Thrombolysis in Myocardial Infarction (TIMI) Study Group

ASCO/IOM Workshop:
Implementing a National Cancer Clinical Trials System for the 21st Century, February 11, 2013

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Associate Physician, Brigham and Women’s Hospital
Associate Professor of Medicine, Harvard Medical School
What is the TIMI Study Group?

An Academic Research Organization (ARO) dedicated to advancing the knowledge and care of patients suffering from cardiovascular disease and its risk factors.
65 Clinical Trials (59 completed, 6 ongoing)

More Than:

- >300,000 Patients enrolled to date
- >4000 Sites worldwide
- >8000 Investigators worldwide
- 52 Countries
- 6 Continents
TIMI Trial Enrollment

Individual TIMI Trial Enrollment (bars)

Cumulative TIMI Trial Enrollment (line)

TIMI Trials
TIMI Integrated Approach

TIMI STUDY GROUP

Principal Investigator

Project Management

Core Services
TIMI Physicians

- **Clinicians (on staff at Brigham and Women’s Hosp)**
  - Experts in practice of cardiovascular medicine
  - On national professional society guideline committees

- **Scientists (on faculty of Harvard Medical School)**
  - Experienced at framing and refining hypotheses
  - Long track record of high impact publications (*NEJM, JAMA, Lancet*)
  - *Dedicate career to research (75-80% research time)*

- **Clinical Trialists (TIMI Investigators)**
  - Highly experienced in the design of clinical trials: protocol, eCRF, ICF, CEC charter, IDMC charter
  - Integral part of Trial Team, *working daily* with Senior Project Director on implementation of trial
  - Provide *physician-to-physician* guidance & motivation
Project Management

• **Director of Operations**
  – Oversees all trials
  – Ensures appropriate resources; problem solves

• **Project Directors**
  – ~10 years of experience with multiple CV mega-trials
  – Leads trial ops team
  – Works hand-in-hand with TIMI Trial PI, Co-PI

• **Project Managers** (1-2 per trial)

• **Research Assistants** (10-12 per trial)
Core Services

- Clinical Events Committee
- Safety Desk
- QA/Regulatory Team
- Trial Hotline
- Biomarker Core Laboratory
- Genetics Core Laboratory
- ECG Core Laboratory
- Independent Biostatistics
Trial Design

• **Protocol**
  – Right patient population
  – Right dose
  – Right endpoints

• **Case Report Form**
  – Gather all the necessary information to test trial’s hypothesis
  – Expand knowledge of disease state
  – Ask the right questions the right way
  – Streamline, make easy for sites, minimize queries

• **Statistical Analysis Plan**
  – Define correct datasets (efficacy vs. safety, censoring rules)
  – Appropriate analyses of secondary endpoints given multiple hypothesis testing
13,608 Patients with ACS and Planned PCI Randomized to Prasugrel (60/10) vs. Clopidogrel (300/75)

CV Death, MI, or Stroke (%) 12.1

Prasugrel

HR 0.81 (0.73-0.90) P=0.0004

Wiviott SD et al. NEJM 2007;357:2001-15
Prasugrel in Medically Managed Patients
(Age < 75 years)

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

Primary Efficacy Endpoint

No. at risk:
Prasugrel: 3620 3248 2359 1611 953 389
Clopidogrel: 3623 3244 2390 1596 946 399
Primary Efficacy Endpoint to 30 Months
(Age < 75 years)

Wiviott et al  TCT 2012

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
**APPRAISE-1 Trial of Apixaban (Factor Xa Inhib)**

Phase 2, 1715 patients, recent acute coronary syndrome

Apixaban 2.5 mg BID, 10 mg QD, 10 mg BID, 20 mg QD, placebo
Apixaban 10 mg BID & 20 mg QD stopped due to excess bleeding

**ISTH Major or CRNM Bleeding**

- HR 2.45 (1.31-4.61)  
  p=0.005

- HR 1.78 (0.91-3.48)  
  p=0.09

**CV Death, MI, Stroke, Sev Recurrent Ischemia**

- HR: 0.73 (0.44-1.19)  
  p=0.21

- HR: 0.61 (0.35-1.04)  
  p=0.07

APPRAISE 2: Primary Outcome
CV Death, MI, Ischemic Stroke

Apixaban (5 mg bid, same dose used for atrial fibrillation)
Placebo
HR 0.95; 95% CI 0.80-1.11; p=0.509

Rivaroxaban (Factor Xa Inhib) post ACS Ph2 Trial (n=3491); 1° Safety Endpoint

(= TIMI Major, TIMI Minor, Bleed Req. Med. Attn.)

<table>
<thead>
<tr>
<th>Total Daily Dose:</th>
<th>Clinically Significant Bleeding (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban 20 mg</td>
<td>15.3%</td>
</tr>
<tr>
<td>Rivaroxaban 15 mg</td>
<td>12.7%</td>
</tr>
<tr>
<td>Rivaroxaban 10 mg</td>
<td>10.9%</td>
</tr>
<tr>
<td>Rivaroxaban 5 mg</td>
<td>6.1%</td>
</tr>
<tr>
<td>Placebo</td>
<td>3.3%</td>
</tr>
</tbody>
</table>

HR
5.1 (3.4-7.4)
3.6 (2.3-5.6)
3.4 (2.3-4.9)
2.2 (1.25-3.91)

*p<0.01 for placebo Vs Riva 5mg. p<0.001 for Riva 10,15,20mg vs placebo

SECONDARY EFFICACY ENDPOINT:
Incidence of Death / MI / Stroke

**Stratum 1: ASA Alone**
- Death / MI / Stroke (%): 11.9
- HR: 0.67, 0.58, 0.37
- P trend = 0.01

**Stratum 2: ASA + Clop.**
- Death / MI / Stroke (%): 3.8
- HR: 0.70, 0.71, 0.79, 3.0
- P trend = 0.72

Recent ACS: STEMI, NSTEMI, UA
Stabilized 1-7 Days Post-Index Event

Exclusions: increased bleeding risk, warfarin use, ICH, prior stroke if on ASA + thienopyridine

ASA 75 to 100 mg/day

Stratified by Thienopyridine Use at MD Discretion

Placebo
n=5,176

Rivaroxaban 2.5 mg BID
n=5,174

Rivaroxaban 5.0 mg BID
n=5,176

PRIMARY ENDPOINTS:
EFFICACY: CV Death, MI, Stroke (Ischemic, Hemorrhagic, or Uncertain Origin)
SAFETY: TIMI major bleeding not associated with CABG

Event driven trial with 1,002 primary efficacy events

Mega JL et al. *NEJM* 2012;366:9-19
EFFICACY ENDPOINTS:
Low Dose 5.0 mg BID

**CV Death / MI / Stroke**

- **Placebo**
  - HR 0.85
  - mITT: HR 0.85, p=0.03
  - ITT: HR 0.85, p=0.01
  - Estimated Cumulative Incidence (ECI): 8.8%

- **Rivaroxaban 5 mg BID**
  - HR 0.85
  - mITT: HR 0.85, p=0.03
  - ITT: HR 0.85, p=0.01
  - Estimated Cumulative Incidence (ECI): 4.1%

- **NNT=53**

**Cardiovascular Death**

- **Placebo**
  - HR 0.94
  - mITT: HR 0.94, p=0.63
  - ITT: HR 0.94, p=0.57
  - Estimated Cumulative Incidence (ECI): 4.0%

- **Rivaroxaban 5 mg BID**
  - HR 0.94
  - mITT: HR 0.94, p=0.63
  - ITT: HR 0.94, p=0.57
  - Estimated Cumulative Incidence (ECI): 4.1%

Mega JL et al. NEJM 2012;366:9-19
EFFICACY ENDPOINTS:
Very Low Dose 2.5 mg BID
Patients Treated with ASA + Thienopyridine

CV Death / MI / Stroke
Placebo
HR 0.85
mITT p=0.04
ITT p=0.01
Rivaroxaban
2.5 mg BID
NNT = 71

Cardiovascular Death
Placebo
HR 0.62
mITT p<0.001
ITT p<0.001
Rivaroxaban
2.5 mg BID
NNT = 59

All Cause Death
Placebo
HR 0.64
mITT p<0.001
ITT p<0.001
Rivaroxaban
2.5 mg BID
NNT = 56

Mega JL et al. NEJM 2012;366:9-19
Vorapaxar (PAR-1 inhibitor) in ACS

Primary Endpoint:
CV Death, MI, Stroke, Hosp for Ischemia, Urgent Revasc

Secondary Endpoint:
CV Death, MI, Stroke

HR (95% CI):
0.92 (0.85, 1.01)
P-value= 0.072

Placebo
Vorapaxar

0% 5% 10% 15% 20%

0 1 4 8 12 18 24

Months from Randomization

HR (95% CI):
0.89 (0.81, 0.98)
P-value= 0.018

Placebo
Vorapaxar

0% 5% 10% 15% 20%

0 1 4 8 12 18 24

Months from Randomization

Trial Organization

**EXEC CMTE**
- 5-7 members; meet 6x/yr
- Study Chairman, PI, Other MDs, Sponsor

**STEERING CMTE**
- ~40 members; meet 3x/yr
- EC + NLIs

**CLINICAL SITES**

**TIMI**

**SPONSOR**

**JOINT MANAGEMENT TEAM**
- Biweekly Mtgs
- Study Chair, PI, Co-PI’s, Dir Ops, Sr PD
- Sponsor Med & Ops Leads

**JOINT WORKING GROUP**
- Weekly Mtgs
- Operational & Med Personnel

**INDEPENDENT BIOSTATISTICS**

**IDMC**

**CEC**
- Safety Desk
- Biomarker & Genetic Cores
- Statistics

**TIMI**
- Study Drug
- IXRS
- Core Safety Labs
- Database

An Academic Research Organization of Brigham and Women's Hospital and Harvard Medical School
Training & Communication

- **Training**
  - Face-to-face mtgs led by TIMI
  - Interactive regional mtgs w/ NLIs (and translation)
  - Separate sessions tailored to person’s role
  - Audience Response Questions

- **Communication**
  - Numbered memos; ensure global consistency
  - Written by Global PI & Proj Director

- **Trial “Hotline”**
  - Responds to all medical and operational inquiries
  - Staffed 24/7 by TIMI
  - Learn from ?s what is unclear/problematic → site retraining vs. global clarification
TIMI Trial Enrollment

TIMI Trial A
- Actual Enrollment
- Original Prediction

TIMI Trial B
- Original Projection
- Actual Enrollment

TIMI Trial C
- Original Projection
- Actual Enrollment

TIMI Trial D
- Original Projection
- Actual Enrollment

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Brigham and Women's Hospital and Harvard Medical School
Biostatistics

• Pre-Trial
  – Analysis of TIMI Trial Databases to aid in refining inclusion & exclusion criteria
  – Review SAP, verify power calcs & alpha spending

• Pre-DB Lock
  – Projections based on aggregate data as needed
  – Review DB fields, validate programming

• Post-DB Lock
  – Receive raw database
  – Perform primary analyses, validate sponsor results
  – Perform secondary analyses
TIMI Study Group Publications

Year


Cumulative Publications

Publications Per year

0 5 10 15 20 25 30 35 40 45 50

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Novel Biomarkers of Cardiovascular Stress to Guide Therapy

Effect of ACEI Trandolapril on Incidence of CV death or Heart Failure in 3717 Patients with Stable CAD, Stratified by Levels of Biomarkers of CV Stress

Biomarkers included MR-proANP, MR-proADM, and CT-proET1. Levels in top quartile were considered to be elevated.

Placebo, ≥2 elevated biomarkers

HR 0.53
(95% CI 0.36-0.80)
P=0.002

Trandolapril, ≥2 elevated biomarkers

Trandolapril, ≤1 elevated biomarkers

Placebo, ≤1 elevated biomarkers

CYP450 Genetic Variants & Pharmacokinetics & Pharmacodynamics of Clopidogrel

162 healthy individuals

PK: active metabolite measured by LC-MS
PD: LTA w/ 20 µM ADP; $\Delta$MPA = abs $\bigtriangledown$ max plt agg from BL (overall 36.0 ± 20.5%)

### Pharmacokinetics

<table>
<thead>
<tr>
<th>Gene</th>
<th>% Difference in AUC$_{0-t}$</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C19</td>
<td>-32.4</td>
<td>0.00006</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>-6.8</td>
<td>0.59</td>
</tr>
<tr>
<td>CYP2B6</td>
<td>-15.7</td>
<td>0.035</td>
</tr>
<tr>
<td>CYP3A5</td>
<td>5.6</td>
<td>0.59</td>
</tr>
<tr>
<td>CYP1A2</td>
<td>11.2</td>
<td>0.45</td>
</tr>
</tbody>
</table>

### Pharmacodynamics

<table>
<thead>
<tr>
<th>Gene</th>
<th>Absolute Difference in $\Delta$MPA</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C19</td>
<td>-9.0</td>
<td>0.00054</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>-0.6</td>
<td>0.86</td>
</tr>
<tr>
<td>CYP2B6</td>
<td>-5.7</td>
<td>0.012</td>
</tr>
<tr>
<td>CYP3A5</td>
<td>7.5</td>
<td>0.012</td>
</tr>
<tr>
<td>CYP1A2</td>
<td>0.5</td>
<td>0.90</td>
</tr>
</tbody>
</table>

CYP2C19 & Clinical Outcomes
1477 Patients w/ ACS and planned PCI Rx’d w/ clopidogrel
