Training course:  
All About Clinical Trials

How to interpret clinical trial data – 
Examples from clinical trials

Sven Wassmann, MD, PhD, FESC

Munich, Germany
Declaration of Conflict of Interest

The existence of potential conflicts of interest does not necessarily indicate a bias. However, it is our ethical obligation to inform organisers and participants so that they are made aware of any relationship that might cause unintentional bias. A potential conflict of interest may arise from various relationships, past or present, such as employment, consultancy, investments, and stock ownerships, funding for research, family relationship, etc.

☐ I have no potential conflict of interest to report
X I have the following potential conflict(s) of interest to report

<table>
<thead>
<tr>
<th>Type of affiliation / financial interest</th>
<th>Name of commercial company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Receipt of grants/research supports:</td>
<td>No</td>
</tr>
<tr>
<td>Receipt of honoraria or consultation fees:</td>
<td>Boehringer Ingelheim, Daiichi Sankyo, AstraZeneca, Pfizer, Apontis</td>
</tr>
<tr>
<td>Participation in a company sponsored speaker’s bureau:</td>
<td>Amgen, AstraZeneca, Berlin Chemie, Bristol Myers Squibb, Boehringer Ingelheim, Daiichi Sankyo, Merck Sharp Dohme, Novartis, Pfizer</td>
</tr>
<tr>
<td>Stock shareholder:</td>
<td>No</td>
</tr>
<tr>
<td>Spouse/partner:</td>
<td>No</td>
</tr>
<tr>
<td>Other support (please specify):</td>
<td>No</td>
</tr>
</tbody>
</table>
What do you have to know from the trial?

• WHY
• WHO
• HOW
WHY — Goals / Hypothesis

IMPROVE-IT

First large trial evaluating clinical efficacy of combination EZ/Simva vs. simvastatin (i.e., the addition of ezetimibe to statin therapy):

➢ Does lowering LDL-C with the non-statin agent ezetimibe reduce cardiac events?

➢ “Is (Even) Lower (Even) Better?” (estimated mean LDL-C ~50 vs. 65mg/dL)

➢ Safety of ezetimibe

Cannon CP AHJ 2008;156:826-32; Califf RM NEJM 2009;361:712-7; Blazing MA AHJ 2014;168:205-12
WHO — Patient Population

Inclusion Criteria:

- Hospitalization for STEMI, NSTEMI/UA < 10 days
- Age ≥ 50 years, and ≥ 1 high-risk feature:
  - New ST chg, + troponin, DM, prior MI, PAD, cerebrovasc,
    prior CABG > 3 years, multivessel CAD
- LDL-C 50-125 mg/dL (50–100 mg/dL if prior lipid-lowering Rx)

Major Exclusion Criteria:

- CABG for treatment of qualifying ACS
- Current statin Rx more potent than simva 40mg
- Creat Cl < 30mL/min, active liver disease
Patients stabilized post ACS ≤ 10 days: LDL-C 50–125*mg/dL (or 50–100**mg/dL if prior lipid-lowering Rx)

Standard Medical & Interventional Therapy

N=18,144

Simvastatin 40 mg

Uptitrated to Simva 80 mg if LDL-C > 79 (adapted per FDA label 2011)

Ezetimibe / Simvastatin 10 / 40 mg

Follow-up Visit Day 30, every 4 months

Duration: Minimum 2 ½-year follow-up (at least 5250 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
## Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Simvastatin (N=9077) %</th>
<th>EZ/Simva (N=9067) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>64</td>
<td>64</td>
</tr>
<tr>
<td>Female</td>
<td>24</td>
<td>25</td>
</tr>
<tr>
<td>Diabetes</td>
<td>27</td>
<td>27</td>
</tr>
<tr>
<td>MI prior to index ACS</td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td>STEMI / NSTEMI / UA</td>
<td>29 / 47 / 24</td>
<td>29 / 47 / 24</td>
</tr>
<tr>
<td>Days post ACS to rand (IQR)</td>
<td>5 (3, 8)</td>
<td>5 (3, 8)</td>
</tr>
<tr>
<td>Cath / PCI for ACS event</td>
<td>88 / 70</td>
<td>88 / 70</td>
</tr>
<tr>
<td>Prior lipid Rx</td>
<td>35</td>
<td>36</td>
</tr>
<tr>
<td>LDL-C at ACS event (mg/dL, IQR)</td>
<td>95 (79, 110)</td>
<td>95 (79, 110)</td>
</tr>
</tbody>
</table>

LDL-C and Lipid Changes

1 Yr Mean

<table>
<thead>
<tr>
<th></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>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>53.2</td>
<td>125.8</td>
<td>120.4</td>
<td>48.7</td>
<td>3.3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Δ in mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simva</td>
<td>-16.7</td>
</tr>
<tr>
<td>EZ/Simva</td>
<td>-19.3</td>
</tr>
</tbody>
</table>

|        | +0.6       | -0.5 |

Median Time avg 69.5 vs. 53.7 mg/dL

Number at risk:

<table>
<thead>
<tr>
<th></th>
<th>EZ/Simva</th>
<th>Simva</th>
</tr>
</thead>
<tbody>
<tr>
<td>QE</td>
<td>8990</td>
<td>9009</td>
</tr>
<tr>
<td>R</td>
<td>8890</td>
<td>8921</td>
</tr>
<tr>
<td>1</td>
<td>8230</td>
<td>8306</td>
</tr>
<tr>
<td>4</td>
<td>7701</td>
<td>7843</td>
</tr>
<tr>
<td>8</td>
<td>7264</td>
<td>7289</td>
</tr>
<tr>
<td>12</td>
<td>6864</td>
<td>6939</td>
</tr>
<tr>
<td>16</td>
<td>6583</td>
<td>6607</td>
</tr>
<tr>
<td>24</td>
<td>6256</td>
<td>6192</td>
</tr>
<tr>
<td>36</td>
<td>5734</td>
<td>5684</td>
</tr>
<tr>
<td>48</td>
<td>5354</td>
<td>5267</td>
</tr>
<tr>
<td>60</td>
<td>4508</td>
<td>4395</td>
</tr>
<tr>
<td>72</td>
<td>3484</td>
<td>3387</td>
</tr>
<tr>
<td>84</td>
<td>2608</td>
<td>2569</td>
</tr>
<tr>
<td>96</td>
<td>1078</td>
<td>1068</td>
</tr>
</tbody>
</table>

Primary Endpoint — ITT

Cardiovascular death, MI, documented unstable angina requiring rehospitalization

What does this mean?

- **RRR 6%**
- **p = 0.016**
- **2742 events**
- **NNT = 50**
- **EZ/Simva — 32.7%**
- **2572 events**


7-year event rates
Primary Endpoint — Interpretation

![Graph showing the relationship between reduction in LDL cholesterol and rate of major vascular events.](image)

Primary and 3 Prespecified Secondary Endpoints — ITT

Secondary endpoints valid?

<table>
<thead>
<tr>
<th>Primary</th>
<th>0.936</th>
<th>34.7</th>
<th>32.7</th>
<th>0.016</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVD/MI/UA/Cor Revasc/CVA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary #1</th>
<th>0.948</th>
<th>40.3</th>
<th>38.7</th>
<th>0.034</th>
</tr>
</thead>
<tbody>
<tr>
<td>All D/MI/UA/Cor Revasc</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary #2</th>
<th>0.912</th>
<th>18.9</th>
<th>17.5</th>
<th>0.016</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD/MI/Urgent Cor Revasc</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary #3</th>
<th>0.945</th>
<th>36.2</th>
<th>34.5</th>
<th>0.035</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVD/MI/UA/All Revasc/CVA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*7-year event rates (%)
“Levels“ of Endpoints

Level 1: All-cause mortality

Level 2: Cause-specific mortality (focal MI)

Level 3: Non-fatal clinical events
  a) Non-fatal MI; b) hospitalisation

Level 4: Surrogates
  e.g. LDL cholesterol

Level 5: Quality of life

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>HR</th>
<th>Simva*</th>
<th>EZ/Simva*</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause death</td>
<td>0.99</td>
<td>15.3</td>
<td>15.4</td>
<td>0.782</td>
</tr>
<tr>
<td>CVD</td>
<td>1.00</td>
<td>6.8</td>
<td>6.9</td>
<td>0.997</td>
</tr>
<tr>
<td>CHD</td>
<td>0.96</td>
<td>5.8</td>
<td>5.7</td>
<td>0.499</td>
</tr>
<tr>
<td>MI</td>
<td>0.87</td>
<td>14.8</td>
<td>13.1</td>
<td>0.002 *</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.86</td>
<td>4.8</td>
<td>4.2</td>
<td>0.052</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>0.79</td>
<td>4.1</td>
<td>3.4</td>
<td>0.008 *</td>
</tr>
<tr>
<td>Cor revasc ≥ 30d</td>
<td>0.95</td>
<td>23.4</td>
<td>21.8</td>
<td>0.107</td>
</tr>
<tr>
<td>UA</td>
<td>1.06</td>
<td>1.9</td>
<td>2.1</td>
<td>0.618</td>
</tr>
<tr>
<td>CVD/MI/stroke</td>
<td>0.90</td>
<td>22.2</td>
<td>20.4</td>
<td>0.003 *</td>
</tr>
</tbody>
</table>

*Cannon et al., N Engl J Med 2015;372:2387-97*
Validity of Subgroup Analysis - Rule of 4 P’s

- Prespecified
- Powered
- Plausible
- Practically relevant
Subgroup Analysis


## Major Pre-specified Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Ezetimibe/Simva Better</th>
<th>Simva Better</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>33.3</td>
<td>31.0</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &lt; 65 years</td>
<td>39.9</td>
<td>36.4</td>
</tr>
<tr>
<td>Age ≥ 65 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No diabetes</td>
<td>30.8</td>
<td>30.2</td>
</tr>
<tr>
<td>Diabetes</td>
<td>45.5</td>
<td>40.0</td>
</tr>
<tr>
<td>Prior LLT</td>
<td>43.4</td>
<td>40.7</td>
</tr>
<tr>
<td>No prior LLT</td>
<td>30.0</td>
<td>28.6</td>
</tr>
<tr>
<td>LDL-C &gt; 95 mg/dl</td>
<td>31.2</td>
<td>29.6</td>
</tr>
<tr>
<td>LDL-C ≤ 95 mg/dl</td>
<td>38.4</td>
<td>36.0</td>
</tr>
</tbody>
</table>

*p-interaction = 0.023, otherwise > 0.05

†7-year event rates
Subgroup Analysis

4,933 (27%) pts with Diabetes

**Primary Endpoint — ITT**

**What does this mean?**

- **HR 0.86 (0.78, 0.94)**
- **RRR 14%**
- **P_{int} = 0.023**

- **HR 0.98 (0.91, 1.04)**

**EZE/Simva**

**40.0%**

**No DM**

**7 yr KM rate**

- **Plac/Simva**
  - 30.8%
- **EZE/Simva**
  - 30.2%
Study Design

Atrial Fibrillation

Rivaroxaban
- 20 mg daily
- 15 mg for CrCl 30–49 ml/min

Randomized Double Blind / Double Dummy
(n ~ 14,264)

Warfarin
- INR target –2.5
- (2.0–3.0 inclusive)

Monthly Monitoring
Adherence to standard of care guidelines

Primary Endpoint:
Stroke or non-CNS Systemic Embolism

Risk Factors
- CHF
- Hypertension
- Age ≥ 75
- Diabetes
- Stroke, TIA or Systemic embolus

At least 2 or 3 required *

* Enrolment of patients without prior Stroke, TIA or systemic embolism and only 2 factors capped at 10%

Mahaffey; Oral presentation at AHA, 15th November 2010
Sample Size
- Warfarin event rate ~2.3
- Type 1 error 0.05 (2-sided)
- 405 events; > 95 % power
- ~14,000 patients

Primary Efficacy Evaluation: Stroke or non-CNS Embolism
- Non-Inferiority: Protocol compliant on treatment
- Superiority: On Treatment and then by Intention-to-Treat

Primary Safety Evaluation:
Major or non-Major Clinically Relevant Bleeding

Statistical Methodologies
Primary Efficacy Outcome
Stroke and non-CNS Embolism

Event Rates are per 100 patient-years
Based on Protocol Compliant on Treatment Population

Primary Efficacy Outcome
Stroke and non-CNS Embolism

Intention-to-treat
or
On-treatment Analysis
for Superiority?

Event Rates are per 100 patient-years
Based on Safety on Treatment or Intention-to-Treat thru
Site Notification populations

Non-inferiority: On-treatment analysis
Superiority: Intention-to-treat analysis
Safety: On-treatment analysis
Atrial Fibrillation with at Least One Additional Risk Factor for Stroke

**Inclusion risk factors**
- Age ≥ 75 years
- Prior stroke, TIA, or SE
- HF or LVEF ≤ 40%
- Diabetes mellitus
- Hypertension

**Randomize double blind, double dummy (n = 18,201)**
- Apixaban 5 mg oral twice daily (2.5 mg BID in selected patients)
- Warfarin (target INR 2-3)

**Primary outcome:** stroke or systemic embolism

**Hierarchical testing:** non-inferiority for primary outcome, superiority for primary outcome, major bleeding, death

**Major exclusion criteria**
- Mechanical prosthetic valve
- Severe renal insufficiency
- Need for aspirin plus thienopyridine

Warfarin/warfarin placebo adjusted by INR/sham INR based on encrypted point-of-care testing device

Presented at ESC 2011; Granger et al. NEJM 2011;365:981-92
To control the overall type I error, a pre-specified hierarchical sequential testing was performed.

1. The primary outcome (stroke or systemic embolism) for non-inferiority (upper limit of 95% CI < 1.38 and upper limit of 99% CI < 1.44)

2. If met, then the primary outcome was tested for superiority

3. If met, then major bleeding was tested for superiority

4. If met, then all-cause mortality was tested for superiority
Primary Outcome
Stroke (ischemic or hemorrhagic) or systemic embolism

- **Apixaban**: 212 patients, 1.27% per year
- **Warfarin**: 265 patients, 1.60% per year

HR 0.79 (95% CI, 0.66 – 0.95); P (superiority)=0.011

P (non-inferiority)<0.001

21% RRR

Presented at ESC 2011; Granger et al. NEJM 2011;365:981-92
Major Bleeding
ISTH definition

Apixaban  327 patients, 2.13% per year
Warfarin  462 patients, 3.09% per year

HR 0.69 (95% CI, 0.60–0.80); P<0.001

No. at Risk
Apixaban  9088  8103  7564  5365  3048  1515
Warfarin  9052  7910  7335  5196  2956  1491

31% RRR
Presented at ESC 2011; Granger et al. NEJM 2011;365:981-92
Atrial Fibrillation with at Least One Additional Risk Factor for Stroke

**Inclusion risk factors**
- Age ≥ 75 years
- Prior stroke, TIA, or SE
- HF or LVEF ≤ 40%
- Diabetes mellitus
- Hypertension

**Randomize double blind, double dummy (n = 18,201)**

- Apixaban 5 mg oral twice daily (2.5 mg BID in selected patients)
- Warfarin (target INR 2-3)

**Major exclusion criteria**
- Mechanical prosthetic valve
- Severe renal insufficiency
- Need for aspirin plus thienopyridine

**Primary outcome: stroke or systemic embolism**

*Hierarchical testing: non-inferiority for primary outcome, superiority for primary outcome, major bleeding, death*

Warfarin/warfarin placebo adjusted by INR/sham INR based on encrypted point-of-care testing device

Presented at ESC 2011; Granger et al. NEJM 2011;365:981-92
What do we know about the 2.5 mg BID dose?
**Study Design**

- **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**
- Non-inferiority
  - Upper 97.5% CI < 1.38

- **2° Efficacy EP = Stroke or SEE or CV mortality**

- **1° Safety EP = Major Bleeding (ISTH criteria)**

---

ENGAGE AF – TIMI 48

Population/Analysis Definitions

Populations

- mITT*, On-Treatment†
- Intent-to-Treat (ITT)
  All randomized
- Safety, On-Treatment†

Analyses

- Primary efficacy
  (Non-inferiority)
- Superiority
  All events
- Principal Safety
  Major Bleeding (ISTH definition)

* mITT = All patients who took at least 1 dose
† On-Treatment = 1st dose → last dose +3 days or end of double-blind treatment
ISTH=International Society on Thrombosis and Haemostasis

ENGAGE AF – TIMI 48

Modified Intention-to-treat Analysis?

mITT*, On-Treatment† → Primary efficacy (Non-inferiority)

Intent-to-Treat (ITT)
All randomized → Superiority
All events

Safety, On-Treatment† → Principal Safety
Major Bleeding (ISTH definition)

* mITT = All patients who took at least 1 dose
† On-Treatment = 1st dose → last dose +3 days or end of double-blind treatment
ISTH=International Society on Thrombosis and Haemostasis

Atrial Fibrillation Trials with NOAC vs Warfarin: Meta-Analysis

Value of Meta-Analysis?

**Stroke / SE**

<table>
<thead>
<tr>
<th>Trial</th>
<th>NOAC (events)</th>
<th>Warfarin (events)</th>
<th>RR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-LY*</td>
<td>134/6076</td>
<td>198/6022</td>
<td>0.66 (0.53-0.82)</td>
<td>0.0001</td>
</tr>
<tr>
<td>ROCKET AF†</td>
<td>269/7081</td>
<td>306/7050</td>
<td>0.88 (0.75-1.03)</td>
<td>0.12</td>
</tr>
<tr>
<td>ARISTOTLE†</td>
<td>212/9120</td>
<td>265/9081</td>
<td>0.80 (0.67-0.95)</td>
<td>0.012</td>
</tr>
<tr>
<td>ENGAGE AF-TIMI 48‡</td>
<td>296/7035</td>
<td>337/7036</td>
<td>0.88 (0.75-1.02)</td>
<td>0.10</td>
</tr>
<tr>
<td>Combined (random)</td>
<td>911/25312</td>
<td>1107/2529</td>
<td>0.81 (0.73-0.91)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

**Heterogeneity:** \(P=47\%\); \(p=0.13\)

**Major Bleeding**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Pooled NOAC (events)</th>
<th>Pooled warfarin (events)</th>
<th>RR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischaemic stroke</td>
<td>665/29292</td>
<td>724/29221</td>
<td>0.92 (0.83-1.02)</td>
<td>0.10</td>
</tr>
<tr>
<td>Haemorrhagic stroke</td>
<td>130/29292</td>
<td>263/29221</td>
<td>0.49 (0.38-0.64)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>433/29292</td>
<td>452/29221</td>
<td>0.97 (0.76-1.20)</td>
<td>0.77</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>2022/29292</td>
<td>1245/29221</td>
<td>0.90 (0.85-0.95)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Safety</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intracranial haemorrhage</td>
<td>204/29287</td>
<td>435/29211</td>
<td>0.48 (0.39-0.59)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>751/29287</td>
<td>551/29211</td>
<td>1.75 (1.01-1.55)</td>
<td>0.043</td>
</tr>
</tbody>
</table>

**Heterogeneity:** \(P=83\%\); \(p=0.001\)

**Secondary Endpoints**

Data are n/N, unless otherwise indicated. Heterogeneity: ischaemic stroke \(P=32\%\); \(p=0.22\); haemorrhagic stroke \(P=34\%\); \(p=0.21\); myocardial infarction \(P=48\%\); \(p=0.13\); all-cause mortality \(P=9\%\); \(p=0.01\); intracranial haemorrhage \(P=32\%\); \(p=0.22\); gastrointestinal bleeding \(P=74\%\); \(p=0.009\). NOAC = new oral anticoagulant.
Objective: To determine the efficacy and safety of rivaroxaban, vascular dose of rivaroxaban plus aspirin or aspirin alone for reducing the risk of MI, stroke and cardiovascular death in CAD or PAD

Antithrombotic investigations* were stopped 1 year ahead of expectations in Feb 2017 due to overwhelming efficacy in the rivaroxaban 2.5 mg bid + aspirin arm

*Patients who were not receiving a proton pump inhibitor (PPI) were randomized to pantoprazole or placebo (partial factorial design); the PPI pantoprazole component of the study is continuing; data will be communicated once complete

# COMPASS: Primary Endpoint and Components

## CV Death significantly lower?

<table>
<thead>
<tr>
<th>Outcomes, n (%)</th>
<th>Rivaroxaban 2.5 mg bid + aspirin 100 mg N=9152</th>
<th>Aspirin 100 mg N=9126</th>
<th>Rivaroxaban 2.5 mg bid + aspirin 100 mg vs aspirin 100 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1°: CV death, stroke, or MI</td>
<td>379 (4.1)</td>
<td>496 (5.4)</td>
<td>HR (95% CI) 0.76 (0.66–0.86) p-value &lt;0.001</td>
</tr>
<tr>
<td>CV death</td>
<td>160 (1.7)</td>
<td>203 (2.2)</td>
<td>HR (95% CI) 0.78 (0.64–0.96) p-value 0.02</td>
</tr>
<tr>
<td>Stroke</td>
<td>83 (0.9)</td>
<td>142 (1.6)</td>
<td>HR (95% CI) 0.58 (0.44–0.76) p-value &lt;0.001</td>
</tr>
<tr>
<td>MI</td>
<td>178 (1.9)</td>
<td>205 (2.2)</td>
<td>HR (95% CI) 0.86 (0.70–1.05) p-value 0.14</td>
</tr>
</tbody>
</table>

### COMPASS: Secondary Endpoints

#### Mortality significantly lower?

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Rivaroxaban 2.5 mg bid + aspirin 100 mg N=9152</th>
<th>Aspirin 100 mg N=9126</th>
<th>Rivaroxaban 2.5 mg bid + aspirin 100 mg vs aspirin 100 mg</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD death, ischaemic stroke, MI, ALI</td>
<td>329 (3.6%)</td>
<td>450 (4.9%)</td>
<td></td>
<td>0.72 (0.63–0.83)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CV death, ischaemic stroke, MI, ALI</td>
<td>389 (4.3%)</td>
<td>516 (5.7%)</td>
<td></td>
<td>0.74 (0.65–0.85)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mortality (all-cause)</td>
<td>313 (3.4%)</td>
<td>378 (4.1%)</td>
<td></td>
<td>0.82 (0.71–0.96)</td>
<td>0.01 §</td>
</tr>
</tbody>
</table>

§ The threshold P value using the Hochberg procedure for each of the above comparisons was 0.0025

CHD coronary heart disease death; death due to acute MI, sudden death, or CV procedure

OSLER Program

Study Design?

into OSLER extension study program
1324 from Ph2 studies into OSLER-1
3141 from Ph3 studies into OSLER-2

Randomized 2:1

Evolocumab plus standard of care (n=2976)

Standard of care alone (n=1489)

Irrespective of study group assignment in parent study

Median follow-up of 11.1 months (IQR 11.0-12.8)

7% discontinued evolocumab early
96% completed follow-up

IQR = Interquartile range;
HeFH = Heterozygous familial hypercholesterolemia;
Hyperchol = Hypercholesterolemia

Data from the two trials (OSLER-1, OSLER-2) were combined


Phase 2 studies
- MENDEL-1 (n=406)
- LAPLACE-TIMI 57 (n=629)

Phase 3 studies
- MENDEL-2 (n=614)
- LAPLACE-2
- GAUSS-1 (n=157)
- GAUSS-2
- RUTHERFORD-1 (n=167)
- RUTHERFORD-2
- YUKAWA-1 (n=307)
- THOMAS-1 (n=149)
- THOMAS-2 (n=164)
- DESCARTES

MONO-THERAPY
HYPERCHOL ON A STATIN
STATIN-INTOLERANT
HeFH
OTHER

MONO- THERAPY

HYPERCHOL ON A STATIN

STATIN-INTOLERANT

HeFH

OTHER

LAPLACE-TIMI 57 (n=629)

GAUSS-1 (n=157)

RUTHERFORD-1 (n=167)

YUKAWA-1 (n=307)

THOMAS-1 (n=149)

THOMAS-2 (n=164)

DESCARTES

MENDEL

GAUSS

RUTHERFORD

YUKAWA

THOMAS

DESCARTES

Phase 2 studies
- MENDEL-1 (n=406)
- LAPLACE-TIMI 57 (n=629)

Phase 3 studies
- MENDEL-2 (n=614)
- LAPLACE-2
- GAUSS-1 (n=157)
- GAUSS-2
- RUTHERFORD-1 (n=167)
- RUTHERFORD-2
- YUKAWA-1 (n=307)
- THOMAS-1 (n=149)
- THOMAS-2 (n=164)
- DESCARTES

MONO- THERAPY
HYPERCHOL ON A STATIN
STATIN-INTOLERANT
HeFH
OTHER

MONO- THERAPY

HYPERCHOL ON A STATIN

STATIN-INTOLERANT

HeFH

OTHER

LAPLACE-TIMI 57 (n=629)

GAUSS-1 (n=157)

RUTHERFORD-1 (n=167)

YUKAWA-1 (n=307)

THOMAS-1 (n=149)

THOMAS-2 (n=164)

DESCARTES

MENDEL

GAUSS

RUTHERFORD

YUKAWA

THOMAS

DESCARTES

HeFH = Heterozygous familial hypercholesterolemia; Hyperchol = Hypercholesterolemia

7% discontinued evolocumab early
96% completed follow-up

Median follow-up of 11.1 months (IQR 11.0-12.8)
OSLER: Methods

- **Evolocumab**
  - Open-label randomized, controlled study; subcutaneous injections
  - Dosed 420 mg QM (OSLER-1); either 140 mg Q2W or 420 mg QM on the basis of patient choice (OSLER-2)

- **Primary Endpoints:**
  - Incidence of adverse events (AE) & tolerability

- **Secondary Endpoints:**
  - Percent change in LDL-C level & other lipid parameters

- **CV clinical events (pre-specified, exploratory outcome):** adjudicated by TIMI Study Group CEC*, blinded to treatment
  - Death
  - Coronary: myocardial infarction (MI), unstable angina (UA) requiring hospitalization, revascularization
  - Cerebrovascular: stroke or transient ischemic attack (TIA)
  - Heart failure (HF) requiring hospitalization

*Thrombolysis in Myocardial Infarction (TIMI) Study Group Clinical Events Committee (CEC)

Patients had in-person clinic visits on day 1 and then quarterly at weeks 12, 24, 36 and 48.
## OSLER: Safety

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Evolocumab + Standard of Care (N=2976)</th>
<th>Standard of Care alone (N=1489)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>2060 (69.2)</td>
<td>965 (64.8)</td>
</tr>
<tr>
<td>Serious</td>
<td>222 (7.5)</td>
<td>111 (7.5)</td>
</tr>
<tr>
<td>Leading to discontinuation of evolocumab</td>
<td>71 (2.4)</td>
<td>n/a</td>
</tr>
<tr>
<td>Injection-site reactions</td>
<td>129 (4.3)</td>
<td>n/a</td>
</tr>
<tr>
<td>Muscle-related</td>
<td>190 (6.4)</td>
<td>90 (6.0)</td>
</tr>
<tr>
<td>Neurocognitive*</td>
<td>27 (0.9)</td>
<td>4 (0.3)</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>137 (4.6)</td>
<td>48 (3.2)</td>
</tr>
<tr>
<td>Headache</td>
<td>106 (3.6)</td>
<td>32 (2.1)</td>
</tr>
<tr>
<td>Limb pain</td>
<td>99 (3.3)</td>
<td>32 (2.1)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>83 (2.8)</td>
<td>15 (1.0)</td>
</tr>
<tr>
<td>Laboratory results</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT or AST &gt;3×ULN</td>
<td>31 (1.0)</td>
<td>18 (1.2)</td>
</tr>
<tr>
<td>Creatine kinase &gt;5×ULN</td>
<td>17 (0.6)</td>
<td>17 (1.1)</td>
</tr>
</tbody>
</table>

*Neurocognitive events were delirium (including confusion), cognitive and attention disorders and disturbances, dementia and amnestic conditions, disturbances in thinking and perception, and mental impairment disorders.

Evolocumab plus standard of care

61% reduction (95%CI 59-63%), P<0.001
Absolute reduction: 73 mg/dL (95%CI 71-76%)

The dashed line indicate that patients were receiving either evolocumab or placebo during the period from baseline to enrollment into OSLER.
**OSLER: Cardiovascular Outcomes**

Composite Endpoint: Death, MI, UA hosp, coronary revascularization, stroke, TIA, or CHF hosp

**What does this mean?**

- **Evolocumab plus standard of care**
  - (N=2976)
  - Cumulative Incidence (%): 0.95%

- **Standard of care alone**
  - (N=1489)
  - Cumulative Incidence (%): 2.18%

**HR 0.47**

95% CI 0.28-0.78

P=0.003

FOURIER: Trial Design

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

FOURIER: Primary Endpoint

Hazard ratio 0.85
(95% CI, 0.79-0.92)
P<0.0001

RRR 15%

Placebo

Evolocumab

Patient and investigator remained blinded to treatment and lipid levels for the entire duration of the study.

18,924 Post-ACS patients (1-12 months)

Run-in period of 2-16 weeks on high-intensity or max tolerated dose of atorvastatin or rosuvastatin

At least one lipid entry criterion met

Alirocumab sc q2w (N=9462)

Placebo sc q2w (N=9462)

Follow-up*: median 2.8 (IQR 2.3-3.4) years
8242 (44%) patients with potential follow-up ≥3 years

Premature treatment discontinuation
1343 (14.2%) (Alirocumab) 1496 (15.8%) (Placebo)

Blinded switch to placebo (2 consecutive LDL-C values <15 mg/dL)
730 (7.7%) (Alirocumab) Not applicable (Placebo)

Patients lost to follow-up (vital status)
14 (Alirocumab) 9 (Placebo)

Patient and investigator remained blinded to treatment and lipid levels for the entire duration of the study.

*Ascertainment was complete for 99.1% and 99.8% of potential patient-years of follow-up for the primary endpoint and all-cause death, respectively

ODYSSEY OUTCOMES: Primary Endpoint

Primary Efficacy Endpoint: MACE

MACE: CHD death, non-fatal MI, ischemic stroke, or unstable angina requiring hospitalization

*Based on cumulative incidence

ARR* 1.6%
RRR 15%

HR 0.85
(95% CI 0.78, 0.93)
P=0.0003

Number at Risk
Placebo 9462
Alirocumab 9462
0 1 2 3 4
Years Since Randomization
0 3 6 9 12 15
MACE (%)

### ODYSSEY OUTCOMES: Secondary Endpoints

**Main Secondary Efficacy Endpoints:**
Hierarchical Testing

<table>
<thead>
<tr>
<th>Endpoint, n (%)</th>
<th>Alirocumab (N=9462)</th>
<th>Placebo (N=9462)</th>
<th>HR (95% CI)</th>
<th>Log-rank P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD event</td>
<td>1199 (12.7)</td>
<td>1349 (14.3)</td>
<td>0.88 (0.81, 0.95)</td>
<td>0.001</td>
</tr>
<tr>
<td>Death, MI, ischemic stroke</td>
<td>973 (10.3)</td>
<td>1126 (11.9)</td>
<td>0.86 (0.79, 0.93)</td>
<td>0.0003</td>
</tr>
<tr>
<td>CHD death</td>
<td>205 (2.2)</td>
<td>222 (2.3)</td>
<td>0.92 (0.76, 1.11)</td>
<td>0.38</td>
</tr>
<tr>
<td>CV death</td>
<td>240 (2.5)</td>
<td>271 (2.9)</td>
<td>0.88 (0.74, 1.05)</td>
<td>0.15</td>
</tr>
<tr>
<td>All-cause death</td>
<td>334 (3.5)</td>
<td>392 (4.1)</td>
<td>0.85 (0.73, 0.98)</td>
<td>0.026*</td>
</tr>
</tbody>
</table>

*Nominal P-value

Mortality significantly lower?
ODYSSEY OUTCOMES: LDL-C Subgroup Analysis

Primary Efficacy in Main Prespecified Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Patients</th>
<th>Alirocumab</th>
<th>Placebo</th>
<th>HR (95% CI)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL (mg/dL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;80</td>
<td>7164</td>
<td>8.3</td>
<td>9.5</td>
<td>0.86 (0.74, 1.01)</td>
<td>0.09</td>
</tr>
<tr>
<td>80 - &lt;100</td>
<td>6128</td>
<td>9.2</td>
<td>9.5</td>
<td>0.96 (0.82, 1.14)</td>
<td></td>
</tr>
<tr>
<td>≥100</td>
<td>5629</td>
<td>11.5</td>
<td>14.9</td>
<td>0.76 (0.65, 0.87)</td>
<td></td>
</tr>
</tbody>
</table>

*P-values for interaction

Subgroup Analysis valid?
RESPECT Trial

Subject Distribution

- Enrolled: N=980
  - Randomization stratified by site and presence/absence of atrial septal aneurysm
  - Randomized to device group: N = 499
    - Study device implant attempted: N = 464
      - Post Implant: clopidogrel 1 month and aspirin 6 months. After 6 months, antiplatelet therapy at discretion of site investigator
      - TEE with bubble study at 6 months
    - Medical treatment specified pre-randomization by site neurologist
      - Aspirin only: 46.5%
      - Warfarin only: 25.2%
      - Clopidogrel only: 14.0%
      - Aspirin + dipyridamole: 8.1%
      - Aspirin + clopidogrel: 6.2%

1. Aspirin + clopidogrel was removed from the protocol in 2009 based on changes to the AF-WASA treatment guidelines

Carroll et al., N Engl J Med 2013;368:1092-100
RESPECT Trial

Primary Endpoint Analysis – ITT Cohort
50.8% risk reduction of stroke in favor of device

• 3/9 device group patients did not have a device at time of endpoint stroke

Cox model used for analysis

Carroll et al., N Engl J Med 2013;368:1092-100
RESPECT Trial

Primary Endpoint Analysis – As Treated Cohort
72.7% risk reduction of stroke in favor of device

- The As Treated (AT) cohort demonstrates the treatment effect by classifying subjects into treatment groups according to the treatment actually received, regardless of the randomization assignment.

Cox model used for analysis

Carroll et al., N Engl J Med 2013;368:1092-100
RESPECT Trial

Totality of Evidence and NNT
46.6%-72.7% risk reduction of stroke in favor of device

Totality of Evidence

ORIGINAL ARTICLE

Long-Term Outcomes of Patent Foramen Ovale Closure or Medical Therapy after Stroke

Jeffrey L. Saver, M.D., John D. Carroll, M.D., David E. Thaler, M.D., Ph.D., Richard W. Smalling, M.D., Ph.D., Lee A. MacDonald, M.D., David S. Marks, M.D., and David L. Tirschwell, M.D., for the RESPECT Investigators


CONCLUSIONS

Among adults who had had a cryptogenic ischemic stroke, closure of a PFO was associated with a lower rate of recurrent ischemic strokes than medical therapy alone during extended follow-up. (Funded by St. Jude Medical; RESPECT ClinicalTrials.gov number, NCT00465270.)

| 2 Year | 70.4 | 1.60% | 3.02% |
| 5 Year | 23.9 | 2.21% | 6.40% |

P-values: ITT Raw Count is calculated using Fisher’s Exact test; all other P-values are calculated using log-rank test
The NNT is the average number of subjects that need to be treated with the AVEPLATZER™ PFO Occluder in order to prevent one stroke in the respective time intervals. The NNT is calculated as the reciprocal of the difference between the control arm and device arm event rates.
Calculated using the Saeian-Meier estimated event rates for each treatment group.
PFO Closure vs. Medical Therapy: Meta-Analysis of Randomized Controlled Trials

Stroke/TIA – intention-to-treat analysis

Intention-to-treat or As-treated or Modified Intention-to-treat Analysis in Device Trials?

Heterogeneity: $\tau^2 = 0.00; \chi^2 = 0.84, df = 2 (P = 0.86); P = 0\%$
Test for overall effect: $Z = 2.27 (P = 0.02)$
Thank you for your attention!

Join the ESC Working Group on Cardiovascular Pharmacotherapy

Membership is FREE!

www.escardio.org/Working-groups/Working-Group-on-Cardiovascular-Pharmacotherapy