrel, 0.7% Prasugrel
- Type 5 Peri-CABG: 0% Clopidogrel, 0.1% Prasugrel

## Efficacy Analysis Peak Biomarker

### MI size using ESC / ACC / AHA / WHF categorization

<table>
<thead>
<tr>
<th>HRR</th>
<th>24% ↓</th>
<th>22% ↓</th>
<th>15% ↓</th>
<th>27% ↓</th>
<th>26% ↓</th>
</tr>
</thead>
<tbody>
<tr>
<td>p-value</td>
<td>0.17</td>
<td>0.33</td>
<td>0.20</td>
<td>0.0077</td>
<td>0.0019</td>
</tr>
</tbody>
</table>

- **Clopidogrel n = 6795**
  - 1 - < 2×ULN: 0.9%
  - 2 - < 3×ULN: 0.7%
  - 3 - < 5×ULN: 0.6%
  - 5 - < 10×ULN: 1.8%
  - ≥ 10×ULN: 1.4%

- **Prasugrel n = 6813**
  - 1 - < 2×ULN: 0.9%
  - 2 - < 3×ULN: 0.7%
  - 3 - < 5×ULN: 0.5%
  - 5 - < 10×ULN: 2.8%
  - ≥ 10×ULN: 2.1%

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# Impact of Prasugrel on MI

Significant reductions in:

<table>
<thead>
<tr>
<th>Type of MI</th>
<th>Spontaneous</th>
<th>Peri-procedural</th>
<th>Stent thrombosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of MIs</td>
<td>24% decrease, $P &lt; 0.0001$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large MIs ($\geq 5 \times$ ULN)</td>
<td>26% decrease, $P = 0.0001$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CV death after MI</td>
<td>42% decrease, $P = 0.02$</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Mortality Following Stent Thrombosis*

<table>
<thead>
<tr>
<th></th>
<th>% Mortality</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stent thrombosis</td>
<td>25.9%</td>
<td>210</td>
</tr>
<tr>
<td>No stent thrombosis</td>
<td>2.6%</td>
<td>12,634</td>
</tr>
</tbody>
</table>

HR 13.1
(95% CI 9.8 - 17.5)
P < 0.0001

* ARC Definite + Probable

Wiviott SD et al SCAI-ACCi2 2008
CEC Adjudicated Stent Thrombosis: Definite/Probable

**DES Only (N = 5743)**
- HR 0.36 [0.22 - 0.58], P < 0.0001
- 1 yr: 0.74% vs 2.05%
  - HR 0.35 [0.21 - 0.58], P < 0.0001

**BMS Only (N = 6461)**
- HR 0.52 [0.35 - 0.77], P = 0.0009
- 1 yr: 1.22 vs 2.27%
  - HR 0.53 [0.36 - 0.79], P = 0.0014

Significant reductions in early and late stent thromboses

## Stent Thrombosis in Subgroups*

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Pras (%)</th>
<th>Clop (%)</th>
<th>Risk reduction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>STEMI</td>
<td>1.5</td>
<td>2.8</td>
<td>42</td>
</tr>
<tr>
<td>UA/NSTEMI</td>
<td>1.0</td>
<td>2.2</td>
<td>57</td>
</tr>
<tr>
<td>Stent &gt; 20 mm</td>
<td>1.4</td>
<td>2.9</td>
<td>53</td>
</tr>
<tr>
<td>Stent ≤ 20mm</td>
<td>0.9</td>
<td>1.9</td>
<td>52</td>
</tr>
<tr>
<td>No bifurcation stent</td>
<td>1.1</td>
<td>2.2</td>
<td>50</td>
</tr>
<tr>
<td>Bifurcation stent</td>
<td>1.4</td>
<td>4.5</td>
<td>69</td>
</tr>
<tr>
<td>CrCl ≥ 60 ml/min</td>
<td>1.1</td>
<td>2.1</td>
<td>51</td>
</tr>
<tr>
<td>CrCl &lt; 60 ml/min</td>
<td>1.1</td>
<td>3.9</td>
<td>70</td>
</tr>
<tr>
<td>No previous MI</td>
<td>1.2</td>
<td>2.1</td>
<td>45</td>
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<tr>
<td>Previous MI</td>
<td>0.8</td>
<td>3.4</td>
<td>75</td>
</tr>
<tr>
<td>No GP IIb/IIIa Inhib. used</td>
<td>0.9</td>
<td>2.0</td>
<td>54</td>
</tr>
<tr>
<td>GP IIb/IIIa Inhibitor used</td>
<td>1.3</td>
<td>2.5</td>
<td>51</td>
</tr>
<tr>
<td>No diabetes mellitus</td>
<td>0.9</td>
<td>2.0</td>
<td>55</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2.0</td>
<td>3.5</td>
<td>48</td>
</tr>
<tr>
<td>Age &lt; 75 yrs</td>
<td>1.0</td>
<td>2.2</td>
<td>54</td>
</tr>
<tr>
<td>Age ≥ 75 yrs</td>
<td>1.8</td>
<td>3.4</td>
<td>44</td>
</tr>
<tr>
<td>Women</td>
<td>0.9</td>
<td>2.3</td>
<td>61</td>
</tr>
<tr>
<td>Men</td>
<td>1.2</td>
<td>2.4</td>
<td>50</td>
</tr>
</tbody>
</table>

* No significant interaction between treatment and subgroup except previous MI (p = 0.047)
Impact of Prasugrel on Stent Thrombosis

Process
Pre-specified
Discussed with FDA
Blinded CEC (unbiased)

Results
Substantial reductions (approximately 50%)
Robust: definitions, patient types, stent types, subgroups

Implications
Benefit of long-term treatment with prasugrel
Critically important information for clinicians
**Diabetic Subgroup - (N=3146)**

- **CV death / MI / stroke**
  - Prasugrel: 12.2% (HR 0.70, P < 0.001, NNT = 21)
  - Clopidogrel: 17.0%

- **TIMI major non-CABG bleeds**
  - Prasugrel: 2.5%
  - Clopidogrel: 2.6%

Wiviott SD et al. *Circulation* 2008; 118: 1626-1636
STEMI Cohort (N= 3534)

- **CV death / MI / stroke**
  - Clopidogrel: 12.4%
  - Prasugrel: 10.0%
  - HR 0.79 (0.65 - 0.97)
  - P = 0.02
  - NNT = 42

- **TIMI major**
  - Non-CABG bleeds
  - Clopidogrel: 2.1%
  - Prasugrel: 2.4%

Bleeding Events Safety Cohort

- **ARD 0.6%**
  - **HR 1.32**
  - **P = 0.03**
  - **NNH = 167**

- **ARD 0.5%**
  - **HR 1.52**
  - **P = 0.01**

- **ARD 0.2%**
  - **P = 0.23**

- **ARD 0%**
  - **P = 0.74**

ICH in Pts w Prior Stroke/TIA (N = 518)
- **Clop 0 (0) %**
- **Pras 6 (2.3)%**
  - **P = 0.02**

Wiviott SD et al. NEJM 2007; 357: 2001-2015
Types of Major Bleeds

- **Instrumented Spontaneous Trauma**
  - Clopidogrel: 0.6%
  - Prasugrel: 0.7%
  - ARD 0.2%
  - P = 0.45

- **Spontaneous**
  - ARD 0.5%
  - P = 0.01
  - Clopidogrel: 1.1%
  - Prasugrel: 1.6%

- **Trauma**
  - ARD 0%
  - P = 0.51
  - Clopidogrel: 0.2%
  - Prasugrel: 0.2%

CABG Surgery and TIMI Major Bleeding–Days from Last Dose of Study Drug (All ACS)
Non-CABG TIMI Major Bleeding Through 3 Days With GPIIib/IIa Use* - All ACS

- Clopidogrel: 0.84%
- Prasugrel: 0.88%

* Any GPIIib/IIa use from symptom onset through 3 days after randomization
Net Benefit Endpoints in TRITON-TIMI 38

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Pras (%)</th>
<th>Clop (%)</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>D / MI / CVA / major bleed</td>
<td>12.2</td>
<td>13.9</td>
<td>0.87</td>
</tr>
<tr>
<td>D/MI/CVA</td>
<td>10.7</td>
<td>12.7</td>
<td>0.83</td>
</tr>
<tr>
<td>D / MI / CVA / transfusion</td>
<td>13.5</td>
<td>14.8</td>
<td>0.90</td>
</tr>
<tr>
<td>D / MI / CVA / major / minor bleed</td>
<td>14.0</td>
<td>15.2</td>
<td>0.91</td>
</tr>
</tbody>
</table>

0.5 Favors Prasugrel 1 HR Favors Clopidogrel 2
Net Clinical Benefit – Death, MI, Stroke, TIMI Major Bleeding

HR 0.87  P = 0.004

Clopidogrel  13.9%

Prasugrel  12.2%

ITT = 13,608

Wiviott SD et al. NEJM 2007; 357: 2001-2015
### Events Per 1000 Patients - All ACS

<table>
<thead>
<tr>
<th></th>
<th>CV Death</th>
<th>Nonfatal MI</th>
<th>Nonfatal Ischemic</th>
<th>Non-CABG Fatal Bleed</th>
<th>Non-CABG TIMI Major</th>
<th>Non-CABG TIMI Minor</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Events</td>
<td>-4</td>
<td>-22</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The chart shows the events per 1000 patients for different categories. The categories include CV Death, Nonfatal MI, Nonfatal Ischemic, Non-CABG Fatal Bleed, Non-CABG TIMI Major, and Non-CABG TIMI Minor. The chart indicates a decrease of 22 events per 1000 patients.
Net Clinical Benefit in Subgroups: Death / MI / CVA / Major Bleed

Post-Hoc Analysis

<table>
<thead>
<tr>
<th>Prior TIA / stroke</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 75 yrs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 75 yrs</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Weight</th>
<th>&lt; 60 kg</th>
<th>≥ 60 kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>Favors Prasugrel</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>Favors Clopidogrel</td>
<td>1</td>
</tr>
</tbody>
</table>

Risk (%)

- Prior TIA / stroke:
  - Yes: +54, P_{int} = 0.006
  - No: -16, P_{int} = 0.18

- Age:
  - ≥ 75 yrs: -1
  - < 75 yrs: -16

- Weight:
  - < 60 kg: +3
  - ≥ 60 kg: -14

Overall: -13

Non-CABG TIMI Major Bleeding (After 3 days) for Prasugrel Group

Impact of Weight and Age

<table>
<thead>
<tr>
<th>Age</th>
<th>Weight</th>
<th>Non-CABG TIMI Major Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 75 Yrs</td>
<td>≥ 60 kg</td>
<td>2.28</td>
</tr>
<tr>
<td>&lt; 75 Yrs</td>
<td>&lt; 60 kg</td>
<td>1.21</td>
</tr>
<tr>
<td>≥ 75 Yrs</td>
<td>≥ 60 kg</td>
<td>4.82</td>
</tr>
<tr>
<td>&lt; 75 Yrs</td>
<td>&lt; 60 kg</td>
<td>3.62</td>
</tr>
</tbody>
</table>

%
Influence of Age and Diabetes on Efficacy

- **Diabetes**
  - Primary EP: HR 0.70 (0.58 - 0.85)
  - ARD 4.8%
  - Net Benefit: HR 0.74 (0.62 - 0.89)
  - N = 3146

- **Very Elderly (≥ 75)**
  - Primary EP: HR 0.94 (0.75 - 1.18)
  - ARD 1.1%
  - Net Benefit: HR 0.99 (0.81 - 1.21)
  - N = 1809

- **DM & ≥ 75**
  - Primary EP: HR 0.64 (0.42 - 0.97)
  - ARD 8.1%
  - Net Benefit: HR 0.70 (0.48 - 1.03)
  - N = 483
Therapeutic Considerations

- Significant Net Clinical Benefit with Prasugrel 80%

Recommend Reduced MD
Guided PK
Wt < 60 kg
Age ≥ 75 y

Avoid Prasugrel
Prior CVA/TIA

16%
4%

Wiviott SD et al. NEJM 2007; 357: 2001-2015
Continued Ischemic Events

High Risk Clinical Features

Genetic Polymorphisms

Drug-Drug Interactions

ACS Managed with PCI

Dual Antiplatelet Therapy

**Inhibition of Platelet Aggregation**
Faster, Greater, More Consistent

Continued Ischemic Events

- 2.2% ARD in CVD/MI/Stroke ($HR = 0.81; \ NNT = 45$)
- 2.3% ARD in MI ($HR = 0.76; \ NNT = 43$)
- 1.22% ARD in stent thrombosis ($HR = 0.48; \ NNT = 82$)
ACS Managed with PCI
Dual Antiplatelet Therapy

High Risk Clinical Features

Genetic Polymorphisms

Drug-Drug Interactions

Inhibition of Platelet Aggregation
Faster, Greater, More Consistent

0.6% ARD in non-CABG TIMI Major Bleeding (HR = 1.32; NNH = 167)

Potential Mitigation of Bleeding Risk:
- Access site selection (radial vs femoral)
- Contraindication for prior TIA/Stroke
- Dose ↓ in patients ≥75 yrs, or <60 kg
Antiplatelet Therapy in ACS

- **ASA**: Reduction in Ischemic Events - 22%
- **ASA + Clopidogrel**: Reduction in Ischemic Events - 20%
- **ASA + Prasugrel**: Reduction in Ischemic Events - 19%

*Increase in Major Bleeds:*
- Placebo: + 60%
- APTC Single Antiplatelet Rx: + 38%
- CURE Dual Antiplatelet Rx: + 32%
- TRITON-TIMI 38 Higher IPA: + 32%

*References*
Special Topics

William Macias, MD, PhD
Senior Medical Director
Cardiovascular and Acute Care
Eli Lilly and Company
Regulatory Review Topics

- Incidence of neoplasms in TRITON-TIMI 38
- Sponsor’s recommendation for reduced maintenance dose in patients < 60 kg or ≥ 75 yrs
- Salt to base conversion
- Proposed risk management plan
Possible Signal of Risk for Neoplasm with Prasugrel
TRITON-TIMI 38 Not Designed to Ask or Answer Questions Related to Cancer Risk

♦ Inclusion/exclusion criteria:
  • Did not exclude patients with cancer
  • Did not exclude patients based on known risk factors for cancer

♦ Did not prospectively collect data on:
  • Risk factors for cancer
  • Cancer history, recurrent cancers, new cancers
  • Tumor burden, metastasis, or treatment

♦ No protocol defined analytical plan for cancer
### Original Dataset: Neoplasms Reported as Adverse Events

<table>
<thead>
<tr>
<th>Condition</th>
<th>Prasugrel n/N, (%)</th>
<th>Clopidogrel n/N, (%)</th>
<th>Hazard ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neoplasm benign, malignant, and unspecified (including cysts and polyps)</td>
<td>175 / 6741 (2.60)</td>
<td>138 / 6716 (2.05)</td>
<td>1.26 (1.01 - 1.57)</td>
<td>0.043</td>
</tr>
<tr>
<td>New non-benign neoplasm</td>
<td>135 / 6741 (2.00)</td>
<td>115 / 6716 (1.71)</td>
<td>1.18 (0.91, 1.50)</td>
<td>0.212</td>
</tr>
<tr>
<td>Malignancy related deaths</td>
<td>21 / 6741 (0.31)</td>
<td>17 / 6716 (0.25)</td>
<td>1.24 (0.65, 2.35)</td>
<td>0.63</td>
</tr>
</tbody>
</table>
Sponsor Agrees with FDA’s Division of Oncology Drug Products*

♦ There are no data in TRITON to support a belief that prasugrel is a “promoter” in humans

♦ Cancers diagnosed in TRITON are likely incidental and the finding is probably spurious

♦ No neoplasm analyses based on TAAL (TRITON-TIMI 38) can be conclusive

* Revised Secondary CDTL Review; page 67 of 77.
Possible Signal of Risk for Neoplasm with Prasugrel

Assessment of Carcinogenicity
- Review: Toxicology data

Assessment of Tumor Stimulation
- Review: Toxicology data
  - Outcomes for patients with pre-existing cancers
  - Outcomes for patients with new cancers
  - Outcomes for patients with prolonged exposure to prasugrel

Assessment of Bleeding Leading To Detection of Tumors
- Review: Number of cancers diagnosed during evaluation of bleeding
  - Analysis excluding colorectal cancers

Chance Finding
- Review: Historical rates of new cancers
- Historical rates of colorectal cancers
Assessment of Carcinogenicity

- Prasugrel not genotoxic in in-vitro and in in-vivo tests
- Two-year toxicology studies in rodents show no increased development of any malignant cell type
  - FDA statement - “Two-year chronic bioassays in two rodent species are the current “gold standard” for assessing carcinogenicity of new drugs as well as other products. Results from these studies have been shown to identify virtually all known human carcinogens.”
- Benign hepatocellular adenoma noted in mice
  - FDA statement - “These tumors are common in mice and are most likely related to chronic enzyme induction and are not considered relevant to human risk.”

Both Sponsor and FDA agree prasugrel not a carcinogen.
Assessment of Tumor Stimulation

Review:

Toxicology data

Outcomes for patients with pre-existing cancers

Outcomes for patients with new cancers

Outcomes for patients with prolonged exposure to prasugrel
Additional Studies Requested by FDA Show Prasugrel Does Not Stimulate Tumor Growth

- Prasugrel did not stimulate growth of lung, colon, or prostate tumor cells in culture
- Prasugrel did not stimulate growth of lung, colon, or prostate tumors implanted in nude mice

![Graph showing tumor volume over time](5146.01)
Comparable Mortality Rates at Study End for Patients with Pre-existing Non-benign Neoplasm*

<table>
<thead>
<tr>
<th>Outcome at database lock</th>
<th>Patients, n (%)</th>
<th>Prasugrel N = 137</th>
<th>Clopidogrel N = 132</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignancy deaths (CEC)</td>
<td></td>
<td>4 (2.9)</td>
<td>3 (2.3)</td>
</tr>
<tr>
<td>Use of anti-neoplastic agents</td>
<td></td>
<td>7 (5.1)</td>
<td>8 (6.1)</td>
</tr>
</tbody>
</table>

*Reported at baseline or reported post baseline as pre-existing neoplasm (excludes non-melanotic skin cancer)
Number of Newly Diagnosed Cancers

Original dataset
(Database Lock- Sept. 2007)

Extended follow-up
of non-randomized cohort
of subjects with neoplasm AE

Follow-up dataset
(Data lock March 2008)

New non-benign neoplasms
(reconciled with FDA*)
Prasugrel = 94
Clopidogrel = 80

Data collected:
- tumor type
- pre-existing or new
- benign, malignant, unknown
- what led to diagnosis
- vital status

Analyses presented based on reconciled dataset

* Meeting in October 2008, included Drs. Temple, Unger, and Marciniak.
Rationale for Including Non-melanotic Tumors

- Pre-clinical data do not support exclusion of any tumor type
- Exclusion of any tumor type is post hoc and subject to bias
- Detecting signal for tumor promotion should assess wide variety of tumors
- Biology of skin cancer is similar to other cancers
- Systemic exposure to some carcinogens result in skin cancers (eg, arsenical poisoning)
- Skin tumors are sensitive to known tumor promoters – Most common laboratory model of tumor promotion
Incidence of Newly Diagnosed Cancers (Non-benign Neoplasms)

Days From first dose

Cumulative Percent

Prasugrel 94/6741 (1.39%)
Clopidogrel 80/6716 (1.19%)

HR 1.172 (0.870 - 1.579)
P-value = 0.30
Comparable Mortality Rates for Patients with Newly Diagnosed Cancers who Received Extended Follow-up

<table>
<thead>
<tr>
<th>Outcome at end of extended follow-up</th>
<th>Prasugrel N = 94</th>
<th>Clopidogrel N = 80</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignancy deaths (CEC and Investigator reported)</td>
<td>30 (31.9)</td>
<td>23 (28.8)</td>
<td>1.11 (0.70-1.75)</td>
</tr>
</tbody>
</table>

♦ Results differ from FDA’s analysis due to:
  • Sponsor’s use of reconciled database
  • Sponsor’s use of only patients with new cancers as at risk population
  • FDA’s use of all treated patients as at risk population
Comparison of Sponsor’s and FDA’s Calculation of Relative Risk for Malignancy-related Deaths in Patients with New Cancers (Through Extended Follow-up)

<table>
<thead>
<tr>
<th>Patients, n (%)</th>
<th>Prasugrel</th>
<th>Clopidogrel</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FDA’s Analysis of Follow-up Data</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignancy deaths (CEC and Investigator reported)</td>
<td>27 (0.40)</td>
<td>19 (0.28)</td>
<td>1.42* (0.79-2.54)</td>
</tr>
<tr>
<td><strong>Sponsor’s Analysis of Follow-up Data</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignancy deaths (CEC and Investigator reported)</td>
<td>27 (27.0)</td>
<td>19 (22.6)</td>
<td>1.19 (0.72-1.99)</td>
</tr>
</tbody>
</table>

Follow-up was only obtained on patients with newly diagnosed cancers. Therefore, not appropriate to use all-treated patients as the at risk population.

* Revised Secondary CDTL Review; page 64 of 77.
Prolonged Exposure to Prasugrel Not Associated with Higher Malignancy Death (Relative to Clopidogrel)

Number of Malignancy Deaths

- Clopidogrel
- Prasugrel

<table>
<thead>
<tr>
<th>Exposure to Study Drug (Days)</th>
<th>Clopidogrel</th>
<th>Prasugrel</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;180</td>
<td>5</td>
<td>12</td>
</tr>
<tr>
<td>≥180</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>63</td>
<td>65</td>
</tr>
</tbody>
</table>
No Evidence that Prasugrel Worsened Outcomes for Patients with Cancer

♦ Similar mortality rates between treatment groups for patients with prior (2.9% vs 2.3%) or newly diagnosed cancers (31.9% vs 28.8%)

♦ Observed difference in number of deaths in patients treated with prasugrel related to:
  • Non-randomized cohort defined by post-baseline event of new neoplasm
  • Extended follow-up for only this cohort (all randomized patients not followed post study end)
  • Unequal number of patients followed-up

♦ Prolonged exposure to prasugrel did not worsen outcomes for patients with cancer (relative to clopidogrel)
Consult from the FDA’s Division of Oncology Drug Products*

- No neoplasm analyses from TRITON-TIMI 38 can be conclusive
  - Study not designed to compare cancer incidence between treatment groups
    - Did not include cancer screening at baseline
  - Clinical significance obtained by combining different cancers hard to interpret

- “There are no data in TRITON-TIMI 38 to support a belief that prasugrel is a “promoter” in humans”
  - Short drug exposure to the study drugs
  - No specified follow-up to detect specific cancers
  - Cancers diagnosed likely to be incidental

* Revised Secondary CDTL Review; page 67 of 77.
Assessment of Bleeding Leading to Detection of New Cancers

Review:

Number of cancers diagnosed during evaluation of bleeding

↓

Analysis excluding colorectal cancers
Incidence of New Non-benign Neoplasms in TRITON-TIMI 38

Prasugrel 94/6741 (1.39%)
Clopidogrel 80/6716 (1.19%)

HR 1.172 (0.870 - 1.579)
p-value = 0.30
## Colorectal Neoplasms Frequently Diagnosed During Evaluation of Bleeding or Anemia

<table>
<thead>
<tr>
<th>Evaluation of anemia or bleeding led to diagnosis*</th>
<th>Prasugrel</th>
<th>Clopidogrel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>16</td>
<td>8</td>
</tr>
<tr>
<td>No</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>19</td>
<td>10</td>
</tr>
</tbody>
</table>

- Approximately 80% of colorectal cancers diagnosed during evaluation of bleeding or anemia
  - Similar percentage in both treatment groups

* As reported by the investigator
### Incidence of New Non-benign Neoplasms Excluding Colorectal Cancers

<table>
<thead>
<tr>
<th>Days From First dose</th>
<th>Cumulative Percent</th>
<th>Prasugrel</th>
<th>Clopidogrel</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td></td>
<td>75/6741 (1.11%)</td>
<td>70/6716 (1.04%)</td>
</tr>
<tr>
<td>90</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>180</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>270</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>360</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>450</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**HR 1.069 (0.772 - 1.481)**  
**p-value = 0.69**

- **Prasugrel**  
- **Clopidogrel**
Chance Finding

Review:

Historical rates of new cancers

↓

Historical rates of colorectal cancers
### Rates of Colorectal Cancers in CURE and TRITON

<table>
<thead>
<tr>
<th>Name of study</th>
<th>Number cancers</th>
<th>Patient-yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CURE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASA</td>
<td>8 (11*)</td>
<td>4728</td>
</tr>
<tr>
<td>ASA + clopidogrel</td>
<td>16 (22*)</td>
<td>4694</td>
</tr>
<tr>
<td><strong>TRITON</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASA + clopidogrel</td>
<td>10</td>
<td>6503</td>
</tr>
<tr>
<td>ASA + prasugrel</td>
<td>19</td>
<td>6464</td>
</tr>
</tbody>
</table>

* Projected number for 6500 patient-yrs
Summary: Sponsor Agrees with FDA’s Division of Oncology Drug Products*

- There are no data in TRITON to support a belief that prasugrel is a “promoter” in humans
- Cancers diagnosed in TRITON are likely incidental and the finding is probably spurious
- No neoplasm analyses based on TAAL (TRITON-TIMI 38) can be conclusive
  - Sponsor plans to prospectively collect additional data in TRILOGY-ACS
    - Oncology experts providing guidance on data collection and analytical plan

* Revised Secondary CDTL Review; 67 of 77.
Sponsor’s Recommendation on Labeling Specific to Neoplasms

♦ Neoplasm information included in labeling
  • Should reflect uncertainty of the observation
  • Should be useful to prescriber
  • Should not create unfounded alarm for physicians or patients
  • Should not have equal prominence to risk of bleeding
    – Evaluation of GI bleeding should be undertaken because it may unmask previously undiagnosed cancers comparable to warfarin

♦ Specific labeling language should
  • Be included in the adverse event section listing
  • Not restrict treatment duration
Rationale for Dose Adjustment in Patients < 60 kg or ≥ 75 yrs
Balance of Efficacy and Safety in Patients < 75 Yrs, ≥ 60 kg, and without Prior TIA/Stroke

CV death, NF MI, or NF stroke

Hazard Ratio, 0.75
(95% CI, 0.66 - 0.84)
P < 0.001

Hazard Ratio, 1.240
(95% CI, 0.91 - 1.69)
P = 0.17

TIMI major bleeding

Prasugrel 8.3%

Prasugrel 2.0%

Clopidogrel 11.0%

Clopidogrel 1.50%
Balance of Efficacy and Safety in Patients ≥75 Yrs (All ACS)

CV death, NF MI, or NF stroke

- Clopidogrel 18.3%
- Prasugrel 17.2%

Hazard ratio: 0.94
(95% CI, 0.75 - 1.18)
P = 0.596

TIMI major bleeding

- Clopidogrel 3.4%
- Prasugrel 4.2%

Hazard ratio: 1.36
(95% CI, 0.81 - 2.27)
P = 0.24
Primary Composite Efficacy Endpoint in Patients ≥ 75 Yrs with Diabetes (All ACS)

CV Death, Nonfatal MI or Nonfatal Stroke (%)

HR 0.626
CI (0.40 - 0.98)
P = 0.039
Cardiovascular Death Following MI in Patients ≥ 75 Yrs Without TIA/Stroke (All ACS)

CV Death After MI (%)

Time From Latest MI

Clopidogrel 19.7%

Prasugrel 7.2%

HR 0.385
CI (0.15 - 0.98)
P = 0.038
Dose Adjustment

♦ Recommendation
  • Reduced maintenance dose of 5 mg in
    – Patients < 60 kg
    – Patients ≥ 75 yrs

♦ Rationale
  • Patients < 60 kg or ≥ 75 yrs had higher exposure to prasugrel active metabolite
  • Increased exposure associated with increased bleeding during the maintenance phase
  • Reduction in dose would maintain estimated exposure similar to general population and reduced risk of bleeding
  • Reduction in dose should maintain efficacy
Predicted Exposure During 5 mg MD in Patients ≥75 Yrs or <60 kg

Patients ≥75 Yrs

Patients <60 kg
Prasugrel is administered as a loading dose of 60 mg and a once daily maintenance dose of 10 mg.

However, for patients at special risk (≥ 75 yrs, < 60 kg), a dose reduction is strongly recommended. Following the administration of a loading dose of 60 mg, the 5 mg once daily maintenance dose is to be given.

Salt to Base Conversion
During manufacture and storage some conversion to Prasugrel base.

Low gastric pH: rate of dissolution, extent of dissolution, and absorption unaffected by base/salt ratio

Only Base Absorbed
During manufacture and storage some conversion to Prasugrel base.

High gastric pH:
rate of dissolution is reduced but extent of dissolution and absorption unaffected by base/salt ratio.
No Effect of Partial Conversion on Absorption of a 60-mg Prasugrel LD at Normal Gastric pH

![Graph showing the absorption of Prasugrel at different base levels.](image-url)
Effect of Partial Conversion on Absorption of a 60-mg Prasugrel LD with Lansoprazole

Active Metabolite

Plasma concentration (ng/mL)

Time (Hours)

0 2 4 6

Active Metabolite

Prasugrel 5% base + Lansoprazole

Prasugrel 58% base + Lansoprazole

Prasugrel 70% base + Lansoprazole
Pharmacodynamic Responses Following 60 mg Prasugrel or 600 mg Clopidogrel LDs With and Without PPI – PRINCIPLE-TIMI 44

Maximum Platelet Aggregation (%)

Time (Hours)

Prasugrel 60 mg LD
Prasugrel 60 mg LD + PPI
Clopidogrel 600 mg LD
Clopidogrel 600 mg LD + PPI

*P<0.05
<table>
<thead>
<tr>
<th>Proton Pump Inhibitors</th>
<th>CV Death, NF MI, or NF Stroke Through 3 days</th>
<th>Hazard Ratio</th>
<th>Observed Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Favors</td>
<td>Prasugrel %</td>
</tr>
<tr>
<td>All ACS</td>
<td></td>
<td>Prasugrel</td>
<td>4.9</td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td>Clopidogrel</td>
<td>4.5</td>
</tr>
<tr>
<td>No</td>
<td></td>
<td>Prasugrel</td>
<td>4.9</td>
</tr>
<tr>
<td>UA/NSTEMI</td>
<td></td>
<td>Clopidogrel</td>
<td>4.4</td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td>Prasugrel</td>
<td>5.3</td>
</tr>
<tr>
<td>No</td>
<td></td>
<td>Clopidogrel</td>
<td>4.9</td>
</tr>
<tr>
<td>STEMI</td>
<td></td>
<td>Prasugrel</td>
<td>4.9</td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td>Clopidogrel</td>
<td>4.4</td>
</tr>
<tr>
<td>No</td>
<td></td>
<td>Prasugrel</td>
<td>5.3</td>
</tr>
</tbody>
</table>

HR (95% CI)

0.5 Favors Prasugrel 1.0 Favors Clopidogrel 2.0
Proposed Product Attributes

♦ PK/PD demonstrated equivalent extents of absorption between tablets with low base content and those with base content within the range used in TRITON-TIMI 38
♦ To-be-marketed tablets will have controlled base content
♦ The dose, purity, stability, and appearance is not affected by the base content
♦ Proposed label statement:
  • Section 11. Description; “During manufacture and storage, partial conversion from salt to base may occur.”
  • Section 16.2 Storage and Handling; “Dispense product in original container.”
Risk Management for Prasugrel
Components of Risk Management

Safety specification
Identified, potential, and unknown risks

Risk minimization
Mitigation of risks to optimize risk-benefit balance

Pharmacovigilance
Ongoing assessment of risks
Safety Specification

♦ Identified risks: bleeding, with increased risk in subgroups
  • History of TIA/stroke
  • Very elderly
  • Low body weight
  • Undergoing urgent surgery including CABG
  • Concomitant medications leading to increased bleeding risk

♦ Other events for focused follow up
  • Neoplasm
  • Thrombocytopenia including thrombotic thrombocytopenic purpura (TTP)
  • Leukopenia/ neutropenia/ agranulocytosis
  • Photosensitivity
Risk Minimization - Communication Plan

♦ Content defined by safety specification
  • US Package Insert
  • Patient Medication Guide
  • HCP communications

♦ Targeted HCP groups defined by windows of risk
  • Cardiologists – treatment initiation and maintenance
  • PCPs and other HCPs – treatment maintenance
Risk Minimization - Letter to Healthcare Professionals at Launch

♦ Broad coverage to HCPs who treat ACS PCI patients or assist in risk communication
  • Interventional and clinical cardiologists (> 10,000)
  • Primary care physicians (> 25,000)
  • Hospitals with cath labs (> 800)
  • Commercial/trade pharmacists (> 30,000).

♦ Emphasizing
  • Indicated population
  • Contraindications and warnings
  • Benefit-risk in subpopulations
  • Management of bleeding risks
Prescriber Brochure

- Emphasizing risk management
- Distributed to prescribers during first contact within the initial post-launch period
- Broad coverage to HCPs who treat ACS PCI patients or assist in risk communication
Pharmacovigilance Plan

- Assessment of spontaneous and clinical trial adverse event reports
- Automated Signal Detection in spontaneous report databases (e.g., FDA Adverse Event Reporting System)
- Aggregate data reviews and periodic safety reporting to agencies
- Pharmacoepidemiology studies in US and EU
- Information from prospective clinical research
Prospective Clinical Research

♦ Randomized controlled trial TRILOGY
  • Prasugrel vs clopidogrel for medically managed ACS
  • > 10,000 patients globally, treated for up to 30 month
  • 5 mg used in very elderly and low body weight
  • Neoplasm focused data collection

♦ US prospective observational study
  • Standardized prospective capture of patient level effectiveness and safety outcomes in a large naturalistic study
  • Link from inpatient to outpatient data (up to 18 month)
Closing Remarks

Eugene Braunwald, M.D.

Hersey Distinguished Professor of Theory and Practice of Medicine, Harvard Medical School
Chairman, TIMI Study Group, Brigham and Women's Hospital
Response to Thienopyridines

Prodrug → Conversion to active metabolite (PK) → Platelet response (PD) → Clinical response

PK/PD substudies

CYP Genotypes
### Public Health Implications

1.6 Million ACS admissions per year in US

850,000 PCIs for ACS per year

<table>
<thead>
<tr>
<th>Events Per Year</th>
<th>US Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benefit</strong></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarctions</td>
<td>23,000</td>
</tr>
<tr>
<td>Urgent target vessel revascularizations</td>
<td>8600</td>
</tr>
<tr>
<td>Stent Thrombosis</td>
<td>7400</td>
</tr>
<tr>
<td>Deaths</td>
<td>4000</td>
</tr>
<tr>
<td><strong>Risk</strong></td>
<td></td>
</tr>
<tr>
<td>Nonfatal major bleed (non CABG)</td>
<td>2300</td>
</tr>
</tbody>
</table>
Back up slides shown
Figure 5.5 Loading dose phase inhibition of platelet aggregation (20 µM ADP) – PRINCIPLE-TIMI 44.

***p<0.0001 Prasugrel vs. Clopidogrel

Prasugrel 60 mg

Clopidogrel 600 mg

***p<0.0001 Prasugrel vs. Clopidogrel

Wiviott SD et al. Circulation 2007; 116: 2923-2932
Figure 6.29 CABG-related TIMI major bleeding.

*N = 437 All treated CABG patients. A patient (not included in the graphs below) who was assigned to prasugrel experienced a CABG-related TIMI Major bleeding event 28 days after the last dose of study drug. However, the patient was treated with open-label clopidogrel after discontinuation of study drug until 4 days prior to CABG.*
# Table 6.26  CABG All-Cause Mortality CEC Adjudicated – All Treated Patients who Underwent CABG

<table>
<thead>
<tr>
<th>Event</th>
<th>Prasugrel % (n/N)</th>
<th>Clopidogrel % (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death in patients after CABG</td>
<td>3.3 (7/213)</td>
<td>7.6 (17/224)</td>
</tr>
<tr>
<td>Death within 30 days of CABG</td>
<td>1.9 (4/213)</td>
<td>5.8 (13/224)</td>
</tr>
<tr>
<td>Death more than 30 days after CABG</td>
<td>1.4 (3/213)</td>
<td>1.8 (4/224)</td>
</tr>
<tr>
<td>Death in patients who had CABG within 7 days of last dose of study drug</td>
<td>3.7 (5/134)</td>
<td>9.0 (14/156)</td>
</tr>
</tbody>
</table>
Relationship Between MPA and Exposure Following Maintenance Dose Administration of Prasugrel
**Percentage of Non-responders with 5-mg Exposure – Dose Adjustment for Elderly**

<table>
<thead>
<tr>
<th>TABR Observed % Non-Responders (&lt;20% IPA)</th>
<th>Predicted* Mean (90% Prediction Interval) % Non-Responders (&lt;20% IPA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;60 kg &amp; ≤75 y</td>
<td>≥60 kg &amp; &lt;75 y</td>
</tr>
<tr>
<td>≥60 kg &amp; ≥75 y</td>
<td>≥60 kg &amp; ≥75 y</td>
</tr>
<tr>
<td>≥60 kg &amp; ≥75 y</td>
<td>≥60 kg &amp; ≥75 y</td>
</tr>
<tr>
<td>N=55</td>
<td>N=996</td>
</tr>
<tr>
<td>N=110</td>
<td>N=110</td>
</tr>
</tbody>
</table>

- Clopidogrel 75 mg
- Prasugrel 10 mg
- Prasugrel 10 mg
- Prasugrel 10 mg
- Prasugrel 5 mg

<p>| | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;60 kg &amp; ≤75 y</td>
<td>&gt;50 kg &amp; &lt;75 y</td>
<td>≥60 kg &amp; &lt;75 y</td>
<td>≥60 kg &amp; ≥75 y</td>
<td>≥60 kg &amp; ≥75 y</td>
<td></td>
</tr>
<tr>
<td>N=55</td>
<td>N=55</td>
<td>N=996</td>
<td>N=110</td>
<td>N=110</td>
<td></td>
</tr>
<tr>
<td>43.0%</td>
<td>4.0%</td>
<td>5.8% (4.6-7.2)</td>
<td>4.8% (1.8-8.2)</td>
<td>8.8% (4.5-13.6)</td>
<td></td>
</tr>
</tbody>
</table>

* Based on 200 simulations
Predicted MPA During 5 mg MD in Subjects ≥75 Years

- Pras 10-mg
- Pras 5-mg
- Clop 75-mg
- Clop 75-mg

EM = extensive metabolizers
RM = reduced metabolizers
No Genetic Effect on Pharmacokinetics for Prasugrel

Relationship Between CYP2C19 and Exposure to Active Metabolite

Box represents median, 25th, and 75th percentiles; whiskers represent the most extreme values within 1.5 times inter-quartile range of the box and individual lines represent outlying values.

TABR: Active Metabolite Exposure to Prasugrel 60 mg and Clopidogrel 600 mg LD by CYP2C19

Extensive = patients with genotype predicted to confer normal metabolic function;
Reduced = patients with genotype predicted to confer reduced metabolic function

Box represents median, 25th, and 75th percentiles; whiskers represent the most extreme values within 1.5 times inter-quartile range of the box

*p<0.002 vs. clopidogrel EM

CYP2C19 Effect on Clinical Outcomes in ACS Patients for Clopidogrel: TRITON-TIMI 38

N=1,459
Reduced n=395 (27%)  Extensive n=1,064 (73%)

Hazard Ratio 1.53
(95% CI 1.07 - 2.19)
P=0.01

Reduced 8.0%
Extensive 12.1%

N=1,389
Reduced n=375 (27%)  Extensive n=1,014 (73%)

Hazard Ratio 3.09
(95% CI 1.19 - 8.00)
P=0.02

Reduced 2.6%
Extensive 0.8%

Primary Composite Efficacy Endpoint in Patients ≥ 75 Years by CYP2C19 for Clopidogrel

CV Death, Nonfatal MI, or Nonfatal Stroke (%)

Hazard Ratio: RM vs. EM, 2.05 (95% CI, 0.86-4.88) P=0.031

Extensive metabolizers 11.1%
Reduced metabolizers 19.6%

Extensive = patients with genotype predicted to confer normal metabolic function
Reduced = patients with genotype predicted to confer reduced metabolic function
Cardiovascular Death by Myocardial Infarction Characteristics: TRITON All ACS

- Abnormal Cardiac Enzyme
- Abnormal Cardiac Enzyme, ECG and Chest Pain
- Abnormal Cardiac Enzyme and Chest Pain
- No MI

Cardiovascular Death (%) vs Time from Randomization/Latest MI
Primary Endpoint: Time From Study Drug Discontinuation: TRITON – All ACS

CV Death, Nonfatal MI, or Nonfatal Stroke (%)

Time from study drug discontinuation

Number at Risk:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Day 2</th>
<th>Day 4</th>
<th>Day 6</th>
<th>Day 8</th>
<th>Day 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prasugrel</td>
<td>1031</td>
<td>1017</td>
<td>1006</td>
<td>993</td>
<td>977</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>995</td>
<td>974</td>
<td>962</td>
<td>950</td>
<td>939</td>
</tr>
</tbody>
</table>

Prasugrel 5.4%
Clopidogrel 9.5%
### Odds Ratio for Statistically Significant Risk Factors of Non-CABG-Related TIMI Major Bleeding with Prasugrel

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Prasugrel</th>
<th>95% Wald Confidence Limits</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight &lt;60 kg</td>
<td>2.768</td>
<td>1.652, 4.640</td>
<td>0.0001</td>
</tr>
<tr>
<td>Age ≥75 years</td>
<td>1.805</td>
<td>1.205, 2.704</td>
<td>0.0042</td>
</tr>
<tr>
<td>Prior TIA/Stroke</td>
<td>2.623</td>
<td>1.480, 4.649</td>
<td>0.0010</td>
</tr>
</tbody>
</table>
TIMI Major Non-CABG Bleeding After 3 Day for Prasugrel by Age

<table>
<thead>
<tr>
<th>Age</th>
<th>≤55 yr</th>
<th>&gt;55 yr</th>
<th>&gt;60 yr</th>
<th>&gt;65 yr</th>
<th>&gt;70 yr</th>
<th>&gt;75 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td># of Subjects</td>
<td>2307</td>
<td>4377</td>
<td>3334</td>
<td>2386</td>
<td>1482</td>
<td>748</td>
</tr>
</tbody>
</table>

TIMI Major Non-CABG Bleeding (%)
TIMI Major Non-CABG Bleeding After 3 Day for Prasugrel by Weight

<table>
<thead>
<tr>
<th>Weight</th>
<th>≥85 kg</th>
<th>&lt;85 kg</th>
<th>&lt;80 kg</th>
<th>&lt;75 kg</th>
<th>&lt;70 kg</th>
<th>&lt;65 kg</th>
<th>&lt;60 kg</th>
</tr>
</thead>
<tbody>
<tr>
<td># of Subjects</td>
<td>2840</td>
<td>3800</td>
<td>2797</td>
<td>1937</td>
<td>1170</td>
<td>683</td>
<td>304</td>
</tr>
</tbody>
</table>
Efficacy Analysis Peak Biomarker

CABG Surgery and Transfusions
≥ 4 Units of PRBC or Whole Blood – Days from Last Dose of Study Drug (All ACS)
Figure 7: Kaplan-Meier Estimates of the 1° Efficacy Endpoint; Delta between Prasugrel and Clopidogrel, STEMI and NSTEMI/UA Populations
## Advantages of Contemporary Therapy

<table>
<thead>
<tr>
<th></th>
<th>Prasugrel</th>
<th>Clopidogrel</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Loading Dose Practice</strong></td>
<td>Pre-Treatment Not Necessary</td>
<td>Pre-Treatment Recommended Guidance</td>
</tr>
<tr>
<td><strong>Wash Out</strong></td>
<td>7-day</td>
<td>5-day Recommended Guidance</td>
</tr>
</tbody>
</table>
Non-CABG TIMI Major Bleeding 30-Day Landmark – All ACS

Cumulative Kaplan-Meier estimates of the rates of key study end points during the follow-up period. Trial was not powered for the 30-day landmark analyses.

HR 1.48
p = 0.028

Prasugrel
Clopidogrel

Antman EM 40th Annual NY Symposium; 2007, December; New York, NY
All-Cause Death After Non-CABG TIMI Major Bleed – Landmark Analysis (30 Days)

Days from Randomization or TIMI Major Bleed

All Cause Death (%)

- Non-CABG
  - TIMI Major Bleed
  - No Non-CABG
    - TIMI Major Bleed

2.5% 1.8% p=0.152
All-Cause Death After Nonfatal MI – Landmark Analysis (30 Days)

All Cause Death (%)

Days from Randomization

Nonfatal MI

No Nonfatal MI

3.8%
p<0.0001

1.7%
All-Cause Death Landmark Analysis (30 Days)

After Non-CABG TIMI Major Bleed
- Non-CABG TIMI Major Bleed
- No Non-CABG TIMI Major Bleed

- 2.5% All-Cause Death (%)
- 1.8% p=0.152

After Nonfatal MI
- Nonfatal MI 3.8%
- No Nonfatal MI 1.7%
- p<0.0001

Days from Randomization or TIMI Major Bleed

Days from Randomization
Predicted Exposure and IPA During 5 mg MD in Subjects ≥ 75 Yrs

- AUC (ng*hr/mL)
- IPA at 24 hr after MD (%)

Groups:
- Pras 5-mg
- Pras 10-mg
- Pras 10-mg
- Clop 75-mg

Subgroups:
- ≥ 75 yr
- ≥ 60kg & < 75 yr