Clinical Trials of PCSK9 Inhibitors for the (Secondary) Prevention of Atherosclerotic Cardiovascular Disease (ASCVD)

Shaun Goodman
Disclosures

- Research grant support, speaker/consulting honoraria (no patents):
  - Amgen
    - Including Guidelines Oriented Approach to Lipid lowering (GOAL) in Canada Steering Committee member; Consultant to the Canadian Heart Research Centre (CHRC; Canadian ARO)
  - Sanofi and Regeneron
    - Including ODYSSEY Outcomes trial Executive Steering Committee member and Canadian National Coordinator; Co-Director of the Canadian VIGOUR Centre (CVC; Canadian ARO)
  - Esperion
    - CLEAR OUTCOMES Steering Committee member
  - Lilly
    - ACCELERATE and LY3015014 trials Steering Committee member
  - AstraZeneca, Bristol-Myers Squibb, HLS Therapeutics, Merck, Pfizer

- Additional relationships (research grant support, speaker/consulting honoraria) with commercial interests but not relevant to this presentation
Impact of a PCSK9 Monoclonal Antibody on LDL Receptor Expression
# PCSK9 Inhibitors vs. No PCSK9 Inhibitors

24 RCTs (n=10,159)
Mean LDL-C reduction 47% (25%-70%)

<table>
<thead>
<tr>
<th>Event</th>
<th>n</th>
<th>Odds Ratio &amp; 95% CI</th>
<th>PCSK9i (%)</th>
<th>No PCSK9i (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause Mortality</td>
<td>40</td>
<td>0.50 (0.23-1.10)</td>
<td>0.31</td>
<td>0.53</td>
</tr>
<tr>
<td>Cardiovascular Mortality</td>
<td>25</td>
<td>0.45 (0.23-0.86)</td>
<td>0.19</td>
<td>0.33</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>38</td>
<td>0.49 (0.26-0.93)</td>
<td>0.58</td>
<td>1.03</td>
</tr>
<tr>
<td>Unstable Angina</td>
<td>2</td>
<td>0.61 (0.06-6.14)</td>
<td>0.04</td>
<td>0.07</td>
</tr>
<tr>
<td>Creatine Kinase Increase</td>
<td>213</td>
<td>0.72 (0.54-0.96)</td>
<td>2.0</td>
<td>2.3</td>
</tr>
<tr>
<td>Serious Adverse Event</td>
<td>880</td>
<td>1.01 (0.87-1.18)</td>
<td>9.3</td>
<td>7.7</td>
</tr>
</tbody>
</table>

Tests for heterogeneity, p=NS

1 PCSK9i (n=6187) and 2 No PCSK9i (n=3972); except 3 (n=3289/1906) and 4 (n=2515/1379)

27,564 high-risk, stable patients with established CV disease:
Prior MI (81%), prior non-hemorrhagic stroke (19%), or symptomatic PAD (13%)

Screening, Lipid Stabilization, and Placebo Run-in
High (69%) or moderate (30%)-intensity statin therapy ± ezetimibe (5%)

LDL-C $\geq$ 1.8 mmol/L or non-HDL-C $\geq$ 2.6 mmol/L

Evolocumab SC
140 mg Q2W or 420 mg Q4W

RANDOMIZED
DOUBLE BLIND

Placebo SC
Q2W or Q4W

Follow-up Q 12 weeks

Baseline LDL-C ~2.4 (2.1,2.8) mmol/L

Relative: 59 (95% CI 58-60) %; p<0.00001

Absolute: 1.45 (95% CI 1.43-1.47) mmol/L

High (69%) or moderate (30%)-intensity statin therapy ± ezetimibe (5%)

~0.78 (0.49,1.2) mmol/L

Median

Primary Endpoint

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

140 mg Q2W or
420 mg SC Q4W

# Types of CV Outcomes

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Evolocumab (N=13,784)</th>
<th>Placebo (N=13,780)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-yr Kaplan-Meier rate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVD, MI, stroke, UA, or revasc</td>
<td>12.6</td>
<td>14.6</td>
<td>0.85 (0.79-0.92)</td>
</tr>
<tr>
<td>CV death, MI, or stroke</td>
<td>7.9</td>
<td>9.9</td>
<td>0.80 (0.73-0.88)</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>2.5</td>
<td>2.4</td>
<td>1.05 (0.88-1.25)</td>
</tr>
<tr>
<td>MI</td>
<td>4.4</td>
<td>6.3</td>
<td>0.73 (0.65-0.82)</td>
</tr>
<tr>
<td>Stroke</td>
<td>2.2</td>
<td>2.6</td>
<td>0.79 (0.66-0.95)</td>
</tr>
<tr>
<td>Hosp. for unstable angina</td>
<td>2.2</td>
<td>2.3</td>
<td>0.99 (0.82-1.18)</td>
</tr>
<tr>
<td>Coronary revasc</td>
<td>7.0</td>
<td>9.2</td>
<td>0.78 (0.71-0.86)</td>
</tr>
<tr>
<td>Urgent</td>
<td>3.7</td>
<td>5.4</td>
<td>0.73 (0.64-0.83)</td>
</tr>
<tr>
<td>Elective</td>
<td>3.9</td>
<td>4.6</td>
<td>0.83 (0.73-0.95)</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>4.8</td>
<td>4.3</td>
<td>1.04 (0.91-1.19)</td>
</tr>
<tr>
<td>CTTC Composite Endpoint*</td>
<td>9.2</td>
<td>11.0</td>
<td>0.83 (0.77-0.90)</td>
</tr>
</tbody>
</table>

*Coronary heart death (CHD), nonfatal MI, stroke, coronary revascularization

Statin Effect Size by Year of Treatment

<table>
<thead>
<tr>
<th>Total number of MVEs</th>
<th>Annual event rate in control arm (% per year)</th>
<th>RR (CI) per 1 mmol/L reduction in LDL cholesterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1 year</td>
<td>4680</td>
<td>9% ↓ 0·91 (0·85-0·97)</td>
</tr>
<tr>
<td>1-2 years</td>
<td>3580</td>
<td>22% ↓ 0·78 (0·73-0·85)</td>
</tr>
<tr>
<td>2-3 years</td>
<td>3124</td>
<td>24% ↓ 0·76 (0·70-0·82)</td>
</tr>
<tr>
<td>3-4 years</td>
<td>2483</td>
<td>28% ↓ 0·72 (0·66-0·79)</td>
</tr>
<tr>
<td>4-5 years</td>
<td>1819</td>
<td>22% ↓ 0·78 (0·71-0·87)</td>
</tr>
<tr>
<td>≥5 years</td>
<td>1018</td>
<td>24% ↓ 0·76 (0·65-0·87)</td>
</tr>
<tr>
<td>All years</td>
<td>16704</td>
<td>20% ↓ 0·80 (0·78-0·82)</td>
</tr>
</tbody>
</table>

Adapted from Cholesterol Treatment Trialists’ (CTT) Collaboration *Lancet* 2010;376:1670-81 (Supplementary Webappendix)
Key Secondary Endpoint

Hazard ratio 0.80 (95% CI, 0.73-0.88) P<0.00001

Median 26 (22-30) months Kaplan Meier estimates

Landmark Analysis: Secondary Outcome

16% RRR
HR 0.84 (95% CI 0.74-0.96)
P = 0.008

25% RRR
HR 0.75 (95% CI 0.66-0.85)
P < 0.00001

## Safety

<table>
<thead>
<tr>
<th>Adverse events (%)</th>
<th>Evolocumab (N=13,769)</th>
<th>Placebo (N=13,756)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>77.4</td>
<td>77.4</td>
</tr>
<tr>
<td>Serious</td>
<td>24.8</td>
<td>24.7</td>
</tr>
<tr>
<td>Allergic reaction</td>
<td>3.1</td>
<td>2.9</td>
</tr>
<tr>
<td>Injection-site reaction</td>
<td>2.1</td>
<td>1.6</td>
</tr>
<tr>
<td>Treatment-related and led to d/c of study drug</td>
<td>1.6</td>
<td>1.5</td>
</tr>
<tr>
<td>Muscle-related</td>
<td>5.0</td>
<td>4.8</td>
</tr>
<tr>
<td>Cataract</td>
<td>1.7</td>
<td>1.8</td>
</tr>
<tr>
<td>Diabetes (new-onset)</td>
<td>8.1</td>
<td>7.7</td>
</tr>
<tr>
<td>Neurocognitive</td>
<td>1.6</td>
<td>1.5</td>
</tr>
</tbody>
</table>

Lowest LDL-C Is Best

Relationship Between the Achieved LDL-C at 4 weeks and Risk of CV Death/MI/Stroke at 3 Years

CV Death, MI or Stroke in Patients with and without Peripheral Artery Disease

Bonaca et al Circulation 2017;137:338-50
Effect of Evolocumab on Primary Endpoint

**Patients w/ Diabetes at Baseline**
- n=11,031 (40%)
- 38% with pre-diabetes, 22% with normoglycemia

- Hazard Ratio 0.83 (95% CI 0.75-0.93)
- P=0.0008

- 17.1% with diabetes at baseline
- Δ 2.7%, NNT 37

**Patients w/o Diabetes at Baseline**
- n=16,533 (60%)
- 38% with pre-diabetes, 22% with normoglycemia

- Hazard Ratio 0.87 (95% CI 0.79-0.96)
- P=0.0052

- 13.0% without diabetes at baseline
- Δ 1.6%, NNT 62

P_{interaction}=0.60

Sabatine et al *Lancet Diabetes Endocrinol* 2017;5:941-50
Benefit of Evolocumab in High-Risk MI Subgroups

N=22,351 with Prior MI → median ~3 (1, 7) yrs ago

- Qualifying MI <2 yrs ago
  n=8,402 (38%)
  24% RRR
  HR 0.76 (95% CI 0.64-0.89) P<0.001
  + 0.6 (0.3, 1.2) yrs

- ≥2 Prior MIs
  n=5,285 (24%)
  21% RRR
  HR 0.79 (95% CI 0.67-0.94) P=0.006

- Residual Multivessel Disease
  n=5,618 (25%)
  30% RRR
  HR 0.70 (95% CI 0.58-0.84) P<0.001

MI patients with ≥1 High-Risk Feature:
Estimated ARR_{5 \text{ years}} = 5% or NNT_{5 \text{ years}} ~ 20

Sabatine et al Circulation 2018;138:756-66
Study Hypothesis

Alirocumab vs. placebo reduces cardiovascular (CV) morbidity and mortality after recent acute coronary syndrome (ACS) in patients with elevated levels of atherogenic lipoproteins despite intensive or maximum-tolerated statin therapy

Schwartz et al Am Heart J 2014;168:682-689.e1
Main Inclusion Criteria

- **Age**: ≥40 years
- **ACS**
  - 1 to 12 months prior to randomization
  - Acute myocardial infarction (MI) or unstable angina
- **High-intensity statin therapy**
  - Atorvastatin 40 to 80 mg daily or
  - Rosuvastatin 20 to 40 mg daily or
  - Maximum tolerated dose of one of these agents for ≥2 weeks

- **Inadequate control of lipids**
  - LDL-C ≥1.8 mmol/L or
  - Non-HDL-C ≥2.6 mmol/L or
  - Apolipoprotein B ≥0.8 mg/L

*Patients not on statins were authorized to participate if tolerability issues were present and documented*

Schwartz et al Am Heart J 2014;168:682-689.e1
Treatment Assignment

Post-ACS patients (1 to 12 months)

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

At least one lipid entry criterion met

Randomization

Alirocumab 75-150 mg SC Q2W

Placebo SC Q2W

67% NOT on statin ≤3 months of index ACS

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

Schwartz et al Am Heart J 2014;168:682-689.e1
We attempted to maximize the number of patients in the target range and minimize the number below target by blindly titrating alirocumab (75 or 150 mg SC Q2W) or blindly switching to placebo.

Schwartz et al Am Heart J 2014;168:682-689.e1
Patient Disposition

Mean 59 years
25% female
34% STEMI, 48% NSTEMI, 17% UA
Index ACS PCI or CABG 72%

Randomized 18,924 patients

Alirocumab (N=9462)
Placebo (N=9462)

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

1955 patients experienced a primary endpoint
726 patients died

1343 (14.2%) 1496 (15.8%)
730 (7.7%) Not applicable
14 9

• Premature treatment discontinuation
• Blinded switch to placebo (2 consecutive LDL-C values <0.39 mmol/L)
• Patients lost to follow-up (vital status)

Time from index ACS to randomization: 2.6 (1.7-4.4) months

*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

## Baseline LDL-C and Lipid-Lowering Therapy

<table>
<thead>
<tr>
<th></th>
<th>Alirocumab (N=9462)</th>
<th>Placebo (N=9462)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C,* mmol/L (Q1-Q4)</td>
<td>2.2 (1.9–2.7)</td>
<td>2.2 (1.9-2.7)</td>
</tr>
<tr>
<td>High-dose atorvastatin/rosvastatin, n (%)</td>
<td>8380 (88.6)</td>
<td>8431 (89.1)</td>
</tr>
<tr>
<td>Low-/moderate-dose atorvastatin/rosvastatin, n (%)</td>
<td>830 (8.8)</td>
<td>777 (8.2)</td>
</tr>
<tr>
<td>Ezetimibe, with or without statin, n (%)</td>
<td>269 (2.8)</td>
<td>285 (3.0)</td>
</tr>
<tr>
<td>No lipid-lowering therapy,+ n (%)</td>
<td>87 (0.9)</td>
<td>91 (1.0)</td>
</tr>
</tbody>
</table>

*92.1% of patients qualified on the basis of LDL-C ≥1.81 mmol/L, 7.2% non-HDL ≥1.81 mmol/L

*Patients not on statins authorized to participate if tolerability issues were present and documented

LDL-C: On-Treatment Analysis

Exposure to the intended trial regimen (% of the total follow-up time) 90%; of total time on treatment with alirocumab 78% on 75 mg, 22% on 150 mg

*Excludes LDL-C values after premature treatment discontinuation or blinded switch to placebo

Primary Efficacy Endpoint: MACE

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

ARR 2.0%*
NNT_{4 yrs} ~49 (28, 64)

*Based on 4-yr KM estimate

HR 0.85
(95% CI 0.78, 0.93)
P<0.001

# Primary Efficacy and Components

<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>MACE</td>
<td>903 (9.5)</td>
<td>1052 (11.1)</td>
<td>0.85 (0.78, 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>Non-fatal MI</td>
<td>626 (6.6)</td>
<td>722 (7.6)</td>
<td>0.86 (0.77, 0.96)</td>
<td>0.006</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>111 (1.2)</td>
<td>152 (1.6)</td>
<td>0.73 (0.57, 0.93)</td>
<td>0.01</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>37 (0.4)</td>
<td>60 (0.6)</td>
<td>0.61 (0.41, 0.92)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

*Cumulative Incidence

All-Cause Death:
All Patients

**All patients (N=18,924)**

- HR 0.85 (95% CI 0.73, 0.98); *P* = .03
- *Nominal P-value due to hierarchical position of all-cause death among secondary endpoints

**Eligible for ≥3 years follow-up**

- (N=8,242)
- HR 0.78 (95% CI 0.65, 0.94); *P* = .01

**ARR 1.1%**

**NNT<sub>4 yrs</sub> ~ 87**

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and Steg et al *Circulation* 2019;10.1161/CIRCULATIONAHA.118.038840

![Graphs showing all-cause death rates for placebo and Alirocumab groups over time.](image-url)
**LDL-C Lowering and Mortality**

*Benefit on mortality was not apparent early, even in trials in which it was the primary endpoint*

- **4S**
- **LIPID**

*All-cause mortality*

Death According to *Achieved LDL-C* in the Alirocumab Group at Month 4

Steg et al *Circulation* 2019;10.1161/CIRCULATIONAHA.118.038840
## Safety

<table>
<thead>
<tr>
<th>Event</th>
<th>Alirocumab (N=9451)</th>
<th>Placebo (N=9443)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-emergent adverse events</td>
<td>7165 (75.8)</td>
<td>7282 (77.1)</td>
</tr>
<tr>
<td>Serious Adverse Events (SAEs)</td>
<td>2202 (23.3)</td>
<td>2350 (24.9)</td>
</tr>
<tr>
<td>ALT &gt;3 × ULN</td>
<td>212/9369 (2.3)</td>
<td>228/9341 (2.4)</td>
</tr>
<tr>
<td>Diabetes worsening or diabetic complications¹</td>
<td>506/2688 (18.8)</td>
<td>583/2747 (21.2)</td>
</tr>
<tr>
<td>New onset diabetes²</td>
<td>648/6763 (9.6)</td>
<td>676/6696 (10.1)</td>
</tr>
<tr>
<td>General allergic reaction</td>
<td>748 (7.9)</td>
<td>736 (7.8)</td>
</tr>
<tr>
<td>Hepatic disorder</td>
<td>500 (5.3)</td>
<td>534 (5.7)</td>
</tr>
<tr>
<td>Local injection site reaction*</td>
<td>360 (3.8)</td>
<td>203 (2.1)</td>
</tr>
<tr>
<td>Neurocognitive disorder</td>
<td>143 (1.5)</td>
<td>167 (1.8)</td>
</tr>
<tr>
<td>Cataracts</td>
<td>120 (1.3)</td>
<td>134 (1.4)</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>9 (&lt;0.1)</td>
<td>16 (0.2)</td>
</tr>
</tbody>
</table>

Patients with¹/without² diabetes at baseline

Small interfering RNA (siRNA): Inhibits Translation of PCSK9

Adapted from Hovingh et al Eur Heart J 2013;34:962-71
Who Might Receive a PCSK9 Inhibitor?

- LDL-C ≥1.8 mmol/L (70 mg/dL) despite maximally tolerated statin ± ezetimibe AND
  - Recent ACS
  - Residual multivessel CAD (e.g., ≥40% stenoses in ≥2 vessels, prior CABG)
  - Polyvascular ASCVD (e.g., CAD + PAD)
  - Diabetes
  - LDL-C far from target (i.e., ≥2.6 mmol/L [100 mg/dL])

ASCVD=Atherosclerotic CV Disease; CAD=Coronary Artery Disease; PAD=Peripheral Artery Disease