Lessons from 25+ Years of Clinical Trials in Cardiology: The TIMI Study Group Experience

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Boston, MA
MISSION STATEMENT:

The TIMI Study Group organized in 1984 by Eugene Braunwald, MD at Brigham and Women’s Hospital, Boston, MA, is committed to advancing the knowledge and care of patients suffering from acute coronary syndromes by performing clinical research.
TIMI TRIALS
1984-2011
62 Cardiac Trials (more than 50 completed)

ACS

1°, 2° Prevent
N=8

STEMI n=25
PCI n=4
nSTEMI/UA n=22
DM n=1
Afib n=1

• 300,000 Pts enrolled to date
• 4000 Hospitals worldwide
• 8000 Investigators worldwide
• 52 Countries
• 6 Continents

TIMI BIBLIOGRAPHY: >500 PEER REVIEWED PUBLICATIONS
COLLABORATIVE PARTNERS

TIMI STUDY GROUP

Non Profit
AHA
ACC

National Institute of Health
NHLBI-Contracts and Investigator Initiated

Pharmaceuticals
Smith Kline Beecham
Ciba Geigy
Biogen
Genentech
Rhone Poulenc Rorer
Centocor
Searle
Bristol Myers Squibb
Merck
Cor Therapeutics
Aventis
Lilly
Sunol
Sanofi Synthelabo
Millennium
British Biotech
Corvas
Astra Zeneca
Schering Plough
Daiichi Sankyo
Inotek
CV Therapeutics
Sanofi-Aventis
Novartis
Nuvelo
Johnson & Johnson PRD
GlaxoSmithKline
Amgen

CROs
Parexel
Covance
Quintiles
WCT
ICON

AROs
DCRI
HCRI
CHRC
LCC
NCRL
The Cycle of Clinical Therapeutics

- Concept
- Clinical Trials
- Guidelines
- Performance Indicators
- Education and Feedback
- Outcomes
- Performance
Top 10 Lessons 1984-1999

1. Better epicardial flow results in lower mortality
2. Development of grading scale for bleeding
3. Speed of flow (frame count) and perfusion of myocardial tissue (perfusion grade) are imp't
4. tPA is better than SK at opening arteries
5. Single bolus TNK-tPA is safe and effective
6. Enoxaparin is superior to unfractionated heparin
7. Risk score predicts outcomes, can guide therapy
8. Early invasive approach is better in UA/nSTE-MI
9. Prehospital lytic is feasible and speeds reperfusion
10. Multimarker approach improves prognostic ability
<table>
<thead>
<tr>
<th>General treatment measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>● Aspirin, nitrates, oxygen, analgesics (morphine)</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Infarct size limitation</th>
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<tr>
<td>● <strong>β-blockers</strong> (not for acute use in patients with evidence of heart failure)</td>
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<th>Reperfusion</th>
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<tr>
<td>● Thrombolysis (within 30 min) or primary PCI (within 90 min)</td>
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<th>Anticoagulant and antiplatelet therapy</th>
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<tr>
<td>● <strong>UFH</strong>, <strong>enoxaparin</strong>, fondaparinux(^a), or bivalirudin(^b)</td>
</tr>
<tr>
<td>● Clopidogrel 75 mg/d added to aspirin for patients undergoing fibrinolysis; 300 mg loading dose for patients &lt;75 y who receive fibrinolytic therapy or who do not receive reperfusion therapy</td>
</tr>
<tr>
<td>● If PCI: clopidogrel, prasugrel, GP IIb/IIIa inhibitors</td>
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\(^a\) Because of the risk of catheter thrombosis, fondaparinux should not be used as the sole anticoagulant to support PCI. An additional anticoagulant with anti-IIa activity should be administered.

\(^b\) For primary PCI with 600 mg clopidogrel

2007 ACC/AHA nSTE-ACS Guidelines

Immediate ASA; Clopidogrel if ASA contraindicated

Aspirin + clopidogrel for up to 1 month

Enoxaparin or UFH for invasive or conservative mgt

Bivalirudin (invasive) or fondaparinux (conservative)

β-blocker (IV→oral) if not contraindicated

Non-dihydropyridine Ca<sup>2+</sup> blckr if β-blocker contraindicated and no LV dysfn, for rec ischemia

ACE-I if ↑ BP with NTG+ β-blocker, if CHF or DM

Any GPI all patients, if cath/PCI planned

Ept or tiro for high-risk* if early cath not planned

Any GP IIb/IIIa inhibitor for patients already on ASA + Heparin + clopidogrel, if cath/PCI is planned

# TIMI Trials 2000-present

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Acute ST elevation MI within 6 hours
N~3000 patients

**ASPIRIN**

HEPARIN (Choice by MD - unfractionated or LMWH)
LYTIC (Choice by MD - RPA, TNK, TPA, or SK)

Randomize

PLACEBO

Double-blind

ECG at 90 & 180 mins

Pre-discharge coronary angiography (Day 3-8)

30 Day Clinical Follow-up

**Primary Endpoint:** Patency of infarct-related artery

**Secondary Endpoints:** ST segment resolution Clinical events

CLOPIDOGREL
300 mg loading dose
75 mg daily

CLARITY - TIMI 28
CLopidogrel as Adjunctive Reperfusion TherapY
Protocol Design
CLARITY-TIMI 28
Main Results

Primary Endpoint:
Occluded Artery (or D/MI thru Angio/HD)

- Odds Ratio 0.64
  (95% CI 0.53-0.76)
  \( P=0.00000036 \)
  36% Odds Reduction

- Clopidogrel: 15.0
- Placebo: 21.7
  \( n=1752 \)  \( n=1739 \)

CV Death, MI, RI

- Odds Ratio 0.80
  (95% CI 0.65-0.97)
  \( P=0.026 \)
  20%

No difference in TIMI bleeding

ExTRACT - TIMI 25
Exnoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment

Lytic Eligible STEMI <6 hrs

ASA

Lytic Choice by MD (TNK, TPA, rPA, SK)

Double-blind

UFH
Bolus 60U/kg
Infusion 12U/kg/h for ≥ 48 h

Enoxaparin
30 mg IV bolus;
sc 1.0 mg/kg q 12h to Hosp DC (0.75 mg/kg q 12 h if ≥ 75 years)

Day 30
Primary Efficacy Endpoint: Death/MI
Primary Safety Endpoint: TIMI Major Hemorrhage

Antman NEJM 2006;354:1477-88
Primary End Point (ITT)  
Death or Nonfatal MI

ARD = 0.021 = 2.1 %
RR = 0.83 (0.77 to 0.90)
RRR = 0.17 (0.23 to 0.10)
NNT = 48

ARD = absolute risk difference
RRR = relative risk reduction
### TIMI Trials 2000-present

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ADVANCE MI

Addressing the Value of Primary Angioplasty after Combination therapy or Eptifibatide monotherapy in acute Myocardial Infarction

Acute ST Elev MI (n=5640)

- Combination Rx-facilitated PCI
  - Eptifibatide + half-dose TNK
  - Immediate PCI

- GP Monotherapy-Direct PCI
  - Eptifibatide + placebo-TNK
  - Immediate PCI

  - Enoxaparin
  - UFH

30-day Composite Death or CHF
ADVANCE MI – MAIN Results

- 1/2 TNK + Ept (N=74)
- Placebo + ept (N=74)

<table>
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<th>Condition</th>
<th>1/2 TNK + Ept (N=74)</th>
<th>Placebo + ept (N=74)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death/CHF</td>
<td>10.8</td>
<td>1.4</td>
</tr>
<tr>
<td>Death</td>
<td>6.8</td>
<td>0</td>
</tr>
<tr>
<td>TIMI Major Bleed</td>
<td>22.3</td>
<td>10.8</td>
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Roe AHJ 2005;150:116-22
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“High Risk ACS (ST ↑/↓ or + Marker) receiving tirofiban

A Phase

Enoxaparin

Death, MI, refractory ischemia at 7 days

UF Heparin

If clinically stable and not “low-risk”

Z Phase

Aggressive simvastatin

40 mg/day x 30 d
80 mg day thereafter

Standard therapy

Placebo and diet x 4 months
Simvastatin 20 mg/day thereafter

1 year follow-up: CV death, MI, rehospitalization for ACS
## 7 Day Primary Endpoint

Composite of Death, MI and Refractory Ischemia

<table>
<thead>
<tr>
<th>Population</th>
<th>ENOX</th>
<th>UFH</th>
<th>Hazard Ratio</th>
<th>P-value</th>
<th>Upper Bound One-Sided 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intent to Treat</td>
<td>8.4%</td>
<td>9.4%</td>
<td>0.88</td>
<td>0.23</td>
<td>1.05</td>
</tr>
</tbody>
</table>

*Non-inferiority = upper bound of one-sided 95% CI < 1.144*

Blazing *JAMA* 2004;292:55
PROXIMATE - TIMI 27

**PROXimal Inhibition of coagulation using a Monclonal Antibody to Tissue factor (Sunol cH36) - TIMI 27**

**Protocol Design**

Stable CAD Receiving ASA (n = 28)

If no safety concerns, proceed to higher dose

- cH36 Bolus Dose # 1
  - n = 7

- cH36 Bolus Dose # 2
  - n = 7

- cH36 Bolus Dose # 3
  - n = 7

- cH36 Bolus Dose # 4
  - n = 7

**Measured at multiple time points:**

- cH36 levels
- Factor Xa activity
- Hgb/Hct
- PT/PTT/fibrinogen
- Platelet count
- Serum chemistries
- Human anti-chimeric ab

Morrow DA EHJ 2004
PROXIMATE - TIMI 27

**Bleeding Events**

**Proximal Inhibition of coagulation using a Monoclonal Antibody to Tissue factor (Sunol cH36)-TIMI 27**

<table>
<thead>
<tr>
<th>Dose Sunol cH36</th>
<th>0.03</th>
<th>0.06</th>
<th>0.08</th>
<th>0.10</th>
<th>0.30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrolled, N</td>
<td>8</td>
<td>4</td>
<td>4</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Major bleeding (pts)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Minor bleeding (pts)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spontaneous</td>
<td>1 (13)</td>
<td>2 (50)</td>
<td>2 (50)</td>
<td>6 (86)</td>
<td>3 (100)</td>
</tr>
<tr>
<td>Provoked</td>
<td>2 (25)</td>
<td>1 (25)</td>
<td>0</td>
<td>1 (14)</td>
<td>1 (33)</td>
</tr>
<tr>
<td>Any minor*</td>
<td>2 (25)</td>
<td>3 (75)</td>
<td>2 (50)</td>
<td>6 (86)</td>
<td>3 (100)</td>
</tr>
<tr>
<td>(Exact CI %)</td>
<td>(3, 65%)</td>
<td>(19, 99%)</td>
<td>(7, 93%)</td>
<td>(44,100%)</td>
<td>(29,100%)</td>
</tr>
</tbody>
</table>

*Individual pts may be classified as having both spontaneous & provoked episodes. Provoked bleeds were those that occurred at the site of IV insertion or as the result of minor trauma; all others were classified as spontaneous.

Morrow DA EHJ 2004
ANTHEM – TIMI 32

Anticoagulation with NAPc2 To Help Eliminate MACE

Protocol Design

Non-ST elevation ACS with planned Early Invasive Strategy (n=125)

ASPIRIN, Enoxaparin or UFH (GP IIb/IIIa, Clopidogrel Encouraged)

Experimental Arm

rNAPc2 IV bolus q 48h
n=20 per panel
5 Escalating Doses

Control Arm

Placebo IV bolus q 48 h
n=5 per panel

RANDOMIZE

Continuous ECG x 7 Days

In-hospital, 42 d, and 6 month follow up

Primary Endpoints:
Safety: Significant Hemorrhage
Efficacy: PK, PD

Secondary Endpoints:
Death, MI, Recurrent Ischemia
Ischemia by Continuous ECG

A Randomised, Double-blind Placebo-controlled Study to Assess the Efficacy and Safety of Factor VIIa/Tissue Factor Inhibitor, Recombinant Nematode Anticoagulant Protein c2 (rNAPc2), in Subjects With Non-ST-Elevation Acute Coronary Syndromes.

Giugliano RP et al. JACC 2007; 49:2398-2407
F1+2 Concentration: A Measure of New Thrombin Generation

F1+2 (nmol/mL) \( \Delta \) from Baseline

- Placebo: 40
- 1-4 ug/kg: 83
- 5.0 ug/kg: 20
- 7.5 ug/kg: 20
- 10 ug/kg: 40

2-6h
48h
7d post

P = 0.009 vs. placebo
P = 0.007 vs. placebo

Giugliano RP et al. JACC 2007; 49:2398-2407
TRITON – TIMI 38
Protocol Design

**TITAN**

**TRITON** – TIMI 38

**Protocol Design**

**ACS (STEMI or UA/NSTEMI) & Planned PCI**

- **ASA**
- **Double-blind**
- **PRASUGREL**
- **CLOPIDOGREL**

- **N= 13,000**

- **Median duration of therapy - 12 months**

**1° endpoint:** CV death, MI, Stroke

**2° endpoints:** CV death, MI, Stroke, Re-ischemia, CV death, MI, UTVR
TRITON-TIMI 38: Treatment effects on primary efficacy and key safety endpoints

- CV death/MI/stroke
  - HR 0.81 (0.73-0.90)
  - P < 0.001
  - Clopidogrel: 12.1 events
  - Prasugrel: 9.9 events
  - ↓ 138 events

- TIMI major non-CABG bleeding
  - HR 1.32 (1.03-1.68)
  - P = 0.03
  - Clopidogrel: 1.8 events
  - Prasugrel: 2.4 events
  - ↑ 35 events

HR = hazard ratio

EARLY ACS

Early (<12h) Eptifibatide in Pts with High-Risk ACS

10,500 pts ≥ 2 of the following:
1. ↑ MB or Tn
2. New STD ≥ 1mm
3. Age ≥ 60

Stratified by early clopidogrel

Eptifibatide 180/2/180
UPSTREAM
Matching Placebo

Cath >12 h after randomization
Optional Study Drug in Cath Lab
Blinded Placebo / Eptifibatide

Primary Endpoint: D/MI/UR/TBO at 96h
Secondary Endpoint: D/MI at 30 days

Giugliano AHJ 2005
Key Findings:
Primary EP, Secondary EP, Bleeding

- **Delayed Provisional**
  - **D/MI/RI->UR/TBO at 96h**
    - OR 0.92 (0.80, 1.06)
    - P = 0.23
  - **D/MI at 30d**
    - OR 0.89 (0.79, 1.01)
    - P = 0.072
  - **TIMI Major/Minor Bleeding at 120h**
    - OR 0.92 (0.80, 1.06)
    - P = 0.23

- **Early Routine**
  - **D/MI/RI->UR/TBO at 96h**
    - OR 1.75 (1.43, 2.13)
    - P < 0.001
  - **D/MI at 30d**
    - OR 1.75 (1.43, 2.13)
    - P < 0.001
  - **TIMI Major/Minor Bleeding at 120h**
    - OR 5.7%

Giugliano RP et al. NEJM 2009;360:2176-90
MERLIN – TIMI 36

Metabolic Efficiency with Ranolazine for Less Ischemia in Non-ST elevation Acute Coronary Syndromes

Protocol Design

N = 5500

UA/NSTEMI

RANDOMIZE (1:1) Double-blind

Ranolazine IV to PO

Placebo Matched IV/PO

Follow-up Q4 mo (Avg 8-12 mo)

Inclusion Criteria:
- Age ≥ 18 yr
- NSTE-ACS
  - ≥ 10 min rest sx
  - rest sx in prior 48H
- At least one of:
  - ↑ cTn or CK-MB
  - ST-↓ ≥ 1 mm
  - DM (rx meds)
  - TIMI Risk Score ≥ 3

Holter at enrollment x 7d

Follow-up Visits:
- Day 14, Month 4, Q4 Months
- ETT Month 8
- Final Visit

Primary EP
CV death, MI or recurrent ischemia

Major Exclusions:
- Persistent ST-Elev
- Revasc of culprit dz
- Shock / intubation
- LBBB, ventric pacing
- Pregnant / lactating
- ESRD on HD
- Significant hepatic dz
- Med comorbid → life expectancy <12m

Morrow DA et al. JAMA 2007; 297: 1775-83
Primary Endpoint

CV Death, MI, or Recurrent Ischemia (%)

Placebo 23.5%*  
(N=3,281)

Ranolazine 21.8%*  
(N=3,279)

HR 0.92 (95% CI 0.83 to 1.02)  
P = 0.11

*KM cumulative incidence (%) at 12 months

Morrow DA et al. JAMA 2007; 297: 1775-83
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Patients stabilized post ACS <10d
Total cholesterol <240 mg/dL (N=4000)

ASA & standard medical therapy

2x2 factorial design

Pravastatin 40 mg qd

Atorvastatin 80 mg qd

Follow-up visit day 15

Gatifloxacin 400 mg qd x 10d/mo

Placebo

Placebo

Gatifloxacin 400 mg qd x 10d/mo

Follow-up visit day 30 then q4 months
(average 2 years, minimum 18 months)

1° Endpoint: death, MI, stroke, rehosp for UA, revasc*

* Revascularization includes only procedures occurring ≥ 30d post randomization
All-Cause Death or Major CV Events in All Randomized Subjects

Pravastatin 40mg (26.3%)

Atorvastatin 80mg (22.4%)

16% RR
(P = 0.005)

Cannon *NEJM* 2004;350:1495
Study Design

335 Patients Enrolled
Stable CAD Pts on Clopidogrel 75 mg daily
(>4 Weeks and <6 Months Post-MI or PCI)

333 Blinded Genotyping

247 CYP2C19*2 Non-Carriers
Randomized to various blinded sequences of daily doses of clopidogrel
75 mg, 150 mg, 75 mg, 150 mg

86 CYP2C19*2 Carriers
(80 Heterozygotes; 6 Homozygotes)
Randomized to various blinded sequences of daily doses of clopidogrel
75 mg, 150 mg, 225 mg, 300 mg

Each dose given for ~14 days followed by platelet function testing (VASP and VerifyNow P2Y<sub>12</sub> assays) and assessment for events

Mega JL, JAMA. 2011;306(20):2221-2228
Squares represent the means and vertical lines the 95% confidence intervals.
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

Gibson CM, Am Heart J 2011
PRIMARY EFFICACY ENDPOINT:
CV Death / MI / Stroke

Rivaroxaban (both doses)

HR 0.84 (0.74-0.96)
mITT p = 0.008
ITT p = 0.002
ARR 1.8%
NNT = 56

2 Yr KM Estimate
Placebo 10.7%
Rivaroxaban 8.9%

No. at Risk
Placebo 5113 4307 3470 2664 1831 1079 421
Rivaroxaban 10229 8502 6753 5137 3554 2084 831

HR and 95% confidence interval estimates from Cox model stratified by thienopyridine use are provided per mITT approach; Stratified log-rank p-values are provided for both mITT and ITT approaches.

Mega JL, NEJM 2011
Current TIMI Trials

**Follow-up Phase (N=5)**
- IMPROVE-IT (T40) Ph3 – Ezetimibe post ACS
- ENGAGE AF-TIMI 48 Ph3 – Edoxaban in AFib
- ICE-T – TIMI 49 Ph3 – IC TNK in Primary PCI
- TRA 2P-TIMI 50 Ph3 – Vorapaxar in CVD
- SOLID-TIMI 52 Ph3 – PLA2 inhibitor in CAD

**Currently Enrolling (N=4)**
- SAVOR-TIMI 53 Ph3 – DPP4 in DM
- PEGASUS-TIMI 54 Ph3 – Ticagrelor post MI
- HPS3-TIMI 55/Reveal Ph3 – Anacetrapib in CAD
- LAPLACE-TIMI 57 Ph2 - PCSK9 Inhibitor in ↑Chol
Future TIMI Trials

Treatments
Old and new antiplatelet agents
More proximal and oral anticoagulants
Novel lipid-modifying therapies
Diabetes treatment / prevention
Cardioprotective agents
Non-pharmacologic Rx

Strategies
Earlier therapy
Aggressive vs conservative
Markers of high-risk (genetic, clinical, biochemical)
Summary
Important Lessons from TIMI 1-50+

• Clinical trials form a key step in the cycle of clinical therapeutics between the concept and the established guidelines

• Completed trials have helped established standards of care across ACS spectrum (lysis, anticoag, antiplatelets, lipid Rx, inv vs cons)

• Ongoing studies will further refine use of antithrombotics, anti-ischemics, lipid Rx, and other therapies in patients with CAD/ACS
Ezetimibe + Simvastatin vs Simvastatin Alone post ACS

Patients stabilized post Acute Coronary Syndrome < 10 days
LDL ≤ 125*mg/dL (or ≤ 100**mg/dL if prior lipid-lowering Rx)

Double-blind

ASA + Standard Medical Therapy

Simvastatin 40 mg
Eze/Simva 10/40 mg

Follow-Up Visit Day 30, Every 4 Months

Duration: Minimum 2 1/2 year follow-up (>5250 events)

Primary Endpoint: CV Death, MI, Hospital Admission for UA, revascularization (> 30 days after randomization), or Stroke

Cannon et al. AHJ 2008; 156:826-832
Edoxaban (oral FXa inhibitor) in Atrial Fib

**Low Exposure Strategy**
Edoxaban 30 mg QD (n ≈ 7000)

**High Exposure Strategy**
Edoxaban 60 mg QD (n ≈ 7000)

**Randomization Stratified By**
1. CHADS<sub>2</sub> 2-3 vs 4-6
2. Drug Clearance

**Primary Objective**
Edoxaban: Therapeutically as Good as Warfarin

1º EP = Stroke or SEE (Noninferiority Boundary HR 1.38)
2º EP = Stroke or SEE or All-Cause Mortality
Safety EP’s = Major Bleeding, Hepatic Function

SEE = systemic embolic event
Ruff CR. AHJ 2010
ICE T – TIMI 49: Intracoronary TNK in Primary PCI

STEMI < 6 hours for 1° PCI

- ASA 160-325 mg
- Clopidogrel 300-600 mg

TIMI 0/1 Flow in Culprit Artery During Diagnostic Angiography

- IC Tenecteplase (4mg) n=20
- Saline (Placebo) n=20

PCI with stent

Post-treatment Angiography (epicardial flow and myocardial perfusion)

Primary Endpoint: Improvement in % diameter stenosis after 1st administration of study drug
Prior MI, Ischemic CVA, or PAD

Randomize 1:1 Double Blind
Stratify by CAD, CVD or PAD
and intent to use thienopyridine

Vorapaxar
(SCH 530348)

Randomize 1:1 Double Blind
Stratify by CAD, CVD or PAD
and intent to use thienopyridine

Placebo

Follow up Visits
Day 30, Mo 4, Mo 8, Mo 12
Q6 months

Final Visit

Primary EP
CV Death, MI, Stroke,
Urgent Coronary Revascularization

Major Secondary EP: CV death, non-fatal MI, non-fatal stroke

Morrow DA et al. AHJ 2009;158:335-341e3
Stabilization Of pLaques usIng Darapladib (Lp-PLA₂ inhibitor)-TIMI 52

High-risk* patients ≤30 days post-ACS: UA, NSTEMI or STEMI

* Must meet ≥1 enrichment criteria

Guideline-recommended background Rx, including statins and antiplatelet drugs

Double-blind

Randomize 1:1

Darapladib (160mg daily)

Placebo (daily)

Event driven

Total N ~11,500

Total events ~ 1500

Anticipated median f/u ~ 3y

Primary Endpoint: CV Death, Non-fatal MI, or Non-Fatal Stroke
Saxagliptin (DPP-4 inhibitor) Assessment of Vascular Outcomes Recorded in DM - TIMI 53

Documented Type 2 Diabetes

N ~ 12000

Established CV disease or Multiple Risk Factors

RANDOMIZE 1:1 DOUBLE BLIND

Dosing based on eGFR

All other DM Rx per treating MD

SAXAGLIPTIN
2.5 or 5 mg/d

PLACEBO

Follow-up
Min. 3 yr

Duration
Event driven (n=1040)
Estimated time ~ 5 yr

Follow up Visits
Q6 months

Final Visit

Primary EP
CV Death, Non-fatal MI, Non-Fatal Ischemic Stroke

Major Secondary EP: CV death, non-fatal MI, non-fatal stroke, or hospitalization for heart failure, unstable angina pectoris, or coronary revascularization
History of MI 1-3 yrs prior + ≥1 additional atherothrombosis risk factor*

N ~ 21,000

RANDOMIZE DOUBLE BLIND

Ticagrelor 90 mg bid

Ticagrelor 60 mg bid

Placebo

Follow-up Visits
Q4 mos for 1st yr, then Q6 mos

Min 12 mos and median 26 mos follow-up
Event-driven trial

Primary Efficacy Endpoint: CV Death, MI, or Stroke

Primary Safety Endpoint: TIMI Major Bleeding

*Age ≥65 yrs, diabetes, 2nd prior MI, multivessel CAD, or chronic non-end stage renal dysfunction

Planned treatment with ASA 75 – 150 mg & Standard background care
Primary Endpoint
- CV death / MI / Coronary Revascularization

Major Secondary Endpoints: CV death, coronary death or MI, coronary revascularization procedure, or ischemic stroke

Randomized EValuation of the Effects of Anacetrapib through Lipid-modification

Age ≥ 50 and ≥1 of following:
Hx of prior MI, CVD, PAD, or Diabetes with Symptomatic CAD

Total Cholesterol ≤ 155mg/dL

Anacetrapib 100mg/d + Atorvastatin

Minimized Randomization
Double-blind

Placebo + Atorvastatin

Follow up Visits
At month 2 and 6, and every 6 months thereafter.

Final visit

Trial features
- ~30,000 subjects
- ~400 hospitals
- Event driven
- ~4y median f/u

CTSU Oxford University and TIMI Study Group
Trial Design

Screening and Placebo Run-in Period

Fasting LDL-C 5-10 days before randomization

Subcutaneous injection of 6 mL placebo

Randomization 1:1:1:1:1:1

Visits:
- Day 1
- Week 2
- Week 4
- Week 6
- Week 8
- Week 10
- Week 12
- Week 14

Investigational Product Administration (AMG 145 or Placebo)

Q2W:

Q4W:

Placebo SC Q2W
~75 Subjects

Dose 1 AMG 145 SC Q2W
~75 Subjects

Dose 2 AMG 145 SC Q2W
~75 Subjects

Dose 3 AMG 145 SC Q2W
~75 Subjects

Placebo SC Q4W
~75 Subjects

Dose 4 AMG 145 SC Q4W
~75 Subjects

Dose 5 AMG 145 SC Q4W
~75 Subjects

Dose 6 AMG 145 SC Q4W
~75 Subjects

Max. 6 weeks

EOS

Enrollment in extension study, if applicable