Thrombolysis in Myocardial Infarction (TIMI) Study Group

Institute of Medicine Workshop:
Transforming Clinical Research in the United States

October 7, 2009

Marc S. Sabatine, MD, MPH

Investigator, TIMI Study Group
Associate Physician, Cardiovascular Division, BWH
Assistant Professor of Medicine, Harvard Medical School
Disclosure Statement

Astra Zeneca (research grant, scientific advisory boards)
Bristol-Myers-Squibb (honoraria, scientific advisory boards)
Eli Lilly & Daiichi-Sankyo (honoraria)
Eisai (research grant)
sanofi-aventis (research grant, honoraria, scientific advisory boards)
Schering-Plough (research grant support)

The TIMI Study Group received research grant support from: Accumetrics, Amgen, AstraZeneca, Bayer Healthcare, Beckman Coulter, Biosite, Bristol-Myers Squibb, CV Therapeutics, Eli Lilly and Company, GlaxoSmithKline, Inotek Pharmaceuticals, Integrated Therapeutics, Merck & Co., Millennium Pharmaceuticals, Novartis Pharmaceuticals, Nuvelo, Ortho-Clinical Diagnostics, Pfizer, Roche Diagnostics, sanofi-aventis, Schering-Plough Research Institute.
The Thrombolysis in Myocardial Infarction (TIMI) Study Group is an Academic Research Organization (ARO) devoted to conducting clinical trials to improve outcomes in patients with cardiovascular disease.

The group is headquartered at Brigham and Women’s Hospital & Harvard Medical School Boston, MA
Trials to Date

- Phase I to Phase IV studies
- Initial trials NHLBI-funded, now trials industry-funded
- NIH grant support for ancillary studies
- 30 to 25,000 subjects

Trial Status
- 45 completed trials
- 6 ongoing trials
- 7 trials in various stages of planning
Current Staff

• Physician Staff
  – Eugene Braunwald, MD – Study Chairman
  – 12 Staff Cardiologists
  – 3 Senior Cardiology Fellows (2-year research fellowships)
  – Rotating BWH Research Residents

• Operational Staff
  – Carolyn McCabe, BS – Director
  – 8 Project Directors & Managers
  – Research Assistants, etc.

• Biostatistical Core
  – Charles Contant, PhD – Director
  – Programmers
Services

- Academic Leadership
- Project Management
- Biostatistics
- Site Management
- Medical Hotline
- Regulatory Services
- Safety Reporting
- Clinical Events Committee
• Review the Compound
  – Pharmacokinetics & Pharmacodynamics
  – Animal & Phase I Data

• Refine Scientific Question
  – Unmet clinical need
  – Potential utility of compound
  – Current and evolving concomitant treatments

• Initiation of study
  – Investigator-initiated
  – Industry-initiated
9. Thienopyridines

Table 11. Updates to Section 6.3.1.6.8.2.2: Thienopyridines

<table>
<thead>
<tr>
<th>2004 STEMI Guideline Recommendation</th>
<th>2007 STEMI Focused Update Recommendation</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Class I</strong></td>
<td><strong>Class IIa</strong></td>
<td></td>
</tr>
<tr>
<td>1. Clopidogrel 75 mg/day orally should be added to aspirin in patients with STEMI regardless of whether they undergo reperfusion with fibrinolytic therapy or do not receive reperfusion therapy. <em>(Level of Evidence: A)</em> Treatment with clopidogrel should continue for at least 14 days. <em>(Level of Evidence: B)</em></td>
<td>1. In patients less than 75 years of age who receive fibrinolytic therapy or who do not receive reperfusion therapy, it is reasonable to administer an oral loading dose of clopidogrel 300 mg. <em>(Level of Evidence: C)</em> <em>(No data are available to guide decision making regarding an oral loading dose in patients 75 years of age or older.)</em> 2. Long-term maintenance therapy (e.g., 1 year) with clopidogrel (75 mg per day orally) is reasonable in STEMI patients regardless of whether they undergo reperfusion with fibrinolytic therapy or do not receive reperfusion therapy. <em>(Level of Evidence: C)</em></td>
<td>New recommendation</td>
</tr>
</tbody>
</table>
Clopidogrel Response Variability and Increased Risk of Ischemic Events
Primary PCI for STEMI (N = 60)

Prasugrel: more potent and predictable platelet inhibition

Inhibition of Platelet Aggregation (%)

Clopidogrel Responder
Clopidogrel Non-responder

*Responder = ≥25% IPA at 4 and 24 h

Prasugrel: Phase II Efficacy

RR = 0.72 [0.4, 1.2]  
P = 0.23

P = NS

Prasugrel LD/MD Treatment Group

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Clop R/N</th>
<th>Pras R/N</th>
</tr>
</thead>
<tbody>
<tr>
<td>20/254</td>
<td>37/650</td>
<td></td>
</tr>
<tr>
<td>Prasugrel LD</td>
<td>40/7.5</td>
<td>60/10</td>
</tr>
<tr>
<td>14/199</td>
<td>13/200</td>
<td>10/251</td>
</tr>
</tbody>
</table>

MI at 30 days
13,608 Patients with ACS and Planned PCI Randomized to Prasugrel (60/10) vs. Clopidogrel (300/75)

CV Death / MI / Stroke

HR 0.81 (0.73-0.90) P=0.0004

Prasugrel

Clopidogrel

1. INDICATIONS AND USAGE

1.1 Acute Coronary Syndrome

Effient™ is indicated to reduce the rate of thrombotic cardiovascular (CV) events (including stent thrombosis) in patients with acute coronary syndrome (ACS) who are to be managed with percutaneous coronary intervention (PCI) as follows:

- Patients with unstable angina (UA) or non-ST-elevation myocardial infarction (NSTEMI).
- Patients with ST-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 death, nonfatal myocardial infarction (MI), or nonfatal stroke compared to clopidogrel. The difference between treatments was driven predominantly by MI, with no difference on strokes and little difference on CV death [see Clinical Studies (14)].
Implications of Recent Clinical Trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines

Circulation 2004;110:227-239

Table 2. ATP III LDL-C Goals and Cutpoints for TLC and Drug Therapy in Different Risk Categories and Proposed Modifications Based on Recent Clinical Trial Evidence

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL-C Goal</th>
<th>Initiate TLC</th>
<th>Consider Drug Therapy**</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk: CHD* or CHD risk equivalents† (10-year risk &gt;20%)</td>
<td>&lt;100 mg/dL</td>
<td>≥100 mg/dL#</td>
<td>≥100 mg/dL†† (&lt;100 mg/dL: consider drug options)**</td>
</tr>
<tr>
<td>Moderately high risk: 2+ risk factors‡ (10-year risk 10% to 20%)§§</td>
<td>&lt;130 mg/dL</td>
<td>≥130 mg/dL#</td>
<td>≥130 mg/dL</td>
</tr>
<tr>
<td>Moderate risk: 2+ risk factors‡ (10-year risk &lt;10%)§§</td>
<td>&lt;130 mg/dL</td>
<td>≥130 mg/dL</td>
<td>≥160 mg/dL</td>
</tr>
<tr>
<td>Lower risk: 0–1 risk factor§</td>
<td>&lt;160 mg/dL</td>
<td>≥160 mg/dL</td>
<td>≥190 mg/dL (160-189 mg/dL: LDL-lowering drug optional)</td>
</tr>
</tbody>
</table>

Cannon et al. NEJM 2003; 350: 1495
Academic Leadership (2)

- **Develop Study Design**
  - Study population
  - Timing of intervention
  - Control arm
  - Background therapy
  - Endpoint(s) and timing of ascertainment
  - Statistical analysis plan

- **Develop Key Trial Documents**
  - Protocol
  - Case Report Form
  - Clinical Events Committee (CEC) Charter
  - Data Safety and Monitoring Board (DSMB) Charter
Academic Leadership (3)

• Study Startup
  – Country & site selection
    • Applicability to U.S.
    • Acceptability to other countries
    • Cost
  – Steering Committee of National Lead Investigators
  – Investigator Training
U.S. Enrollment

Population | STEMI w/ lytic | STEMI w/ lytic | NSTE-ACS | Post ACS | STEMI w/ lytic | STEMI w/ lytic | NSTE-ACS | ACS | NSTE-ACS | Post ACS
---|---|---|---|---|---|---|---|---|---|---
N | 3002 | 15,078 | 2220 | 4162 | 20,506 | 3491 | 6560 | 13,608 | 3241 | 3491
Intervent. | Hirudin vs. Heparin | nPA vs. TPA | INV vs. CONS | Atorva vs. Prava | ENOX vs. UFH | Clopi vs. pbo | Ranolaz. vs. pbo | Prasugrel vs. clopi | Phase II: OTAM vs. UFH | Phase II: Rivarox. vs. pbo

Enrollment from U.S. (%)

- 9B: 59%
- 17: 13%
- 18: 83%
- 22: 71%
- 25: 1%
- 28: 4%
- 36: 11%
- 38: 30%
- 42: 5%
- 46: 12%
K-M estimate of time to first primary efficacy event (composite of CV death, MI or stroke)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Hazard Ratio (95% CI)</th>
<th>Total Patients</th>
<th>KM % at Month 12</th>
<th>HR (95% CI)</th>
<th>P value (Interaction)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Treatment Effect</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary Endpoint</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Region</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asia/Australia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central/South America</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Europe/Middle East/Africa</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>North America</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

K-M = Kaplan-Meier; HR = hazard ratio; CI = confidence interval

Academic Leadership (4)

- **Monitor Study Progress**
  - Enrollment
  - Changes in medical landscape
  - Aggregate event rates (efficacy & safety)
  - Retention

- **Lead Study Analysis**
  - Data analysis
  - Separate copy of the database
  - Rapidly move to presentation of data at scientific meeting
  - Drafting of primary manuscript and subsequent analyses
PPI Use & Thienopyridines

PPI use at randomization (n= 4529)

- CLOPIDOGREL: PPI vs no PPI: Adj HR 0.94, 95% CI 0.80-1.11
- PRASUGREL: PPI vs no PPI: Adj HR 1.00, 95% CI 0.84-1.20

Clinical Events Committee

- **Physician Staff**
  - Stephen D. Wiviott, MD – Director
  - Board-certified cardiologists, neurologists, oncologists, endocrinologists, hepatologists
  - Seamless integration with eCRF

- **Adjudicate Key Endpoints**
  - Efficacy & Safety, including non-cardiovascular events
  - 2 Independent reviewers with 3rd as needed
  - Consistent application of definitions
  - High-level of granularity
Efficacy Analysis by Universal MI Classification

<table>
<thead>
<tr>
<th></th>
<th>Type 1 Spont.</th>
<th>Type 2 Secondary</th>
<th>Type 3 SCD</th>
<th>Type 4 PCI-related</th>
<th>Type 5 Peri-CABG</th>
</tr>
</thead>
<tbody>
<tr>
<td>p</td>
<td>0.0015</td>
<td>0.53</td>
<td>--</td>
<td>&lt;0.0001</td>
<td>--</td>
</tr>
<tr>
<td>CLOPIDOGREL</td>
<td>3.4</td>
<td>0.4</td>
<td>0.1</td>
<td>4.8</td>
<td>0</td>
</tr>
<tr>
<td>PRASUGREL</td>
<td>2.5</td>
<td>0.3</td>
<td>0</td>
<td>4a</td>
<td>0.1</td>
</tr>
</tbody>
</table>
Core Labs – Biomarker

• **Laboratory**
  – David A. Morrow, MD, MPH - Director
  – 2000 sq ft CLIA-accredited lab with state-of-the-art equipment

• **Samples**
  – Baseline
  – Follow-up

• **Analytes**
  – Existing protein biomarkers
  – Discovery using proteomics & metabolomics

• **Analysis**
  – Independent risk prediction
  – Guiding therapy
Troponin levels in NSTE-ACS

<table>
<thead>
<tr>
<th>Cardiac Troponin I</th>
<th>Mortality at 42 days (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to &lt;0.4</td>
<td>1.0</td>
</tr>
<tr>
<td>0.4 to &lt;1.0</td>
<td>3.4</td>
</tr>
<tr>
<td>1.0 to &lt;2.0</td>
<td>3.7</td>
</tr>
<tr>
<td>2.0 to &lt;5.0</td>
<td>6.0</td>
</tr>
<tr>
<td>5.0 to &lt;9.0</td>
<td>7.5</td>
</tr>
<tr>
<td>&gt;9.0</td>
<td>67.0</td>
</tr>
</tbody>
</table>

N=1404

P<0.001 \( \chi^2 \) for trend

Antman et al. *NEJM* 1996; 335: 1342
Troponin T: Treatment Interaction

Table 11. Selection of Initial Treatment Strategy: Invasive Versus Conservative Strategy

<table>
<thead>
<tr>
<th>Preferred Strategy</th>
<th>Patient Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive</td>
<td>Recurrent angina or ischemia at rest or with low-level activities despite intensive medical therapy</td>
</tr>
<tr>
<td></td>
<td>Elevated cardiac biomarkers (TnT or TnI)</td>
</tr>
<tr>
<td></td>
<td>New or presumably new ST-segment depression</td>
</tr>
<tr>
<td></td>
<td>Signs or symptoms of HF or new or worsening mitral regurgitation</td>
</tr>
<tr>
<td></td>
<td>High-risk findings from noninvasive testing</td>
</tr>
<tr>
<td></td>
<td>Hemodynamic instability</td>
</tr>
<tr>
<td></td>
<td>Sustained ventricular tachycardia</td>
</tr>
<tr>
<td></td>
<td>PCI within 6 months</td>
</tr>
<tr>
<td></td>
<td>Prior CABG</td>
</tr>
<tr>
<td></td>
<td>High risk score (e.g., TIMI, GRACE)</td>
</tr>
<tr>
<td></td>
<td>Reduced left ventricular function (LVEF loss than 40%)</td>
</tr>
<tr>
<td></td>
<td>Low risk score (e.g., TIMI, GRACE)</td>
</tr>
<tr>
<td>Conservative</td>
<td>Patient or physician preference in the absence of high-risk features</td>
</tr>
</tbody>
</table>

TnT cut point = 0.01 ng/ml

(54% of Pts TnT +)

Cannon NEJM 2001; 344: 1879
Lp-PLA$_2$ Levels and Risk of Major Adverse CV Events

**Adj HR = 1.33 (1.01-1.74)**

**P trend = 0.002**

**Event Rate (%)**

- **Q1**: 17.6, 654
- **Q2**: 21.8, 649
- **Q3**: 22.6, 657
- **Q4**: 22.6, 654
- **Q5**: 26.4, 651

**MV Model: age, index dx, prior MI, DM, renal, Rx arm, 30d LDL, 30d CRP**

O'Donoghue M et al., *Circulation* 2006;113:1745
Hypothesis
Targeting Lp-PLA₂ a Key Player in Atherosclerosis

Lumen
- native LDL carrier of Lp-PLA₂
- Lp-PLA₂

Intima
- Oxidized LDL substrate for Lp-PLA₂
- Lp-PLA₂
- Darapladib (Lp-PLA₂ inhibitor)

Leukocyte
- Lp-PLA₂

Atheroma
- Sustained Inflammation
- Necrotic Core Expansion

Core Labs – Pharmacogenetics

- **Laboratory**
  - Marc S. Sabatine, MD, MPH - Director
  - Multiple core genotyping laboratories at Harvard & MIT

- **Genotyping**
  - Candidate genes
  - Arrays

- **Analysis**
  - Risk prediction
  - Response to therapy
CYP2C19 & Clinical Outcomes
1477 Patients w/ ACS and planned PCI Rx’d w/ clopidogrel

CYP2C19 Reduced-Function Allele Carriers
Non-carriers

HR 1.53 (95% CI 1.07-2.19)
P=0.014

CYP2C19 Reduced-Function Allele Carriers
Non-carriers

HR 3.09 (95% CI 1.19-8.00)
P=0.015

* Carriers ~30% of the population

**PLAVIX®**
clopidogrel bisulfate tablets

**Pharmacogenetics**

To date, the impact of CYP2C19 genotype on the pharmacokinetics of clopidogrel’s active metabolite has been evaluated in 227 subjects from 7 reported studies. Reduced CYP2C19 metabolism in intermediate and poor metabolizers decreased the C_{max} and AUC of the active metabolite by 30-50% following 300- or 600 mg loading doses and 75 mg maintenance doses. Lower active metabolite exposure results in less platelet inhibition or higher residual platelet reactivity. To date, diminished antiplatelet responses to clopidogrel have been described for intermediate and poor metabolizers in 21 reported studies involving 4,520 subjects.

The association between CYP2C19 genotype and clopidogrel treatment outcome was evaluated in 2 post-hoc clinical trial analyses (substudies of CLARITY-TIMI 28^1 [n=465] and TRITON-TIMI 38^2 [n=1,477]) and 5 cohort studies (total n=6,489). In CLARITY-TIMI 28 and one of the cohort studies (n=765; Trenk^3), cardiovascular event rates did not differ significantly by genotype. In TRITON-TIMI 38 and 3 of the cohort studies (n= 3,516; Collet,^4 Sibbing,^5 Giusti^6), patients with an impaired metabolizer status (intermediate and poor combined) had a higher rate of cardiovascular events (death, myocardial infarction, and stroke) or stent thrombosis compared to extensive metabolizers. In the fifth cohort study (n=2,208; Simon^7), the increased event rate was observed only in poor metabolizers.

Pharmacogenetic testing can identify genotypes associated with variability in CYP2C19 activity. There may be genetic variants of other CYP450 enzymes with effects on the ability to form clopidogrel’s active metabolite.

Plavix Prescribing Information, Revised May 2009
Value Added by ARO

- **Internal validity of a clinical trial**
  - Compliance with the protocol
  - Data collection & adjudication
  - Statistical analyses

- **External validity or generalizability of a clinical trial**
  - Hypothesis to be tested
  - Study population (including location)
  - Endpoints

- **Answering additional questions**
  - Well-characterized dataset
  - Embedded mechanistic studies