PCSK9 Inhibition and Clinical Outcomes
Lessons from FOURIER

Subodh Verma
Cardiac Surgeon
Professor
University of Toronto
Canada Research Chair Atherosclerosis
Disclosures

Subodh Verma has received speaking honoraria and/or grant support from the following companies:
- AstraZeneca
- Abbott
- Amgen
- Bayer
- BI
- Novartis
- Sanofi
- Valeant
- Lilly
- Merck
- Mylan
Historical Perspective

1. Aging Hypothesis
2. Response to Injury Hypothesis
3. Inflammatory Hypothesis
4. Lipid Hypothesis
2015 - Definition

“Atherosclerosis is an inflammatory disease in which immune mechanisms interact with lipid particles to initiate, propagate and activate lesions in the arterial wall”
Patients dying from stable vs unstable coronary syndromes: Atheromas have varying composition

Percent of plaques with lipid content > 40%

- Stable*: 0%
- Unstable†: 100%

Macrophage volume (%)

- Stable*: 8%
- Unstable†: 16%

SMC volume (%)

- Stable: 8%
- Unstable: 16%

*Stable plaque = smooth surface
†Unstable plaque = fissured

Effects of Diet on Blood Lipids In Man
Particularly Cholesterol and Lipoproteins

Ancel Keys, Joseph T. Anderson, Flaminio Fidanza,*
Margaret Haney Keys, and Bengt Swahn†

Clin Chem 1955;1:34-52

There are good reasons for the current great interest in the effects of the diet on the blood lipids. It is now generally agreed that there is an important relationship between the concentration of certain lipid fractions in the blood and the development of atherosclerosis and the coronary heart disease it produces. The outstanding characteristic of atherosclerosis is the presence of lipid deposits, mainly cholesterol, in the walls of the arteries. And both in man and animals the most obvious factor that affects the blood lipids is the diet.
Factors of Risk in the Development of Coronary Heart Disease—Six-Year Follow-up Experience

The Framingham Study

WILLIAM B. KANNEL, M.D., THOMAS R. DAWBER, M.D., F.A.C.P.,
ABRAHAM KAGAN, M.D., F.A.C.P., NICHOLAS REVOTSKIE, M.D.,
AND JOSEPH STOKES, III, M.D.
Framingham, Massachusetts

Elevated cholesterol is a novel and previously unrecognized factor of risk for CHD
Chicken or Egg?
Cholesterol Crystals Trigger Inflammation through NLRP3
Courtesy, George S. Abela, MD.
## Risk of AMI associated with Risk Factors in INTERHEART

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>% Cont</th>
<th>% Cases</th>
<th>PAR (99% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ApoB/ApoA-1 (5 v 1)</td>
<td>20.0</td>
<td>33.5</td>
<td>54.1 (49.6, 58.6)</td>
</tr>
<tr>
<td>Curr smoking</td>
<td>26.8</td>
<td>45.2</td>
<td>36.4 (33.9, 39.0)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>7.5</td>
<td>18.5</td>
<td>12.3 (11.2, 13.5)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>21.9</td>
<td>39.0</td>
<td>23.4 (21.7, 25.1)</td>
</tr>
<tr>
<td>Abd Obesity (3 v 1)</td>
<td>33.3</td>
<td>46.3</td>
<td>33.7 (30.2, 37.4)</td>
</tr>
<tr>
<td>Psychosocial</td>
<td>-</td>
<td>-</td>
<td>28.8 (22.6, 35.8)</td>
</tr>
<tr>
<td>Veg &amp; fruits daily</td>
<td>42.4</td>
<td>35.8</td>
<td>12.9 (10.0, 16.6)</td>
</tr>
<tr>
<td>Exercise</td>
<td>19.3</td>
<td>14.3</td>
<td>25.5 (20.1, 31.8)</td>
</tr>
<tr>
<td>Alcohol</td>
<td>24.5</td>
<td>24.0</td>
<td>13.9 (9.3, 20.2)</td>
</tr>
<tr>
<td>Combined</td>
<td>-</td>
<td>-</td>
<td>90.4 (88.1, 92.4)</td>
</tr>
</tbody>
</table>
LDL-C Lowering

Keep Going... and Going... and Going...
CV Event Reduction with Statins...

- is proportional to LDL-C reduction
- applies to a broad population
- is independent of baseline LDL-C
- is independent of baseline risk
Will be eradicate CHD by further LDL-C lowering?

MAJOR LIPID TRIALS: LDL-C LEVELS VS RATES OF CORONARY EVENTS

Primary prevention
1. JUPITER-Ros20
2. CARD5-Atv10
3. SHARP-S20+ez
4. ASCOT-LLA-rx
5. JUPITER-pbo
6. SHARP-pbo
7. AFCAPS-rx
8. CARD5-pbo
9. MEGA-Prv10-20
10. ASCOT-LLA-pbo
11. AFCAPS-pbo
12. MEGA-pbo
13. WOSCOPS-rx
14. WOSCOPS-pbo

Secondary prevention
1. PROVE-IT-Atv80
2. MIRACL-Atv80
3. A to Z-540-80
4. HPS-rx
5. A to Z-520
6. TNT-Atv80
7. IDEAL-Atv80
8. CARE-rx
9. PROVE-IT-Prv40
10. IDEAL-Sim20-40
11. ALLIANCE-rx
12. TNT-Atv10
13. LIPID-rx
14. CARE-pbo
15. HPS-pbo
16. MIRACL-pbo
17. 4S-Rx
18. ALLIANCE-pbo
19. LIPID-pbo
20. 4S-pbo
Primary Endpoint — ITT

Cardiovascular death, MI, documented unstable angina requiring rehospitalization, coronary revascularization (≥30 days), or stroke

HR 0.936 CI (0.887, 0.988)  
p=0.016

Simva — 34.7%  
2742 events

EZ/Simva — 32.7%  
2572 events

NNT= 50

15 out of 16 events are not prevented

7-year event rates
In main statin trials, the greatest reductions in CV events were observed in patients who had achieved the lowest on-treatment LDL-C.

**TNT Study**

**Rate of major cardiovascular events**

<table>
<thead>
<tr>
<th>LDL-C (mmol/L)</th>
<th>% patients with major CV events</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1.7</td>
<td>1.7</td>
</tr>
<tr>
<td>1.7 - 2.0</td>
<td>2.0</td>
</tr>
<tr>
<td>2.0 - 2.3</td>
<td>2.3</td>
</tr>
<tr>
<td>≥ 2.3</td>
<td>2.7</td>
</tr>
</tbody>
</table>

* p value for trend in each LDL-C category

**JUPITER Trial**

**Time to occurrence of major cardiovascular events**

- Placebo
- C-LDL > 1.3 mmol/L (rosuvastatin)
- C-LDL < 1.3 mmol/L (rosuvastatin)

* p for trend < 0.0001

**PROVE-IT Study**

**Hazard ratio of the primary end point**

<table>
<thead>
<tr>
<th>LDL-C (mmol/L)</th>
<th>Hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 2.1 - 2.6</td>
<td>0.80 (0.59-1.07)</td>
</tr>
<tr>
<td>&gt; 1.6 - 2.1</td>
<td>0.67 (0.50-0.92)</td>
</tr>
<tr>
<td>&gt; 1.0 - 1.6</td>
<td>0.61 (0.40-0.91)</td>
</tr>
<tr>
<td>≤ 1.0</td>
<td>1.0</td>
</tr>
</tbody>
</table>


*CHD = coronary heart disease; CV= cardiovascular; MI = myocardial infarction; RCT = Randomized controlled trial
“Compound interest is the eighth wonder of the world. He who understands it, earns it ... he who doesn't ... pays it.”

— Albert Einstein
Concept of Lifetime Cumulative LDL-C Exposure and Vascular Risk

Cumulative LDL Exposure

Age (years)

0  20  40  60  80

HoFH  HeFH  Normal

Horton, Cohen, Hobbs Journal of Lipid Research 2009
Long term follow up in statin studies
WOSCOPS experience

CHD mortality

- Over entire period 27% risk reduction
- P<0.001

Placebo  Pravastatin

Original trial

Percentage with event vs. Years since randomisation

55  65  75 y
 Average age of cohort

All-cause mortality

- Over entire period 13% risk reduction
- P<0.001

Placebo  Pravastatin

Percentage with event vs. Years since randomisation

Circulation 2016
Screen early, treat early, think about lifetime risk

54.5% relative risk reduction per 1 mM/L (38.7 mg/dL) LDL-C lowering

22% relative risk reduction per 1 mmol/L (38.7 mg/dL) LDL-C lowering

FOURIER Trial Results:
Clinical Efficacy & Safety of Evolocumab in Patients with Cardiovascular Disease
**Background**

**Proprotein convertase subtilisin/kexin type 9 (PCSK9)**
- Chaperones LDL-R to destruction $\to \uparrow$ circulating LDL-C
- Loss-of-fxn genetic variants $\to \uparrow$ LDL-R $\to \downarrow$ LDL-C & $\downarrow$ risk of MI

**Evolocumab**
- Fully human anti-PCSK9 mAb
- $\sim60\% \downarrow$ LDL-C
- Safe & well-tolerated in Ph 2 & 3 studies
- Exploratory data suggested $\downarrow$ CV events

Sever P & Mackay J. *Br J Cardiol* 2014;21:91-3
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 (1.8 mmol/L) or non-HDL-C ≥100 mg/dL (2.6 mmol/L)

Evolocumab SC
140 mg Q2W or 420 mg QM

Placebo SC
Q2W or QM

RANDOMIZED DOUBLE BLIND

Follow-up Q 12 weeks

Follow-up

Randomized 27,564 patients

Evolocumab (N=13,784)  Placebo (N=13,780)

Follow-up median 26 months (IQR 22-30)

2907 patients experienced primary endpoint
1829 experienced key secondary endpoint

Premature perm. drug discontinuation

5.6%/yr  5.8%/yr

Withdraw consent

0.29%/yr  0.35%/yr

Lost to follow-up

5 patients  13 patients

Ascertainment for primary endpoint was complete for 99.5% of potential patient-years of follow up
Baseline Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean (SD)</td>
<td>63 (9)</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>75</td>
</tr>
<tr>
<td>White race (%)</td>
<td>85</td>
</tr>
<tr>
<td>Region (%)</td>
<td></td>
</tr>
<tr>
<td>North America</td>
<td>17</td>
</tr>
<tr>
<td>Europe</td>
<td>63</td>
</tr>
<tr>
<td>Latin America</td>
<td>7</td>
</tr>
<tr>
<td>Asia Pacific &amp; South Africa</td>
<td>14</td>
</tr>
</tbody>
</table>

Pooled data; no clinically meaningful differences between treatment arms

Sabatine MS et al. *NEJM* 2017;epub ahead of print
### Baseline CV Disease

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of cardiovascular disease</strong></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction (%)</td>
<td>81</td>
</tr>
<tr>
<td>Median time from MI – y (IQR)</td>
<td>3.3 (1.0-7.5)</td>
</tr>
<tr>
<td>Stroke (non-hemorrhagic) (%)</td>
<td>19</td>
</tr>
<tr>
<td>Median time from stroke – y (IQR)</td>
<td>3.3 (1.1-7.2)</td>
</tr>
<tr>
<td>Symptomatic PAD</td>
<td>13</td>
</tr>
<tr>
<td><strong>Cardiovascular risk factor (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>80</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>37</td>
</tr>
<tr>
<td>Current cigarette use</td>
<td>28</td>
</tr>
</tbody>
</table>

Pooled data; no clinically meaningful differences between treatment arms

Sabatine MS et al. *NEJM* 2017;epub ahead of print
## Baseline CV Meds

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA and/or P2Y$_{12}$ Inhibitor (%)</td>
<td>92</td>
</tr>
<tr>
<td>Beta-blocker (%)</td>
<td>76</td>
</tr>
<tr>
<td>ACE inhibitor or ARB and/or aldosterone antagonist (%)</td>
<td>78</td>
</tr>
</tbody>
</table>

Pooled data; no clinically meaningful differences between treatment arms

Sabatine MS et al. *NEJM* 2017;epub ahead of print
## Lipid Lowering Therapy & Lipid Levels at Baseline

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Statin use (%)</strong></td>
<td></td>
</tr>
<tr>
<td>High-intensity</td>
<td>69</td>
</tr>
<tr>
<td>Moderate-intensity</td>
<td>30</td>
</tr>
<tr>
<td><strong>Ezetimibe use (%)</strong></td>
<td>5</td>
</tr>
<tr>
<td><strong>Median lipid measures (IQR)</strong></td>
<td></td>
</tr>
<tr>
<td>LDL-C</td>
<td>92 (80-109)</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>168 (151-189)</td>
</tr>
<tr>
<td>HDL-C</td>
<td>44 (37-53)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>133 (100-182)</td>
</tr>
</tbody>
</table>

*Per protocol, patients were to be on atorva ≥20 mg/d or equivalent. 1% were on low intensity or intensity data were missing. Statin intensity defined per ACC/AHA 2013 Cholesterol Guidelines. Pooled data; no clinically meaningful differences between treatment arms.

Sabatine MS et al. *NEJM* 2017;epub ahead of print
LDL Cholesterol

Placebo

59% mean reduction (95%CI 58-60), P<0.00001
Absolute reduction: 56 mg/dl (95%CI 55-57)

Evolocumab

(median 30 mg/dl, IQR 19-46 mg/dl)
(median 0.78 mmol/L, IQR 0.5-1.2 mmol/L)

Sabatine MS et al. NEJM 2017;epub ahead of print
Primary Endpoint

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

Sabatine MS et al. *NEJM* 2017;epub ahead of print
Key Secondary Endpoint

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

Evolocumab
Placebo

Sabatine MS et al. *NEJM* 2017; epub ahead of print
# 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>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></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death due to acute MI</td>
<td>2.5</td>
<td>2.4</td>
<td>1.05 (0.88-1.25)</td>
</tr>
<tr>
<td>Death due to stroke</td>
<td>0.26</td>
<td>0.32</td>
<td>0.84 (0.49-1.42)</td>
</tr>
<tr>
<td>Other CV death</td>
<td>0.29</td>
<td>0.30</td>
<td>0.94 (0.58-1.54)</td>
</tr>
<tr>
<td>MI</td>
<td>1.9</td>
<td>1.8</td>
<td>1.10 (0.90-1.35)</td>
</tr>
<tr>
<td>Stroke</td>
<td><strong>4.4</strong></td>
<td><strong>6.3</strong></td>
<td><strong>0.73 (0.65-0.82)</strong></td>
</tr>
<tr>
<td>Stroke</td>
<td><strong>2.2</strong></td>
<td><strong>2.6</strong></td>
<td><strong>0.79 (0.66-0.95)</strong></td>
</tr>
</tbody>
</table>

Sabatine MS et al. *NEJM* 2017;epub ahead of print
LDL-C Lowering & CV Death

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

4S

LIPID

Cumulative Risk of Death Due to CHD (%)

Years after Randomization

Placebo

Pravastatin

Reduction in risk, 24%
P<0.001

Lancet 1994;344:1383-89
NEJM 1998;339:1349-57
More Intensive LDL-C Lowering & CV Death

**No clear benefit on CV mortality**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Year</th>
<th>More Intensive Rx Arm</th>
<th>Less Intensive Rx Arm</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROVE-IT TIMI 22</td>
<td>2004</td>
<td>27</td>
<td>36</td>
<td>0.74 (0.45-1.22)</td>
</tr>
<tr>
<td>A2Z</td>
<td>2004</td>
<td>86</td>
<td>111</td>
<td>0.76 (0.57-1.01)</td>
</tr>
<tr>
<td>TNT</td>
<td>2005</td>
<td>101</td>
<td>127</td>
<td>0.80 (0.61-1.03)</td>
</tr>
<tr>
<td>IDEAL</td>
<td>2005</td>
<td>223</td>
<td>218</td>
<td>1.03 (0.85-1.24)</td>
</tr>
<tr>
<td>SEARCH</td>
<td>2010</td>
<td>565</td>
<td>572</td>
<td>0.99 (0.88-1.11)</td>
</tr>
<tr>
<td>IMPROVE-IT</td>
<td>2015</td>
<td>538</td>
<td>537</td>
<td>1.00 (0.89-1.13)</td>
</tr>
<tr>
<td><strong>Summary</strong></td>
<td></td>
<td>1540</td>
<td>1601</td>
<td><strong>0.96 (0.90-1.03)</strong></td>
</tr>
</tbody>
</table>

NEJM 2004;350:1495-504
JAMA 2004;292:1307-16
NEJM 2005;352:1425-35
JAMA 2005;294:2437-45
Lancet 2010;376:1658-69
NEJM 2015;372:2387-97
## 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></td>
<td>3-yr Kaplan-Meier rate</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>
</tbody>
</table>

Sabatine MS et al. *NEJM* 2017;epub ahead of print
Key Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Patients</th>
<th>1° Endpoint HR (95% CI)</th>
<th>Key 2° Endpoint HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td>27564</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Type of disease</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI alone</td>
<td>19113</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke alone</td>
<td>3366</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAD alone</td>
<td>1505</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polyvascular disease</td>
<td>3563</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Baseline LDL-C</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q1 (&lt;80 mg/dl; &lt;2.1 mM/L)</td>
<td>6961</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q2 (80-&lt;92 mg/dl; 2.1-2.4 mM/L)</td>
<td>6886</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q3 (92-109 mg/dl; 2.4-2.8 mM/L)</td>
<td>6887</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q4 (&gt;109 mg/dl; &gt;2.8 mM/L)</td>
<td>6829</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Baseline statin intensity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>19103</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not high</td>
<td>8461</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ezetimibe</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1440</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>26124</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Initial Dosing Regimen</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Every 2 weeks</td>
<td>24774</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monthly</td>
<td>2790</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Timing of Benefit of LDL-C Lowering

Data from CTTC Meta-Analysis of Statin Trials

<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>3.8</td>
</tr>
<tr>
<td>1-2 years</td>
<td>3580</td>
<td>3.4</td>
</tr>
<tr>
<td>2-3 years</td>
<td>3124</td>
<td>3.6</td>
</tr>
<tr>
<td>3-4 years</td>
<td>2483</td>
<td>3.6</td>
</tr>
<tr>
<td>4-5 years</td>
<td>1819</td>
<td>3.7</td>
</tr>
<tr>
<td>≥5 years</td>
<td>1018</td>
<td>3.9</td>
</tr>
<tr>
<td>All years</td>
<td>16704</td>
<td>3.6</td>
</tr>
<tr>
<td>Years 1-5</td>
<td>12024</td>
<td>3.6</td>
</tr>
</tbody>
</table>

Landmark Analysis

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

CV Death, MI, Stroke

Evolocumab
Placebo

Months from Randomization

Sabatine MS et al. NEJM 2017; epub ahead of print
Fatal or Nonfateful MI or Stroke

19% RRR
HR 0.81 (95% CI 0.70-0.93)
P = 0.003

33% RRR
HR 0.67 (95% CI 0.59-0.77)
P < 0.00001

Sabatine MS et al. *NEJM* 2017;epub ahead of print
Comparison to Cholesterol Treatment Trialists Collaboration

Hazard Ratio (95% CI) per 1 mmol/L reduction in LDL-C

- **Major Coronary Events**: 0.78 (0.70-0.86)
- **Stroke**: 0.77 (0.66-0.91)
- **Coronary revascularization**: 0.75 (0.67-0.84)
- **Major Vascular Events**: 0.77 (0.73-0.82)

CTTC Meta-analysis Year 2

Lipid-lowering therapy better

Lipid-lowering therapy worse

CTTC data from *Lancet* 2010;376:1670-81
Comparison to Cholesterol Treatment Trialists Collaboration

Hazard Ratio (95% CI) per 1 mmol/L reduction in LDL-C

- Major Coronary Events
  - CTTC Meta-analysis Year 2: 0.78 (0.70-0.86)
  - FOURIER Year 2: 0.80 (0.71-0.90)

- Stroke
  - CTTC Meta-analysis Year 2: 0.77 (0.66-0.91)
  - FOURIER Year 2: 0.77 (0.63-0.94)

- Coronary revascularization
  - Urgent
    - CTTC Meta-analysis Year 2: 0.75 (0.67-0.84)
    - FOURIER Year 2: 0.73 (0.62-0.86)
  - Elective
    - CTTC Meta-analysis Year 2: 0.84 (0.73-0.98)

- Major Vascular Events
  - CTTC Meta-analysis Year 2: 0.77 (0.73-0.82)
  - FOURIER Year 2: 0.83 (0.76-0.90)

CTTC data from Lancet 2010;376:1670-81
### Absolute Risk Reductions

**In stable secondary prevention setting**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Setting</th>
<th>Absolute ↓ in MACE</th>
<th>Follow-up</th>
<th>NNT over 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>CARE</td>
<td>Statin vs. placebo in Pts w/ avg LDL-C</td>
<td>3.0-4.2%</td>
<td>5.0 yrs</td>
<td>24-34</td>
</tr>
<tr>
<td>LIPID</td>
<td>Statin vs. placebo in Pts w/ avg LDL-C</td>
<td>3.6-4.4%</td>
<td>6.1 yrs</td>
<td>28-34</td>
</tr>
<tr>
<td>TNT</td>
<td>High vs. moderate intensity statin Rx</td>
<td>2.2%</td>
<td>4.9 yrs</td>
<td>45</td>
</tr>
</tbody>
</table>

MACE defined as composite of coronary or CV death, MI or stroke. Range provided when trials did not report triple composite. For FOURIER, lower range of NNT based on extrapolating RRR for MACE beyond first year to subsequent years.

## Safety (1)

<table>
<thead>
<tr>
<th></th>
<th>Evolocumab (N=13,769)</th>
<th>Placebo (N=13,756)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse events (%)</strong></td>
<td></td>
<td></td>
</tr>
<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><strong>Laboratory results (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Binding Ab</td>
<td>0.3</td>
<td>n/a</td>
</tr>
<tr>
<td>Neutralizing Ab</td>
<td>none</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td>Evolocumab (N=13,769)</td>
<td>Placebo (N=13,756)</td>
</tr>
<tr>
<td>------------------</td>
<td>-----------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td><strong>Adverse events (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle-related</td>
<td>5.0</td>
<td>4.8</td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
<td>0.1</td>
<td>0.1</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>
<tr>
<td><strong>Laboratory results (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aminotransferase &gt;3× ULN</td>
<td>1.8</td>
<td>1.8</td>
</tr>
<tr>
<td>Creatine kinase &gt;5× ULN</td>
<td>0.7</td>
<td>0.7</td>
</tr>
</tbody>
</table>

New-onset diabetes assessed in patients without diabetes at baseline; adjudicated by CEC.
EBBINGHAUS Trial Design

**Randomized Double Blind**

- **Placebo SC**
  - Q2W or QM
- **Evolocumab SC**
  - 140 mg Q2W or 420 mg QM

2442 patients screened for EBBINGHAUS

1974 Enrolled (Full Analysis Pop)
Median F/U 19.8 months

Primary Analysis Cohort (N=1204)
Baseline cognitive testing on/before 1st dose of study drug and had f/u cognitive testing post dosing*
Additional 770 pts w/ baseline assessment before week 12 visit

**Major Exclusions**
1. Not enrolled in FOURIER
2. >12 wk FOURIER visit
3. H/O dementia, cognitive impairment or other conditions interfering with participation

* Cognitive tests performed at baseline; at 6, 12, 24 months; and end of study

Endpoints

1. Cambridge Neuropsychological Test Automated Battery (CANTAB) Assessments, a standardized, well-validated computer tablet-based testing platform.
   Assessed at baseline, 6, 12, 24, 48 mos and study end.
   - Primary: Spatial working memory strategy index of executive function
   - Secondary: Spatial working memory between errors
   - Paired associates learning
   - Reaction time
   - Exploratory: Global score (combines above 4 tests)

2. Patient survey of everyday cognition* at study end

3. Investigator report of cognitive AEs

*Memory and executive function domains

Owen 1990 PMID: 2267054; Sahakian 1988, PMID: 3382917; Owen 1996 PMID: 8714706; Kollins PMID: 21476931

CANTAB - Spatial Working Memory (SWM)

- Search for the blue token hidden within a red box
- Number of red boxes increases each round (3, 4, 6, 8).
- Critical instruction: *Do not return to a box where a blue token was found.*

SWM strategy index: = # inefficient searches started. Range 4-28.

Lower scores represent better performance.
Primary Endpoint
Spatial Working Memory Strategy Index

Mean Number of boxes

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

Raw Scores

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

Non-inferiority boundary 0.19

P_non-inferiority < 0.001

PNI is from fixed estimate
Summary for Evolocumab

• ↓ LDL-C by 59%
  – Consistent throughout duration of trial
  – Median achieved LDL-C 30 mg/dl (IQR 19-46) [0.78 (0.5-1.2) mmol/L]

• ↓ CV outcomes in patients already on statin therapy
  – 15% ↓ broad primary endpoint; 20% ↓ CV death, MI, or stroke
  – Consistent benefit, incl. in those on high-intensity statin, low LDL-C
  – 25% reduction in CV death, MI, or stroke after 1st year
  – Long-term benefits consistent w/ statins per mmol/L ↓ LDL-C

• Safe and well-tolerated
  – Similar rates of AEs, incl DM & neurocog events w/ EvoMab & pbo
  – Rates of EvoMab discontinuation low and no greater than pbo
  – No neutralizing antibodies developed
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)
Lowering LDL—Not Only How Low, But How Long?

Michael S. Brown and Joseph L. Goldstein

The causal relation between plasma low-density lipoprotein (LDL) cholesterol (LDL-C) levels and coronary heart disease is well established. Compelling evidence from between-country comparisons shows that large and lifelong diet-related differences in LDL-C levels are associated with 10-fold differences in coronary mortality (1) (see the figure). Strong support comes from observations on genetic diseases such as heterozygous familial hypercholesterolemia, in which mutations in the LDL receptor gene double LDL-C levels throughout life and increase the risk of early heart attack by more than 10-fold (2). So, it has been somewhat disappointing that treatment with cholesterol-lowering statins for 5 years reduces the incidence of heart attacks by only 40%, even when LDL-C concentration is reduced by 80 mg/dl (3), a reduction that should give much more protection based on the population studies. A likely explanation is provided by Cohen, Hobbs, and their colleagues in this week’s issue of the New England Journal of Medicine (4). In lowering LDL levels, the appropriate consideration may be not only how low, but also how long.

Cohen et al. studied middle-aged Americans with lifelong low LDL levels, owing to loss-of-function mutations in the gene encoding PCSK9, a secreted enzyme of the serine protease family. In a small number of subjects with severe nonsense mutations, the concentration of LDL-C was reduced by 38 mg/dl, and the prevalence of coronary heart disease declined by a remarkable 88%. In a larger number of subjects with a less severe missense mutation, LDL-C concentration was reduced by only 21 mg/dl, yet coronary heart disease incidence declined by 47%.

What is the function of PCSK9, and how do mutations in the PCSK9 gene lower the concentration of LDL? Experiments in mice showed that overproduction of PCSK9 in liver and cultured hepatocytes severely reduces the number of LDL receptors (5, 6). The simplest hypothesis is that PCSK9 directly catalyzes the breakdown of LDL receptors, but this has not been demonstrated experimentally. Inasmuch as LDL receptors mediate high-efficiency removal of LDL from plasma, a reduction in the number of LDL receptors causes LDL to accumulate. Ablation of the PCSK9 gene in mice through gene-knockout technology increased the number of LDL receptors in liver and enhanced the clearance of LDL from the plasma (7). This striking finding indicates that PCSK9 functions tonically in mice to keep LDL receptor number lower and plasma LDL concentration higher than they would be otherwise.

PCSK9 appears to have the same effect on LDL in humans. A role for PCSK9 was first rea-
Six year-old girl with homozygous Familial Hypercholesterolemia. Bumps on skin are deposits of cholesterol derived from LDL.
How Low is Too Low?

The Nobel Prize in Physiology or Medicine 1985

“...a level of LDL-cholesterol in plasma of 25 mg/dL would be sufficient...”

Michael S. Brown
Prize share: 1/2

Joseph L. Goldstein
Prize share: 1/2

The Nobel Prize in Physiology or Medicine 1985 was awarded jointly to Michael S. Brown and Joseph L. Goldstein "for their discoveries concerning the regulation of cholesterol metabolism"
Heart Attacks: Gone with the Century?

This issue of Science highlights the progress and promise of research in cardiovascular disease, the most frequent cause of death in men over age 35 and women over age 65 in the United States. Heart attacks were recognized as a public health problem only in this century. They are likely to lose this notoriety early in the next. The reason: Four decades of progress in understanding cholesterol and the lipoproteins that carry it in blood plasma.

Atherosclerosis begins when plasma lipoproteins of intermediate and low density (here called LDL) are deposited in artery walls. Evidence for the causative role of LDL comes from three sources. (i) Experimental: Animals with low levels of LDL have no atherosclerosis, and manipulations that raise LDL universally cause the disease. (ii) Epidemiologic: Human populations with low LDL levels have very little atherosclerosis; the disease increases in proportion to LDL in all populations studied. (iii) Genetic: Mutations that impair the receptor-mediated removal of LDL from plasma cause fulminating atherosclerosis. The final (thera-
Intensive BP Lowering?
Polypill?
Inflammation reduction?
Dietary interventions?
Yoga?
Coconut Oil?
Niacin?
Fibrates?
CETP inhibition
Ridker PM et al. Circulation 2016 LDL-C lowering is the preferred polypill
Which would you rather have, a cholesterol test or a final exam?

For many, the first sign of heart disease is a heart attack. Did you know that one out of two adult Canadians is at risk of developing heart disease because they have high cholesterol? And that cardiovascular disease is the leading cause of death in Canada?

High cholesterol is a major risk factor for heart disease but managing your cholesterol can be quite simple.

If any of these apply to you, cut this screening test out and ask your doctor about getting your cholesterol tested:

- Woman 50 years or older
- Man 40 years or older
- Heart disease (angina, heart attack, coronary bypass, stroke, angioplasty)
- Diabetes
- Family history (mother, father, sister, brother or grandparent) of heart disease or high cholesterol
- Two or more of the following:
  - Overweight
  - Physically inactive
  - Smoker
  - High blood pressure

Call toll-free at 1-877-4-LOW-LDL (1-877-456-9535) or visit www.makingtheconnection.ca and you will receive a free booklet describing the connection between cholesterol and heart disease.
Is there something in this room we need to talk about?
“DEATH IS THE CURE FOR ALL DISEASES.”

THOMAS BROWNE
# Outcome trials with PCSK9 inhibitors

<table>
<thead>
<tr>
<th>Study</th>
<th>FOURIER</th>
<th>ODYSSEY OUTCOMES</th>
<th>SPIRE-1/ SPIRE-2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment</strong></td>
<td>Evolocumab: 420 mg QM or 140 mg Q2W</td>
<td>Alirocumab: 75 mg Q2W (up titrated to 150 mg Q2W if LDL &gt;1.3 mmol/L; down titrated if LDL &lt;0.65 mmol/L)</td>
<td>Bococizumab: 150 mg Q2W</td>
</tr>
<tr>
<td></td>
<td>Background: optimal lipid lowering therapy</td>
<td>Background: optimized lipid lowering therapy</td>
<td>Background: lipid lowering therapy</td>
</tr>
<tr>
<td><strong>Population</strong></td>
<td>MI or stroke (≥ last 4 weeks) OR PAD (plus Risk factors for CVD)</td>
<td>Patients hospitalized for ACS (&lt;12 months before randomization)</td>
<td>Patients at high risk of a CV event</td>
</tr>
<tr>
<td><strong># patients</strong></td>
<td>27,500</td>
<td>18,000</td>
<td>SPIRE-1: 17,000</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>SPIRE-2: 9,000</td>
</tr>
<tr>
<td><strong>LDL-C for eligibility</strong></td>
<td>LDL-C ≥ 1.8 mmol/L (or non-HDL-C ≥ 2.6 mmol/L) after 4 week stabilization with optimal lipid lowering therapy</td>
<td>≥ 1.8 mol/L or non-HDL-C ≥ 2.6 mmol/L</td>
<td>SPIRE-1: LDL-C ≥1.8 and &lt;2.6 mmol/L</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>SPIRE-2: LDL-C ≥2.6 mmol/L or non-HDL-C ≥3.4 mmol/L</td>
</tr>
<tr>
<td><strong>Study completion</strong></td>
<td>Completed</td>
<td>Estimated December 2017</td>
<td>Completed</td>
</tr>
</tbody>
</table>

ACS, acute coronary syndrome; CAD, coronary artery disease; CHD, coronary heart disease; CVD, coronary vascular disease; EZE, ezetimibe; FH, familial hypercholesterolemia; HeFH, heterozygous familial hypercholesterolemia; PAD: peripheral artery disease; T2DM: type 2 diabetes mellitus.
Primary Pre-Specified Endpoint* of SPIRE-2 (Baseline LDL-C ≥2.6 mmol/L)

HR (95% CI) = 0.79 (0.65-0.97)
P = 0.021

Baseline LDL-C = 3.44 mmol/L
Placebo event rate = 4.19/100py
Median follow-up = 12 months

*Non-fatal myocardial infarction, non-fatal stroke, hospitalization for unstable angina requiring urgent revascularization, or CV death.

ODYSSEY Outcomes: Study Design

Post-ACS (4-52 weeks) patients\(^1\) age ≥40 yrs (n~18,000) with \(LDL-C \geq 1.81\) mmol/L, or \(ApoB \geq 0.8\) g/L, or \(Non-HDL-C \geq 2.59\) mmol/L despite high-intensity (or maximally tolerated) statin (atorvastatin 40-80 mg or rosuvastatin 20-40 mg/daily) x ≥2 wks ± other lipid-modifying therapy (e.g., ezetimibe, fenofibrate)\(^2\)

Randomization\(^3\)

Alirocumab 75 mg SC Q2wks x 2 months → 150 mg SC Q2wks based upon Month 1 LDL-C ≥50 mg/dL (1.29 mmol/L)\(^4\)

Placebo SC Q2wks

Primary Endpoint: Time to first CHD death/non-fatal MI/fatal and non-fatal ischemic stroke/unstable angina requiring hospitalization

Follow-Up: Minimum 24 months or target number of events (~1600) → estimated 11.4% rate at 4 yrs, 15% risk reduction; 90% power, 1-sided \(p=0.025\), 1% lost

\(^1\) Elevated troponin or CK-MB or resting ECG changes + obstructive coronary disease (new/presumed new ischemia/infarction by perfusion imaging, regional wall motion abnormality, coronary stenosis ≥70% by angiography)

\(^2\) Key exclusion criteria: Uncontrolled hypertension; NYHA III-IV or LVEF<25%; prior hemorrhagic stroke; TG>4.52 mmol/L; hepatitis; eGFR<30 ml/min

\(^3\) Following ≥2 wk (+ 5 days) run-in period with placebo (1 mL volume in an autoinjector) SC Q2wks

\(^4\) Titration downwards for very low LDL-C
NEWTON CABG
Randomized Trial of Evolocumab on Graft Patency post CABG

EVO CEA
Randomized Trial of Evolocumab on Carotid Atherosclerosis

Subodh Verma, David Mazer, Deepak Bhatt, Michael Koren, Mohammed Al-Omran, Lawrence Leiter
Conclusions

1. PCSK9 inhibition with evolocumab significantly & safely ↓ major cardiovascular events when added to statin therapy

2. The achieved benefit further validates the LDL-C hypothesis, now down to 20-25 mg/dL

3. We should strive to achieve very low levels of LDL-C early in individuals to maximize cardiovascular benefit