What Have We Learned from 35 Years of TIMI Trials?

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Disclosure Information (last 12 m):

- **Grants/Research Support**
  - Amgen, Daiichi Sankyo

- **Consultant**
  - Akcea, Amarin, Amgen, Boehring-Ingelheim, CVS Caremark, Daiichi-Sankyo, Janssen, Merck, Pfizer

- **Honoraria for CME Programs**
  - Amgen, Daiichi-Sankyo, Merck
Objectives

• Describe the cardiovascular guideline recommendations based on TIMI trial findings
• Recall the major findings from the recent TIMI Trials
• Discuss future avenues for clinical research in cardiovascular disease
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
1984-2019

72 Cardiovascular Trials (68 completed)

ACS

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

TIMI BIBLIOGRAPHY: >1000 PEER REVIEWED PUBLICATIONS
Special Report

The Thrombolysis in Myocardial Infarction (TIMI) Trial: Phase I Findings

THE TIMI STUDY GROUP
The first demonstration of the superiority of tissue plasminogen activator over streptokinase in producing successful reperfusion.
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 impot
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
The Prior Decade (2000-2009)

1. Established the risk/benefit for clopidogrel (CLARITY-TIMI 28) and enoxaparin (ExTRACT-TIMI 25) as adjuncts to fibrinolysis for STEMI

2. Intensive statin is better than moderate statin post ACS (PROVE IT-TIMI 22)

3. Prasugrel in ACS treated with PCI (TRITON-TIMI 38)

4. Early Routine vs Late Provisional Use of Eptifibatide (IV GP Ib/IIa) in nSTE-ACS (EARLY-ACS)

5. Ranolazine in nSTE-ACS (MERLIN-TIMI 36)
Impact on Practice Guidelines

**STEMI**

- **I**
  - A
  - Fibrinolytic therapy (fibrin-specific agents preferred)
- **IIa**
  - A
  - Enoxaparin in patients receiving fibrinolytic therapy
- **IIb**
  - A
  - Clopidogrel in patients receiving fibrinolytic therapy
- **III**
  - B
  - Prasugrel should be given as early as possible or at time of primary PCI
  - B
  - Beta-blockers

**UA/NSTEMI**

- **A**
  - Enoxaparin in patients managed either invasively or conservatively
- **B**
  - Prasugrel at the time of PCI in patients at medium or high risk
  - B
  - Early invasive strategy in patients who have an elevated risk for clinical events
  - B
  - Conservative strategy in women with low-risk features
  - A
  - High-intensity statin

ACCF/AHA Guidelines for STEMI (2013) and UA/NSTEMI (2014)
## TIMI Trials 2010-present

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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$_{12}$ assays) and assessment for events

Mega JL, JAMA. 2011;306(20):2221-2228
Platelet Reactivity with ↑ Clopidogrel

Non-Carriers

CYP2C19*2 Heterozygotes

CYP2C19*2 Homozygotes

Squares represent the means and vertical lines the 95% confidence intervals.

Mega JL, JAMA. 2011; 306(20):2221-2228
Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events

Prior MI, CVA, or PAD (MI/PAD Cohort = 20,170)

Standard care including oral antiplt rx

Randomize 1:1 double blind

Stratified by:
1) Qualifying athero
2) Use of thienopyridine

Vorapaxar 2.5 mg/d

Placebo

Follow up visits:
Day 30, Mo 4, Mo 8, Mo 12 Q6 months

Final visit

Median F/U 30 Months

First Efficacy Endpoint: CV Death/MI/Stroke

MI / PAD Inclusion:
1) Type 1 MI (2 wks - 12 mo)
2) Symptoms of claudication and ABI < 0.85 OR
3) prior peripheral revasc

ClinicalTrials.gov NCT00526474c

Morrow DA et al. AHJ 2009;158:335-341e3
Vorapaxar in Stable Atherosclerosis

CV Death, MI, or Stroke

N = 26449 with prior MI, stroke, PAD
Mean f/u: 2.5 years

Hazard Ratio 0.87
p < 0.001

Placebo

Vorapaxar

Morrow et al. NEJM 2012; 366: 1404-1413
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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
Rivaroxaban (oral anticoagulant inhibits FXa) Added to AntipltS Reduces CV events in ACS

**PRIMARY EFFICACY ENDPOINT:**

CV Death / MI / Stroke

- **Placebo**
  - CV death 4.1% vs. 2.7% (HR 0.66)
  - All deaths 4.5% vs 2.9% (HR 0.68)
  - Both p = 0.002

- **Rivaroxaban**
  - (both 2.5 mg and 5 mg)
  - Mortality reduced with 2.5 mg
  - CV death 4.1% vs. 2.7% (HR 0.66)
  - All deaths 4.5% vs 2.9% (HR 0.68)
  - Both p = 0.002

**Estimated Cumulative Incidence (%)**

- Placebo
  - 5113
  - 4307
  - 3470
  - 2664
  - 1831
  - 1079
  - 421

- Rivaroxaban
  - 10229
  - 8502
  - 6753
  - 5137
  - 3554
  - 2084
  - 831

**2 Yr KM Estimate**

- **Placebo:** 10.7%
- **Rivaroxaban:** 8.9%

**HR 0.84 (0.74-0.96)**

**mITT p = 0.008**

**ITT p = 0.002**

**ARR 1.8%**

**NNT = 56**

**TIMI Major Bleed**

- 0.6% vs 1.8% vs. 2.4% (per 2 yr)
- P-values: <0.001, <0.001

**Intracranial Hemorrhage**

- 0.2% vs. 0.4% vs 0.7% (per 2 yr)
- P-values: 0.037, 0.005

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Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin

- History of MI 1-3 yrs prior + ≥1 additional atherothrombosis risk factor*
  - N ~ 21,000
  - RANDOMIZE DOUBLE BLIND
  - Ticagrelor 60 mg bid
  - Ticagrelor 90 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

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

Primary Efficacy Endpoint: CV Death, MI, or Stroke

Primary Safety Endpoint: TIMI Major Bleeding

Bonaca MP. AHJ 2014; 167:437–444
Ticagrelor in Patients w/ Prior MI

21,162 Patients w/ MI 1-3 years prior
All on low-dose ASA
Median follow-up 33 months

Ticagrelor 90 mg
HR 0.85 (95% CI 0.75-0.96)
P=0.008

Ticagrelor 60 mg
HR 0.84 (95% CI 0.74-0.95)
P=0.004

Bonaca et al.. N Engl J Med 2015;
Bleeding

Ticag 90: HR 2.69 (1.96-3.70)
Ticag 60: HR 2.32 (1.68-3.21)

P<0.001

3-Year KM Event Rate (%)

TIMI Major
TIMI Minor
Fatal bleeding or ICH
ICH
Fatal Bleeding

Ticagrelor 90 mg
Ticagrelor 60 mg
Placebo

Bonaca et al.. N Engl J Med 2015;
# TIMI Trials 2010-present

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Study Design

Patients stabilized post ACS ≤ 10 days:
LDL-C 50–125 mg/dL (or 50–100 mg/dL if prior lipid-lowering Rx)

N=18,144

Standard Medical & Interventional Therapy

Simvastatin 40 mg

Ezetimibe / Simvastatin 10 / 40 mg

Duration: Median 6 years follow-up (5314 events)

Primary Endpoint: CV death, MI, hospital admission for UA, coronary revascularization (≥ 30 days after randomization), or stroke

Cannon CP AHJ 2008;156:826-32; Califf RM NEJM 2009;361:712-7; Blazing MA AHJ 2014;168:205-12
**LDL-C and Lipid Changes**

<table>
<thead>
<tr>
<th></th>
<th>1 Yr Mean</th>
<th>LDL-C</th>
<th>TC</th>
<th>TG</th>
<th>HDL</th>
<th>hsCRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simva</td>
<td></td>
<td>69.9</td>
<td>145.1</td>
<td>137.1</td>
<td>48.1</td>
<td>3.8</td>
</tr>
<tr>
<td>EZ/Simva</td>
<td></td>
<td>53.2</td>
<td>125.8</td>
<td>120.4</td>
<td>48.7</td>
<td>3.3</td>
</tr>
<tr>
<td>Δ in mg/dL</td>
<td></td>
<td>-16.7</td>
<td>-19.3</td>
<td>-16.7</td>
<td>+0.6</td>
<td>-0.5</td>
</tr>
<tr>
<td>Δ in mmol/L</td>
<td></td>
<td>-0.43</td>
<td>-0.50</td>
<td>-0.19</td>
<td>+0.02</td>
<td></td>
</tr>
</tbody>
</table>

**Median Time avg**

1.79 vs 1.39 mM
(69.5 vs. 53.7 mg/dL)

Cannon CP, NEJM 2015;372:2387-97
No statistically significant differences in cancer or muscle- or gallbladder-related events

<table>
<thead>
<tr>
<th>Event</th>
<th>Simva n=9077 %</th>
<th>EZ/Simva n=9067 %</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT and/or AST≥3x ULN</td>
<td>2.3</td>
<td>2.5</td>
<td>0.43</td>
</tr>
<tr>
<td>Cholecystectomy</td>
<td>1.5</td>
<td>1.5</td>
<td>0.96</td>
</tr>
<tr>
<td>Gallbladder-related AEs</td>
<td>3.5</td>
<td>3.1</td>
<td>0.10</td>
</tr>
<tr>
<td>Rhabdomyolysis*</td>
<td>0.2</td>
<td>0.1</td>
<td>0.37</td>
</tr>
<tr>
<td>Myopathy*</td>
<td>0.1</td>
<td>0.2</td>
<td>0.32</td>
</tr>
<tr>
<td>Rhabdo, myopathy, myalgia with CK elevation*</td>
<td>0.6</td>
<td>0.6</td>
<td>0.64</td>
</tr>
<tr>
<td>Cancer* (7-yr KM %)</td>
<td>10.2</td>
<td>10.2</td>
<td>0.57</td>
</tr>
</tbody>
</table>

* Adjudicated by Clinical Events Committee

% = n/N for the trial duration
Cannon CP, NEJM 2015;372:2387-97
**IMPROVE-IT vs. CTT: Ezetimibe vs. Statin Benefit**

CTT Collaboration. 
Lancet 2005; 366:1267-78; 
NEJM 2-15;372:2387-97

Using CTT methods: LDL difference between groups using baseline LDL for Pts without blood samples. Endpoint of CV Death, MI, stroke or revasc >30days post Rand. Cox HR reported.
27,564 high-risk, stable patients with established CV disease (prior MI, prior stroke, or symptomatic PAD)

Screening, Lipid Stabilization, and Placebo Run-in
High or moderate intensity statin therapy (± ezetimibe)

LDL-C ≥70 mg/dL or non-HDL-C ≥100 mg/dL

RANDOMIZED DOUBLE BLIND
Evolocumab SC
140 mg Q2W or 420 mg QM

Placebo SC
Q2W or QM

Follow-up Q 12 weeks
Median 26 mth [22,30]

LDL > 1.8 mM
Non-HDL > 2.6 mM

Summary of FOURIER

• ↓ LDL-C by 59% (from 2.4 -> 0.8 [0.5, 1.2] mM)
• ↓ CV outcomes in patients already on statin therapy
• Evolocumab was safe and well-tolerated

CV Death, MI, or Stroke

<table>
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<tr>
<th>LDL-C (mg/dL)</th>
<th>Adj usted HR (95% CI)</th>
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<tr>
<td>&lt;20</td>
<td>0.69 (0.56-0.85)</td>
</tr>
<tr>
<td>20-50</td>
<td>0.75 (0.64-0.86)</td>
</tr>
<tr>
<td>50-70</td>
<td>0.87 (0.73-1.04)</td>
</tr>
<tr>
<td>70-100</td>
<td>0.90 (0.78-1.04)</td>
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<tr>
<td>≥ 100</td>
<td>referent</td>
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*P = 0.0001*
EBBINGHAUS Primary Endpoint
Spatial Working Memory Strategy Index

Mean Number of boxes

Baseline: Placebo 17.8, Evolocumab 17.8
Post baseline: Placebo 17.6, Evolocumab 17.5
Change: Placebo -0.29, Evolocumab -0.21

Treatment Difference in Z score
(Placebo minus Evolocumab)
Favors Evolocumab
Favors Placebo

P_{non-inferiority} < 0.001

Non-inferiority boundary 0.19

A Quarter of a Century of Treating LDL-C

High is bad
Average is not good
Lower is better
Even lower is even better
Lowest is best

LDL-C (mg/dL)
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**Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with DM - TIMI 53**

**Documented Type 2 Diabetes**

N = 16,492

**RANDOMIZED 1:1 DOUBLE BLIND**

**SAXAGLIPTIN**
5 mg/d

2.5 mg/d if eGFR ≤ 50 ml/min

**PLACEBO**

**Established CV Disease or Multiple Risk Factors**

**Duration**
Event driven (n=1040)
Median duration 2.1y
LTFU 0.2%
W/C 2.4%

**Follow up Visits**
Q6 months

**Final Visit**

**Primary EP**
CV Death, MI, Ischemic Stroke

**Major Secondary EP**: CV death, MI, ischemic stroke, or hosp. for heart failure, unstable angina, or coronary revascularization

### Individual Endpoints

<table>
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<tr>
<th>ITT Population</th>
<th>2-year KM rate (%)</th>
<th>HR</th>
<th>$p$ value for superiority</th>
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<tr>
<td>Placebo (N=8,212)</td>
<td>Saxagliptin (N=8,280)</td>
<td></td>
<td></td>
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<tr>
<td>CV Death, MI, Isc stroke</td>
<td>7.2</td>
<td>7.3</td>
<td>1.00 (0.89-1.12)</td>
</tr>
<tr>
<td>CV Death</td>
<td>2.9</td>
<td>3.2</td>
<td>1.03 (0.87-1.22)</td>
</tr>
<tr>
<td>MI</td>
<td>3.4</td>
<td>3.2</td>
<td>0.95 (0.80-1.12)</td>
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<tr>
<td>Ischemic Stroke</td>
<td>1.7</td>
<td>1.9</td>
<td>1.11 (0.88-1.39)</td>
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<tr>
<td>Hosp for Cor. Revasc</td>
<td>5.6</td>
<td>5.2</td>
<td>0.91 (0.80-1.04)</td>
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<td>Hosp for UA</td>
<td>1.0</td>
<td>1.2</td>
<td>1.19 (0.89-1.60)</td>
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<td>Hosp for Heart Failure</td>
<td>2.8</td>
<td>3.5</td>
<td>1.27 (1.07-1.51)</td>
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<tr>
<td>All-Cause Mortality</td>
<td>4.2</td>
<td>4.9</td>
<td>1.11 (0.96-1.27)</td>
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Scirica BM et al. NEJM 2013; 369:1317-26
Dapagliflozin Effect on Cardiovascular Events

**DIAGNOSED TYPE 2 DIABETES**
- ESTABLISHED CV DISEASE OR MULTIPLE RISK FACTORS

**RANDOMIZE 1:1 DOUBLE BLIND**
- DAPAGLIFLOZIN 10 mg DAILY
- PLACEBO
  - All other DM Rx per treating MD

**FOLLOW-UP CLINIC VISITS**
- Q 6 MO. & TELEPHONIC CONTACT / VISIT Q 3 MO.

**SECONDARY EPS**
- HOSPITALIZATION FOR CHF
- EXPANDED MACE
- ALL-CAUSE MORTALITY
- WEIGHT CHANGE

**PRIMARY EP**
- MACE: CV DEATH, MI, ISCHEMIC STROKE

**N ~ 17150**

**MEDIAN FOLLOW-UP APPROX. 4.5 YRS**

**DURATION**
- EVENT DRIVEN
- 1390 EVENTS TOTAL ~ 6YRS

Primary Endpoints

CVD/HHF

4.9% vs 5.8%
HR 0.83 (0.73-0.95)
P(Superiority) 0.005

MACE

8.8% vs 9.4%
HR 0.93 (0.84-1.03)
P(Noninferiority) <0.001
P(Superiority) 0.17

[Graphs showing probability of event over analysis time for Dapagliflozin and Placebo]
Secondary Endpoints

Renal Composite EP
40% ↓ eGFR, ESRD, Renal or CV death

4.3% vs. 5.6%
HR 0.76 (0.67-0.87)
P<0.001

All-Cause Mortality

6.2% vs 6.6%
HR 0.93 (0.82-1.04)
P=0.20

# Key Safety Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Dapagliflozin (%)</th>
<th>Placebo (%)</th>
<th>Between Group Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment emergent SAE</td>
<td>34.1</td>
<td>36.2</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Treatment emergent AE leading to drug D/C</td>
<td>8.1</td>
<td>6.9</td>
<td>P=0.01</td>
</tr>
<tr>
<td>Major Hypoglycemia</td>
<td>0.7</td>
<td>1.0</td>
<td>P=0.02</td>
</tr>
<tr>
<td>Diabetic Ketoacidosis* (DKA)</td>
<td>0.3</td>
<td>0.1</td>
<td>P=0.02</td>
</tr>
<tr>
<td>Amputation</td>
<td>1.4</td>
<td>1.3</td>
<td>NS</td>
</tr>
<tr>
<td>Fracture</td>
<td>5.3</td>
<td>5.1</td>
<td>NS</td>
</tr>
<tr>
<td>Acute Kidney Injury</td>
<td>1.5</td>
<td>2.0</td>
<td>P=0.002</td>
</tr>
<tr>
<td>Symptoms of volume depletion</td>
<td>2.5</td>
<td>2.4</td>
<td>NS</td>
</tr>
<tr>
<td>Genital infection (SAE, DAE)</td>
<td>0.9</td>
<td>0.1</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Urinary tract infection (SAE, DAE)</td>
<td>1.5</td>
<td>1.6</td>
<td>NS</td>
</tr>
<tr>
<td>Fournier’s Gangrene</td>
<td>0.01</td>
<td>0.08</td>
<td>NS</td>
</tr>
<tr>
<td>Cancer of Bladder*</td>
<td>0.3</td>
<td>0.5</td>
<td>P=0.02</td>
</tr>
</tbody>
</table>

*CEC Adjudicated*
Meta-Analysis of CVOTs: MACE by Presence of ASCVD

<table>
<thead>
<tr>
<th>MACE</th>
<th>Treatment Events per 1000 pt-ys</th>
<th>Placebo Events per 1000 pt-ys</th>
<th>HR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atherosclerotic Cardiovascular Disease:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EMPA-REG OUTCOME</td>
<td>37.4</td>
<td>43.9</td>
<td>0.86 [0.74, 0.99]</td>
</tr>
<tr>
<td>CANVAS Program</td>
<td>34.1</td>
<td>41.3</td>
<td>0.82 [0.72, 0.95]</td>
</tr>
<tr>
<td>DECLARE-TIMI 58</td>
<td>36.8</td>
<td>41</td>
<td>0.90 [0.79, 1.02]</td>
</tr>
<tr>
<td>FE Model for ASCVD (P-value = 0.0002)</td>
<td></td>
<td></td>
<td>0.86 [0.80, 0.93]</td>
</tr>
<tr>
<td>Multiple Risk Factor:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CANVAS Program</td>
<td>15.8</td>
<td>15.5</td>
<td>0.98 [0.74, 1.30]</td>
</tr>
<tr>
<td>DECLARE-TIMI 58</td>
<td>13.4</td>
<td>13.3</td>
<td>1.01 [0.86, 1.20]</td>
</tr>
<tr>
<td>FE Model for MRF (P-value = 0.98)</td>
<td></td>
<td></td>
<td>1.00 [0.87, 1.16]</td>
</tr>
</tbody>
</table>

Test for Subgroup Differences p=0.05
# Meta-Analysis of CVOTs: CVD/HHF by Presence of ASCVD

<table>
<thead>
<tr>
<th>CVD/HHF</th>
<th>Treatment Events per 1000 pt-yrs</th>
<th>Placebo Events per 1000 pt-yrs</th>
<th>HR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atherosclerotic Cardiovascular Disease:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EMPA-REG OUTCOME</td>
<td>19.7</td>
<td>30.1</td>
<td>0.66 [0.55, 0.79]</td>
</tr>
<tr>
<td>CANVAS Program</td>
<td>21</td>
<td>27.4</td>
<td>0.77 [0.65, 0.92]</td>
</tr>
<tr>
<td>DECLARE-TIMI 58</td>
<td>19.9</td>
<td>23.9</td>
<td>0.83 [0.71, 0.98]</td>
</tr>
<tr>
<td>FE Model for ASCVD (P-value &lt;0.0001)</td>
<td></td>
<td></td>
<td>0.76 [0.69, 0.84]</td>
</tr>
<tr>
<td>Multiple Risk Factor:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CANVAS Program</td>
<td>8.9</td>
<td>9.8</td>
<td>0.83 [0.58, 1.19]</td>
</tr>
<tr>
<td>DECLARE-TIMI 58</td>
<td>7</td>
<td>8.4</td>
<td>0.84 [0.67, 1.04]</td>
</tr>
<tr>
<td>FE Model for MRF (P-value = 0.0634)</td>
<td></td>
<td></td>
<td>0.84 [0.69, 1.01]</td>
</tr>
</tbody>
</table>

Test for Subgroup Differences p=0.41

## TIMI Trials 2010-present

<table>
<thead>
<tr>
<th>Population</th>
<th>Experimental Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACS</td>
<td>antiplatelet, anti-inflammatory</td>
</tr>
<tr>
<td>Post ACS</td>
<td>oral factor Xa, Lp-PLA(_2) inhibitor</td>
</tr>
<tr>
<td>Lipid-lowering</td>
<td>ezetimibe, PCSK9, CETP</td>
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<td>Diabetes</td>
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<tr>
<td>Atrial Fib</td>
<td>oral factor Xa</td>
</tr>
<tr>
<td>Metabolic syndr.</td>
<td>serotonin receptor agonist\</td>
</tr>
<tr>
<td>Heart failure</td>
<td>neprilysin inhibitor</td>
</tr>
</tbody>
</table>
Effective aNTicoaGulation with factor xA next GEneration in Atrial Fibrillation

21,105 PATIENTS
AF on electrical recording within last 12 m
CHADS₂ ≥2

RANDOMIZATION
1:1:1 randomization is stratified by CHADS₂ score 2–3 versus 4–6 and need for edoxaban dose reduction*

Double-blind, Double-dummy

Warfarin (INR 2.0–3.0)

High-dose Edoxaban 60* mg QD

Low-dose Edoxaban 30* mg QD

*Dose reduced by 50% if:
- CrCl 30–50 mL/min
- weight ≤60 kg
- strong P-gp inhibitor

1° Efficacy EP = Stroke or SEE
2° Efficacy EP = Stroke or SEE or CV mortality
1° Safety EP = Major Bleeding (ISTH criteria)

Non-inferiority
Upper 97.5% CI <1.38

CI = confidence interval; CrCl = creatinine clearance; ISTH=International Society on Thrombosis and Haemostasis; P-gp = P-glycoprotein; SEE = systemic embolic event

Ruff CR. AHJ 2010; 160:635-41.
Primary Efficacy and Safety Results
(2.8 years median f/u)

Stroke/SEE: Noninferiority Analysis (mITT, On Treatment)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Hazard ratio (97.5% CI)</th>
<th>P Values</th>
</tr>
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<tr>
<td>Edoxaban 60 mg QD</td>
<td>0.79</td>
<td>Non-inferiority: P&lt;0.0001</td>
</tr>
<tr>
<td>vs warfarin</td>
<td></td>
<td>Superiority: P=0.017</td>
</tr>
<tr>
<td>Edoxaban 30 mg QD</td>
<td>1.07</td>
<td>Non-inferiority: P=0.005</td>
</tr>
<tr>
<td>vs warfarin</td>
<td></td>
<td>Superiority: P=0.44</td>
</tr>
</tbody>
</table>

Warfarin TTR 68.4%

ISTH Major Bleeding

<table>
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<tr>
<th>Treatment</th>
<th>Hazard ratio (97.5% CI)</th>
<th>P Values</th>
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<tbody>
<tr>
<td>Edoxaban</td>
<td>0.80</td>
<td>Non-inferiority: P&lt;0.001</td>
</tr>
<tr>
<td>vs warfarin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Dose reduced by 50% in selected pts

Giugliano RP. NEJM 2013; 369:2093-2104
## TIMI Trials 2010-present

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<td>Heart failure</td>
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</tr>
</tbody>
</table>
Obese or Overweight (BMI ≥ 27 kg/m²) Established CV disease* or T2DM & other CV risk factors†

Exercise & Reduced-Calorie Diet

RANDOMIZE 1:1 DOUBLE BLIND Stratified by CV disease or CV RF

Lorcaserin 10mg BID

PLACEBO

Follow up visits Q 3mo x 2yr then Q 4mo

Interim Analysis (Safety)

End of Treatment (Efficacy)

Primary Safety: Non-inferiority for MACE with boundary of 1.4
Efficacy: Superiority for MACE+

Primary CV Safety EP: MACE (CV Death, MI, CVA)
Primary CV Efficacy EP: MACE+ (MACE, Hosp for HF or UA, cor revasc)

N = 12,000

Median Follow up: 3.3 yrs

*Coronary, cerebrovascular or peripheral artery disease; †T2DM with ≥ 1 of following: HTN, HL, hsCRP > 3, eGFR 30-60, albuminuria

Primary CV Outcomes

CV Death, MI, Stroke (Safety)

- **Lorc**: n (%)/yr
  - CV death, MI, or stroke: 364 (2.0)
- **Pbo**: n (%)/yr
  - CV death, MI, or stroke: 369 (2.1)

MACE HR (95%CI)
- MACE HR: 0.99* (0.85, 1.14)

Hazard Ratio (95% CI)
- Favors Lorcaserin
- Favors Placebo

*P (non-inferiority) < 0.001

*Non-inferiority boundary: HR 97.5% upper bound of 1.4

CV Death, MI, Stroke, HF, Hosp for UA, Cor Revasc (Efficacy)

- HR 0.97 (0.87, 1.07)
- P=0.55 for superiority

Cumulative Incidence of MACE+

- Lorcaserin
  - 13.3% (727 events)
- Placebo
  - 12.8% (707 events)

Bohula EA et al. New Engl J Med 2018
Hemoglobin A1c

Pts w/ Diabetes

Pts w/ Pre-Diabetes

Pts w/ Normoglycemia

Change in HbA1c from Baseline (%)

Months Since Randomization

Lorcaserin
Placebo

Δ-0.3%
p<0.001

Δ-0.1%
p<0.001

Δ-0.1%
p<0.001

Bohula EA et al. Lancet 2018
Incident Diabetes

Cumulative Incidence of New Onset Diabetes in pts w/ pre-DM

Placebo 1976 1883 1784 826
Lorcaserin 2015 1950 1872 890

HR 0.81 (0.66, 0.99)
P=0.038

10.3% (204 events)
8.5% (172 events)

Adjudicated by a blinded clinical events committee according to ADA definition
## TIMI Trials 2010-present

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</tr>
</tbody>
</table>
Hospitalized with ADHF (HFrEF) → Stabilized

- Evaluate biomarker surrogates of efficacy
- Evaluate safety and tolerability
- Explore clinical outcomes

In-hospital initiation

Titration algorithm over 8 weeks

sacubitril/valsartan vs enalapril

Velazquez EJ, Am Heart J 2018;198:145-151
Primary Endpoint: % Change in NT-proBNP

29% greater reduction with sacubitril/valsartan
CI 19%, 37%; P < 0.0001

Velazquez EJ, NEJM 2018 (online DOI: 10.1056/NEJMoa1812851)
Serious Composite Clinical Endpoint

Death, HF re-hosp, LVAD, Transplant listing

HR = 0.54; 95% CI 0.37, 0.79
P = 0.001
NNT = 13

enalapril
N = 441
16.8%
sacubitril/valsartan
N = 440
9.3%

Velazquez EJ, NEJM 2018 (online DOI: 10.1056/NEJMoa1812851)
Summary

Important Lessons from TIMI 1-60+

• 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, antiplts, 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
Ongoing TIMI Trials

**FOURIER OLE**: Open label ext w/ evolocumab

**FOURIER Legacy**: 5-year f/u (observational)

**REAL CVD-TIMI 63**: LCAT inhibitor in stable CAD (63a) and STEMI (63b)

**HPS-4/TIMI 65 ORION-4**: PCSK9 RNA synthesis inhibitor in stable CAD
Future Clinical Trials

**Treatments**
- Old and new antiplatelet agents
- Safer, more effective oral anticoagulants
- Novel lipid-modifying therapies
- Diabetes / metabolic syndrome / obesity
- Cardioprotective and anti-inflammatory agents
- Non-pharmacologic Rx

**Strategies**
- Earlier, more intensive therapies
- Aggressive vs conservative
- Markers of high-risk (genetic, biochemical)
The Future of Clinical Trials

• Targets
  – Reductionist biology
  – Harness genetics and systems biology to identify optimal targets

• Subjects
  – Clinical criteria
  – Personalized based on biochemical, genetic, and imaging data

• Drugs
  – One size fits all
  – Multiple doses, tailor dose for a particular patient

• Trials
  – Fixed design, SOPs, heavy regulatory burden
  – Adaptive, simpler procedures, tailored need, social media & tech
Goals of Clinical Trials

• Identify new treatments
• Bring new drugs/devices into the clinic
• Extend indications on existing therapies
• Test new strategies
• Provide new insights
• Change guidelines for care

Improve outcomes for our patients