La prevenzione secondaria dopo sindrome coronarica acuta

Aldo Pietro Maggioni
Centro Studi ANMCO
Firenze
Cardiovascular diseases are the leading global cause of death

Top 5 Global Causes of Death in 2012

1. 13.2% Ischemic Heart Disease
2. 11.9% Stroke
3. 5.6% Chronic Obstructive Pulmonary Disease
4. 5.5% Lower Respiratory Infections
5. 2.9% Trachea, Bronchus, Lung Cancers

CVD includes ischemic heart disease and stroke.
Trial and community-based assessments of in-hospital (A) and 30-day (B) mortality relative to age stratifications

A) In-hospital Mortality

<table>
<thead>
<tr>
<th>Age Group (yrs)</th>
<th>Trials</th>
<th>Community</th>
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<tbody>
<tr>
<td>&lt; 65</td>
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<td>65–74</td>
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<td>75–84</td>
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B) 30-day Mortality

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Circulation. 2013;128:2422-2446
Results on patients’ outcomes

IMA - Mortalità intraospedaliera

- GISSI-1: 13.0%
- GISSI-2: 9.0%
- GISSI-3: 7.0%
- BLITZ-1: 7.5%
- BLITZ-3: 5.1%
- IN-ACS Outcome: 4.8%
- MANTRA: 4.2%
Recommended treatments for secondary prevention

- Dual antiplatelet treatment
  - treatment of stent for 12 months
  - for secondary prevention (life long ???)
- RAS Blockers (ACE-I/ARBs)
- Beta Blockers
- MRAs if HF with LV dysfunction
- Lipid lowering therapy (C-LDL <70 mg/dL)
- Omega 3 fatty acids
- Blood pressure control (<140/90 mmHg)
- Diabetes mellitus management (Hb1Ac ≤7%)
- Smoking cessation
- Physical activity (at least 30min 5 days per week)
- Weight management (18.5-24.9 Kg/m2)
Prevenzione cardiovascolare: i risultati raggiunti sono importanti ma non ancora sufficienti

- Riduzione della colesterolemia
- Terapia anti-ipertensiva
- Terapia antiaggregante
- Modificazione degli stili di vita
Statins after ACS: Residual risk remains high despite intensive treatment

MIRACL
- Placebo
- Atorvastatin 80 mg
- RRR 16%
- p=0.048
- Months

PROVE-IT
- Pravastatin 40 mg
- Atorvastatin 80 mg
- RRR 16%
- p=0.005
- Months

JAMA 2001;285:1411
Hazard Ratio = 0.75 (95% CI: 0.64 to 0.89)

Hazard Ratio = 0.73 (95% CI: 0.60 to 0.90)

Blood pressure treatment:
SBP <140 vs <120 mm Hg
Long-Term Use of Ticagrelor in Patients with Prior Myocardial Infarction

Marc P. Bonaca, M.D., M.P.H., Deepak L. Bhatt, M.D., M.P.H., Marc Cohen, M.D., Philippe Gabriel Steg, M.D., Robert F. Storey, M.D., Eva C. Jensen, M.D., Ph.D., Giulia Magnani, M.D., Sameer Bansilal, M.D., M. Polly Fish, B.A., Kyungah Im, Ph.D., Olof Bengtsson, Ph.Lic., Ton Oude Ophuis, M.D., Ph.D., Andrzej Budaj, M.D., Ph.D., Pierre Théroux, M.D., Mikhail Ruda, M.D., Christian Hamm, M.D., Shinya Goto, M.D., Jindrich Spinar, M.D., José Carlos Nicolau, M.D., Ph.D., Robert G. Kiss, M.D., Ph.D., Sabina A. Murphy, M.P.H., Stephen D. Wiviott, M.D., Peter Held, M.D., Ph.D., Eugene Braunwald, M.D., and Marc S. Sabatine, M.D., M.P.H., for the PEGASUS-TIMI 54 Steering Committee and Investigators

- Ticagrelor, 90 mg vs. placebo: Hazard ratio, 0.85 (95% CI, 0.75–0.96) P=0.008
- Ticagrelor, 60 mg vs. placebo: Hazard ratio, 0.84 (95% CI, 0.74–0.95) P=0.004

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Placebo</th>
<th>Ticagrelor, 90 mg</th>
<th>Ticagrelor, 60 mg</th>
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<tr>
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<td>7067</td>
<td>6979</td>
<td>6892</td>
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<td>6681</td>
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<td>2028</td>
<td>2038</td>
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<td></td>
<td>2055</td>
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</table>
Current standard of care does not eliminate CV events and significant CV risk remains in diabetes

The reduction in CV events at the end of the Steno-2 trial was attributed to lipid lowering (70%), HbA1c (13%) and systolic BP (10%)\(^1\)

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CV events include CV death, MI, stroke, CABG or amputation due to ischemia
Prevenzione secondaria cardiovascolare: cosa possiamo fare di più?
Prevenzione secondaria cardiovascolare: le ipotesi senza successo

Few recent secondary prevention lipid treatment trials have demonstrated a CV outcomes benefit

<table>
<thead>
<tr>
<th>Category</th>
<th>Study</th>
<th>Medication</th>
<th>Outcome</th>
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<tr>
<td>Fibrates</td>
<td>FIELD</td>
<td>Fenofibrate</td>
<td>Neutral</td>
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<tr>
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<td>ACCORD</td>
<td>Fenofibrate</td>
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<td>Niacin</td>
<td>AIM-HIGH</td>
<td>Niaspan</td>
<td>Neutral</td>
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<td>HPS2-THRIVE</td>
<td>Niacin / Laropiprant</td>
<td>Neutral</td>
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<td>Chol Absorption Inhibition</td>
<td>IMPROVE-IT</td>
<td>Ezetimibe</td>
<td>Positive</td>
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<tr>
<td>CETP Inhibition</td>
<td>ILLUMINATE</td>
<td>Torcetrapib</td>
<td>Negative</td>
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<td></td>
<td>ACCELERATE</td>
<td>Evacetrapib</td>
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<td>sPLA2 Inhibition</td>
<td>VISTA-16</td>
<td>Varespladib</td>
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<td>Lp-PLA2 Inhibition</td>
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Prevenzione secondaria cardiovascolare: le ipotesi in corso di studio

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<th>REVEAL</th>
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<th>Enrolled</th>
<th>Dal-GENE</th>
<th>Dalcetrapib PGx</th>
<th>Enrolling</th>
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- What is the evidence supporting LDL-C reduction even when levels are low?
- Is LDL-C lowering without inflammation inhibition effective?
- Will our patients live longer and more productive lives?
Association between cholesterol levels and CHD

Positive association between non-HDL cholesterol and risk of CHD

Inverse association between HDL-cholesterol and risk of CHD

Prospective Studies Collaboration; Lancet 2007;370:1829-39
Experience of CETP inhibitors is limited

<table>
<thead>
<tr>
<th>Name of Study</th>
<th>Drug used</th>
<th>Sample size</th>
<th>Duration</th>
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<tbody>
<tr>
<td>ILLUMINATE</td>
<td>Torcetrapib</td>
<td>15,067</td>
<td>Median follow up: 1.5 yr</td>
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<tr>
<td>Dal-Outcomes</td>
<td>Dalcetrapib</td>
<td>15,000</td>
<td>5 years</td>
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<tr>
<td>ACCELERATE</td>
<td>Evacetrapib</td>
<td>12,095</td>
<td>Median follow up: 1.5 yr</td>
</tr>
<tr>
<td>DEFINE</td>
<td>Anacetrapib</td>
<td>1623</td>
<td>Median follow up: 1.5 yr</td>
</tr>
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ILLUMINATE: Outcomes

All-cause mortality:

93 (1.2%) Torcetrapib vs. 59 (0.8%) placebo

HR 1.58 (95% CI 1.14-2.19); P=0.006

Major cardiovascular events:

464 (6.2%) Torcetrapib vs. 373 (5.0%) placebo

HR 1.25 (95% CI 1.09-1.44) P=0.001

Effects of Dalcetrapib in Patients with a Recent Acute Coronary Syndrome

Gregory G. Schwartz, M.D., Ph.D., Anders G. Olsson, M.D., Ph.D., Markus Abt, Ph.D., Christie M. Ballantyne, M.D., Philip J. Barter, M.D., Ph.D., Jochen Brumm, Ph.D., Bernard R. Chaitman, M.D., Ingar M. Holme, Ph.D., David Kallend, M.B., B.S., Lawrence A. Leiter, M.D., Eran Leitersdorf, M.D., John J.V. McMurray, M.D., Hardi Mundl, M.D., Stephen J. Nicholls, M.B., B.S., Ph.D., Prediman K. Shah, M.D., Jean-Claude Tardif, M.D., and R. Scott Wright, M.D., for the dal-OUTCOMES Investigators*

This article was published on November 5, 2012, at NEJM.org.

DOI: 10.1056/NEJMoal206797
dal-Outcomes:
Effects on HDL and LDL cholesterol

HDL-Col

LDL-Col
Dal-Outcomes: Main results

![Graph showing cumulative incidence of primary outcome (\% of patients) over years. The graph compares Placebo and Dalcetrapib groups. The y-axis represents the cumulative incidence, ranging from 0 to 100 \%, and the x-axis represents the years from 0 to 3. Placebo and Dalcetrapib lines are shown, with Placebo having a slightly higher incidence in the first year. The graph includes a note: P=0.52 by log-rank test.]

<table>
<thead>
<tr>
<th>Year</th>
<th>Placebo</th>
<th>Placebo</th>
<th>Placebo</th>
<th>Placebo</th>
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<td>7933</td>
<td>7386</td>
<td>6551</td>
<td>1743</td>
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<tr>
<td></td>
<td>7938</td>
<td>7372</td>
<td>6495</td>
<td>1736</td>
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</table>
Lilly to Discontinue Development of Evacetrapib for High-Risk Atherosclerotic Cardiovascular Disease

INDIANAPOLIS, Oct. 12, 2015 /PRNewswire/ -- Eli Lilly and Company (NYSE: LLY) and the ACCELERATE study's academic leadership have accepted the recommendation of the independent data monitoring committee to terminate the Phase 3 trial of the investigational medicine evacetrapib, due to insufficient efficacy. Lilly will discontinue development of evacetrapib for the treatment of high-risk atherosclerotic cardiovascular disease and will now conclude other studies in the program.

The independent data monitoring committee based its recommendation on data from periodic data reviews, which suggested there was a low probability the study would achieve its primary endpoint based on results to date. The study is not being stopped for safety findings. After further analysis, results of the study will be presented in scientific forums in the future.

"We're obviously disappointed in this outcome, as we hoped that evacetrapib would offer an advance in treatment for people with high-risk cardiovascular disease. We'll be working with investigators to appropriately conclude these trials," said David Ricks, Lilly senior vice president and president of Lilly Bio-Medicines. "We remain confident in our pipeline as we prepare for launches in other therapeutic areas with significant unmet needs."

"This unfortunate outcome for evacetrapib does not change our ability to generate long-term growth," said Derica Rice, Lilly executive vice president and chief financial officer. "Our recent string of positive data-readouts and our strong pipeline position us to grow revenue and expand margins through the remainder of this decade."

The decision to discontinue development of evacetrapib is expected to result in a fourth-quarter charge to research and development expense of up to $90 million (pre-tax), or approximately $0.05 per share (after-tax). The company will incorporate this estimated charge into its updated 2015 guidance that will be provided as part of its third quarter 2015 earnings press release on Thursday, Oct. 22, 2015.
Anacetrapib-DEFINE: changes in cholesterol levels

LDL cholesterol
-40% (p<0.001)

HDL cholesterol
+138% (p<0.001)

Anacetrapib: early efficacy and safety data are encouraging

- Lowers LDL-cholesterol by ~40%
- Raises HDL-cholesterol by ~140%
- No adverse effect on blood pressure
- No effects on aldosterone or other known safety concerns
- Effects on clinical outcomes unknown…
REVEAL: Aims of study

To assess the effect of CETP inhibition with anacetrapib 100 mg versus matching placebo on time to first “major coronary event” among 30,000 individuals with pre-existing vascular disease.

Major coronary event (MCE):

- Myocardial infarct
- Coronary death
- Coronary revascularization
Study design: Treatment comparisons

- Screening Visit
  - Placebo + Atorvastatin
  - Randomization Visit
    - Placebo + Atorvastatin
    - Anacetrapib + Atorvastatin
      - Visits 2 & 6 months then 6-monthly
        - Final Visit
        - Final Visit

8.12 weeks
4 years
Prevenzione secondaria cardiovascolare: le ipotesi in corso di studio

<table>
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- Will our patients live longer and more productive lives?
dal-Outcome Genetic substudy

Event rates

<table>
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<tr>
<th>rs1967309 genotypes</th>
<th>Dalcetrapib</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>AA</td>
<td>8%</td>
<td>12%</td>
</tr>
<tr>
<td>AG</td>
<td>13%</td>
<td>14%</td>
</tr>
<tr>
<td>GG</td>
<td>18%</td>
<td>15%</td>
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</table>

n events: 38, 59, 176, 192, 176, 146
Primary Objective: To **prospectively** evaluate the potential of dalcetrapib to reduce cardiovascular morbidity and mortality in patients with a documented recent ACS and the AA genotype at rs1967309
Key Inclusion Criteria at Screening

- 5,000 hospitalized patients for ACS (index event within 4-12 weeks) defined as the occurrence of at least one of the following events
  - Spontaneous MI
  - Procedure-Related MI after PCI
  - Hospitalization for ACS (ECG Abnormalities without biomarkers)
- AA genotype at rs1967309
- Other key inclusion criteria:
  - Males and females at least 45 years old
  - Clinically stable at least 1 week prior to randomization
  - Evidence of guidelines-based management of LDL-C
The primary endpoint of this study is the time to first occurrence of any component of the composite endpoint, as adjudicated by the Clinical Event Committee (CEC). Components of the primary endpoint are:

- Cardiovascular (CV) death
- Resuscitated cardiac arrest
- Non-fatal myocardial infarction (MI)
- Non-fatal ischemic stroke
Prevenzione secondaria cardiovascolare: le ipotesi in corso di studio

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Original Investigation

Effect of Losmapimod on Cardiovascular Outcomes in Patients Hospitalized With Acute Myocardial Infarction: A Randomized Clinical Trial

Michelle L. O'Donoghue, MD, MPH; Ruchira Glaser, MD, MSCE; Matthew A. Cavender, MD; Philip E. Aylward, BM, BCh, PhD; Marc P. Bonaca, MD, MPH; Andrzej Budaj, MD, PhD; Richard Y. Davies, MS; Mikael Dellborg, MD; Keith A. A. Fox, MBChB; Jorge Antonio T. Gutierrez, MD; Christian Hamm, MD; Robert G. Kiss, MD, PhD; František Kovar, MD, PhD; Julia F. Kuder, MA; Kyung Ah Im, PhD; John J. Lepore, MD; Jose L. Lopez-Sendon, MD; Ton Oude Ophuis, MD, PhD; Alexandr Parkhomenko, MD; Jennifer B. Shannon, MS; Jindrich Spinar, MD; Jean-Francois Tanguay, MD; Mikhail Ruda, MD, PhD; P. Gabriel Steg, MD; Pierre Theroux, MD; Stephen D. Wiviott, MD; Ian Laws, PhD; Marc S. Sabatine, MD, MPH; David A. Morrow, MD, MPH; for the LATITUDE-TIMI 60 Investigators

Published online April 4, 2016.
Losmapimod Background

- Anti-inflammatory agent that inhibits p38 mitogen-activated protein kinase (MAPK) dependent cytokine induction
- Preclinical: suppression of vascular inflammation; myocardial protection; attenuate reperfusion injury
- Phase II results in NSTEMI patients (SOLSTICE trial)*
  - Blunted rise in C-reactive protein (hsCRP)
  - \( \downarrow \) B-type natriuretic peptide (BNP) and improved left ventricular function (exploratory) at 3 months
  - Trend toward lower risk of recurrent myocardial infarction
  - Favorable safety/tolerability

*Newby et al., Lancet 2014;384:1187

Deaths, MI, RIUR, CVA or HF (%)

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Losmapimod</th>
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</thead>
<tbody>
<tr>
<td>Death, MI, RIUR, CVA or HF (%)</td>
<td>16.3</td>
<td>13.6</td>
</tr>
</tbody>
</table>

HR 0.82
(95% CI 0.49-1.37)

526 NSTEMI patients treated for 90d

Published online April 4, 2016.
Figure 4. Serial Biomarker Concentrations

Concentration of high-sensitivity C-reactive protein (hs-CRP) and N-terminal pro–brain natriuretic peptide (NT-pro-BNP) over time with losmapimod vs placebo. The errors bars indicate the 95% confidence interval around the geometric mean. For hs-CRP, *P*<.001 for losmapimod vs placebo at 48 hours and at week 12; *P*=.004 at week 4. For NT-pro-BNP, *P*<.001 for losmapimod vs placebo at week 4 and at week 12.

Published online April 4, 2016.
Primary Endpoint (MACE) through Week 12

HR 1.16 (95% CI 0.91-1.47)
P value (log rank) = 0.24

Losmapimod 8.1%
Placebo 7.0%

*SRI-UR: severe recurrent ischemia requiring urgent coronary revascularization

Published online April 4, 2016.
Prevenzione secondaria cardiovascolare: le ipotesi in corso di studio

<table>
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<th>Therapeutic Approach</th>
<th>Study</th>
<th>Drug Formulation</th>
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- What is the evidence supporting LDL-C reduction even when levels are low?
- Is LDL-C lowering without inflammation inhibition effective?
- Will our patients live longer and more productive lives?
COLchicine Cardiovascular Outcomes Trial (COLCOT) MHIPS-003

Study Background & Rationale
The COLCOT trial

A worldwide, randomized, double-blind, placebo-controlled, multi-center, event-driven study

**Indication:**

Reduction of the cardiovascular risk in patients with atherosclerotic coronary artery disease.
Study Background

• COPE  Colchicine for Acute Pericarditis
• CORE  Colchicine for Recurrent Pericarditis
• CORP  Colchicine for Recurrent Pericarditis
• COPPS Colchicine for the Prevention of Post-Pericardiotomy Syndrome
• LODOCO Low Dose Colchicine for Secondary Prevention of Cardiovascular Disease
The effect of adding colchicine became evident early, continued to accrue over time, and was largely driven by a reduction in ACS unrelated to stent disease.
Colchicine is an inexpensive anti-inflammatory drug used in patients with gout and Familial Mediterranean Fever at doses between 0.3 and 2.4 mg/day.

Colchicine’s MOA is through the inhibition of tubulin polymerization and potentially also through a direct effect on cellular adhesion molecules and inflammatory chemokines.

Direct inhibition of the migration of neutrophils is considered colchicine’s main MOA in gout.
Primary Objective:
Determine whether long-term treatment with colchicine reduces rates of recurrent cardiovascular events in patients who have suffered MI.

Secondary Objective:
Determine the safety of long-term treatment with colchicine.

Tertiary Objective:
Evaluate links between soluble and genetic biomarkers and treatment effects.
Prevenzione secondaria cardiovascolare: le ipotesi in corso di studio

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<tr>
<th>CETP Inhibition</th>
<th>REVEAL</th>
<th>Anacetrapib</th>
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Exploratory and Post Hoc Analyses Suggest Outcomes Benefit With PCSK9 Inhibition

OSLER 1/2
Cumulative Incidence of CV Events

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

HR 0.47
95% CI 0.28-0.78
P=0.003

Standard of care alone
(N=1489)

Evolocumab plus standard of care
(N=2976)

2.18%
0.95%

Days since Randomization

ODYSSEY LONG TERM
Time to First Positively Adjudicated CV Event During the TEAE Period

Cox model analysis
HR = 0.52 (95% CI 0.31 to 0.90)
Nominal P-value = 0.02

Placebo+Statin

Alirocumab + Statin
150 mg Q2W

Weeks

• CV outcomes declined by 53% over 1 year
  – Prespecified exploratory outcome with relatively few events

• In a post hoc analysis, the rate of death from CHD, nonfatal MI, ischemic stroke, or unstable angina requiring hospitalization was 3.3% in the placebo group and 1.7% in the intervention group
  – Low number of CV events limits ability to draw conclusions on outcomes

Despite Initial Findings, Data from Ongoing CVOTs Are Needed To Confirm Outcomes Benefit With PCSK9 Inhibition

“...The ODYSSEY LONG TERM and OSLER studies whet our appetites for further results that show cardiovascular benefit and documented safety, even at substantially lower LDL cholesterol ranges than achieved before. However, it would be premature to endorse these drugs for widespread use before the ongoing randomized trials, appropriately powered for primary endpoint analysis and safety assessment, are available. Reports from several lipid treatment trials provide important object lessons in this regard...”

Ongoing CVOTs Will Evaluate the Impact of PCSK9 Inhibition on CV Events in Distinct Populations Throughout the CV Risk Continuum