“S-18 Lipids: looking forward to 2017”

Heart and Stroke Clinical Update
1010-1140 - 10 Dec 2016

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Faculty/Presenter Disclosure

- **Faculty:** Rob Hegele

- **Relationships with commercial interests:**
  - **Grants/Research Support:** Amgen, Pfizer, Lilly, Aegerion, Sanofi, Cerenis, Ionis
  - **Speakers Bureau/Honoraria:** Valeant, Amgen, Aegerion, Sanofi
  - **Consulting Fees:** Amgen, Sanofi, Valeant, Aegerion, Lilly, Pfizer, Gemphire, Ionis, Cerenis, Boston Heart Diagnostics
Patient Presentation

- 60-year-old woman with a history of hypertension and hyperlipidemia admitted with unstable angina
- Had urgent PCI with stent for 95% proximal LAD lesion
- Multiple < 50% lesions in RCA, Circ, LAD
- Father had fatal MI at age 50 years
- Patient on previous statin but stopped due to myalgias over a year ago
On Exam

- BMI 28.6 kg/m², waist 38 inches (96.5 cm)
- Current meds:
  - Lisinopril 20 mg/HCTZ 12.5 mg
  - ASA 81 mg

<table>
<thead>
<tr>
<th>Labs</th>
<th>mmol/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Cholesterol</td>
<td>7.1</td>
</tr>
<tr>
<td>LDL-C</td>
<td>4.9</td>
</tr>
<tr>
<td>HDL-C</td>
<td>1.1</td>
</tr>
<tr>
<td>TG</td>
<td>2.3</td>
</tr>
<tr>
<td>Glucose</td>
<td>6.7</td>
</tr>
</tbody>
</table>

Counseled on diet, exercise, need for statin therapy
Patient Follow-Up
8 Weeks

- Walking 4 times weekly for 30 minutes
- Atorvastatin 40 mg daily
- Complains of muscle pain
- Gained 1 kg

<table>
<thead>
<tr>
<th>Labs</th>
<th>mmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C</td>
<td>3.0</td>
</tr>
<tr>
<td>HDL-C</td>
<td>1.1</td>
</tr>
<tr>
<td>TG</td>
<td>1.8</td>
</tr>
<tr>
<td>Glucose</td>
<td>7.5</td>
</tr>
</tbody>
</table>
Patient issues

1. adequately treated?
2. myalgia
3. glycemia
Objectives

1. To review 2016 Canadian Lipid Guidelines

2. To appreciate the role of established treatments

3. To evaluate the potential of recently approved lipid treatments
Issues in the 2016 guidelines

- keep LDL-C targets < 2.0 mmol/L
- lower is better
- non-fasting lipids to screen
- non-HDL-C and apo B are alternate targets
- Framingham or cardiovascular age
- statins remain foundational Rx
- non-statins: ezetimibe OK; niacin, fibrates less so
- PCSK9-inhibitors

### 2016 Lipid Guidelines

**WHO TO SCREEN**

<table>
<thead>
<tr>
<th>Men ≥40 years of age; women ≥40 years of age (or postmenopausal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients with the following conditions regardless of age:</td>
</tr>
</tbody>
</table>

- Clinical evidence of atherosclerosis
- Abdominal aortic aneurysm
- Diabetes mellitus
- Arterial hypertension
- Current cigarette smoking
- Stigmata of dyslipidemia (arcus cornea, xanthelasma or xanthoma)
- Family history of premature CVD*
- Family history of dyslipidemia
- Chronic kidney disease
- Obesity (BMI ≥30 kg/m²)
- Inflammatory bowel disease
- HIV infection
- Erectile dysfuntion
- Chronic obstructive pulmonary disease
- Hypertensive diseases of pregnancy

*Consider earlier in ethnic groups at increased risk such as South Asian or First Nations individuals.
2016 Lipid Guidelines

Treatment Targets:
• **LDL-C consistently <2.0 mmol/L** or >50% reduction
• Consider <1.8 mmol/L in patients with clinical atherosclerosis
• Apo B ≤0.80 g/L or non-HDL-C ≤2.6 mmol/L be considered as alternative treatment targets

Statin Indicated Conditions
(those who will benefit the most):
• Clinical atherosclerosis*
• Abdominal aortic aneurysm
• Most diabetes mellitus
• CKD (age >50 years)
• LDL-C ≥5.0 mmol/L

*Clinical atherosclerosis, i.e. previous MI, or coronary revascularization by PCI or CABG surgery, other arterial revascularization procedures, angina pectoris, cerebrovascular disease including TIA, or peripheral arterial disease (claudication and/or ABI <0.9)

Non-fasting lipids

Langsted et al. Circulation 2008;118:2047-2056
Non-HDL-C as an alternate target

\[
\text{non-HDL-C} = \text{TC} - \text{HDL-C}
\]
Here's your personalized Heart & Stroke Risk Assessment.

Having trouble viewing our email? View it online.

Your Personalized Risk Assessment Report

Your life expectancy* is:

*Based on specific lifestyle risk factors. Read more.

88 years

A Canadian male your age lives an average of 82 years.

Your life expectancy is higher than other people of your age group and gender. You can still make positive changes to improve your cardiac health and protect what matters. The Heart and Stroke Foundation is here to support you and your family, every step of the way.

Risk factors you cannot control

Non-controllable risk factors for heart disease and stroke include your age, gender, ethnicity and family history. While our researchers find ways to stop heart disease and stroke before they happen, we've uncovered realistic ways so you can minimize your risks.

FAMILY HISTORY
See how your family history is affecting your life today, and how to take action with powerful steps that help break the cycle of heart disease and stroke.

http://www.heartage.me/
https://ehealth.heartandstroke.ca/

Lower on-Rx LDL-C and reduced risk

Boekholdt SM et al. JACC 2014; 64:5485-94
Reduced all-cause mortality with statins

Reduced major vascular events with statins

CTTC 2016; 25 RCTs of statins; >170,000 patients

Lancet 2016 Sep 8; doi 10.1016/S0140-6737(16)31357-5.
LDL-C and vascular event risk

A Twenty-five statin trials

JAMA 2016; 316: 1289-1297.
Patients with Genetically Lower LDL-C have even Greater CV Event Reduction

Adapted from Ference BA et al. J Am Coll Cardiol. 2015;65:1552-1561.

Proportional Risk Reduction (SE) log scale

Lower LDL-C (mmol/L)

Adapted from Ference BA et al. J Am Coll Cardiol. 2015;65:1552-1561.
Extent of LDL-C Reduction is Accompanied by a Proportional Decrease in CV Events

Every 1.0 mmol/L Decrease in LDL-C Reduces Relative Risk for CV Events by 20-25%

On treatment duration ranged from 10 to 24 months.

Statin indicated conditions

<table>
<thead>
<tr>
<th>CLINICAL ATHEROSCLEROSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction, acute coronary syndromes</td>
</tr>
<tr>
<td>Stable angina, documented coronary disease by angiography (&gt;10% stenosis)</td>
</tr>
<tr>
<td>Stroke, TIA, documented carotid disease</td>
</tr>
<tr>
<td>Peripheral artery disease, claudication and/or ABI &lt;0.9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ABDOMINAL AORTIC ANEURYSM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal aorta &gt;3.0 cm or</td>
</tr>
<tr>
<td>Previous aneurysm surgery</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DIABETES MELLITUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥40 years of age or</td>
</tr>
<tr>
<td>&gt;15 years duration and age ≥30 years or</td>
</tr>
<tr>
<td>Microvascular complications</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CHRONIC KIDNEY DISEASE</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;3 months duration and</td>
</tr>
<tr>
<td>ACR &gt;3.0 mg/mmol or</td>
</tr>
<tr>
<td>eGFR &lt;60 ml/min/1.73m²</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>LDL-C ≥5.0 MMOL/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C ≥5.0 mmol/L or</td>
</tr>
<tr>
<td>Documented familial hypercholesterolemia</td>
</tr>
<tr>
<td>Excluded 2nd causes</td>
</tr>
</tbody>
</table>

Statin indicated primary prevention conditions

<table>
<thead>
<tr>
<th>Intermediate Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>FRS 10-19% and LDL-C $\geq$3.5 mmol/L or Non-HDL-C $\geq$4.3 mmol/L or ApoB $\geq$1.2 g/L or Men $\geq$50 and women $\geq$60 with one additional risk factor: low HDL-C, impaired fasting glucose, high waist circumference, smoker, hypertension</td>
<td>FRS $\geq$20% or alternative method</td>
</tr>
</tbody>
</table>

Statin doses and efficacy

LDL-C: mean change (%) from baseline at week 6

- Rosuvastatin
  - 10 mg
  - 20 mg
  - 40 mg
  - 40mg

- Atorvastatin
  - 10 mg
  - 20 mg
  - 40 mg
  - 80 mg

- Simvastatin
  - 10 mg
  - 20 mg
  - 40 mg
  - 80 mg

- Pravastatin
  - 10 mg
  - 20 mg
  - 40 mg

Am J Cardiol 2003; 92:152-60.
Benefits vs risks of lowering LDL-C with statins

10,000 patients receiving effective statin therapy for 5 years and lowered LDL-C by 2 mmol/L would result in:

<table>
<thead>
<tr>
<th>Major vascular events prevented</th>
<th>Muscle pain or weakness</th>
<th>Myopathy (symptoms + CK &gt; 10xULN)</th>
<th>Rhabdomyolysis (if statin not stopped upon myopathy)</th>
<th>New-onset diabetes</th>
<th>Haemorrhagic stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,000 (secondary prevention patients)</td>
<td>50-100</td>
<td>~ 5</td>
<td>~ 1</td>
<td>~ 50</td>
<td>~ 5</td>
</tr>
</tbody>
</table>

Based on CTT Collaboration meta-analyses of RCTs. Includes 22 trials (135,000 patients) comparing routine statin therapy to no routine statin therapy and 5 trials (40,000 patients) comparing more versus less intensive statin therapy.

Statin discontinuation = reduced survival

• Side effects are the most common reason patients discontinue statins

• Survival is reduced in patients who discontinue, even compared to those on non-daily statin doses

1) statins not withheld on the basis of a potential, small risk of new-onset DM *(Strong/Very Low).*

2) evaluate purported statin-associated symptoms *systematically*, observe during *cessation, re-initiation* (same or *switch*), altered dosing *frequency* to find a tolerated, statin-based therapy. *(Strong/Very Low).*

3) we *do not recommend vitamins, minerals or supplements* for symptoms of myalgia perceived to be statin-associated. *(Strong/Very Low).*
Statins: summary

- proven, evidence-based, life-saving
- 30+ years real-world experience
- first line Rx to reach targets
- 5 statin-eligible conditions + intermediate risk
- benefits >>> risks in properly selected patients
- encourage compliance
Nonstatin Low-Density Lipoprotein–Lowering Therapy and Cardiovascular Risk Reduction—Statement From ATVB Council


Abstract—Pharmacological reduction of low-density lipoprotein (LDL) cholesterol using statin drugs is foundational therapy to reduce cardiovascular disease (CVD) risk. Here, we consider the place of nonstatin therapies that also reduce LDL cholesterol in prevention of CVD. Among conventional nonstatins, placebo-controlled randomized clinical trials showed that bile acid sequestrants, niacin, and fibrates given as monotherapy each reduce CVD end points. From trials in which patients’ LDL cholesterol was already well controlled on a statin, adding ezetimibe incrementally reduced CVD end points, whereas adding a fibrate or niacin showed no incremental benefit. Among emerging nonstatins, monoclonal antibodies against proprotein convertase subtilisin kexin type 9 added to a statin and given for ≤78 weeks showed preliminary evidence of reductions in CVD outcomes. Although these promising early findings contributed to the recent approval of these agents in Europe and in North America, much larger and longer duration outcomes studies are ongoing for definitive proof of CVD benefits. Other nonstatin agents recently approved in the United States include...
## CVD end point reduction

<table>
<thead>
<tr>
<th>Drug class</th>
<th>No background statin</th>
<th>With background statin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bile acid sequestrants</td>
<td>Yes (LRC-CPPT)</td>
<td>Not done</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>Not done</td>
<td>Yes (SHARP; IMPROVE-IT)</td>
</tr>
<tr>
<td>Fibrates</td>
<td>Yes (HHS, VA-HIT)</td>
<td>No (ACCORD, FIELD)</td>
</tr>
<tr>
<td>Niacin</td>
<td>Yes (CDP)</td>
<td>No (AIM-HIGH, HPS2)</td>
</tr>
</tbody>
</table>
Emerging LDL-C therapies

- lomitapide  
  effect: lowers LDL-C by 50%
- mipomersen  
  effect: lowers LDL-C by 50%
- anti-PCSK9  
  effect: lowers LDL-C by 70%
- CETP inh (ana, eva)  
  effect: lowers LDL-C by 40%
PCSK9 Inhibitors

Case of 68-year-old Man

- History
  - Stroke
  - Type 2 diabetes mellitus
  - Vasculopathy

- Presents with acute MI. Not taking a statin because in the past it caused backache.

- LDL-C level (no statin) is 5.0 mmol/L

- Discussion: Treatment?
Where did PCSK9 inhibitors come from?
The PCSK9 Variant Story

- Patients with hyperactive PCSK9 have fewer LDL receptors and higher levels of circulating LDL-C and premature atherosclerosis
- Attempts to block the PCSK9 protein
- Monoclonal antibodies against the PCSK9 protein lead to expression of a greater number of LDL receptors and dramatically reduced circulating LDL-C
Emerging lipid therapies

Proprotein
Emerging lipid therapies

Proprotein Convertase
Emerging lipid therapies

Proprotein Convertase
Emerging lipid therapies

Proprotein
Convertase
Subtilisin
Emerging lipid therapies

Proprotein
Convertase
Subtilisin
Kexin
Emerging lipid therapies

Proprotein
Convertase
Subtilisin
Kexin
9
Statin Influence on LDL-C Metabolism, LDL-R and PCSK9

PCSK9 Role in LDL-R Metabolism

Acetyl-CoA + acetoacetyl-CoA

HMG-CoA

Intracellular Cholesterol Biosynthesis

HMG-CoA reductase

STATIN

Hepatocyte Cholesterol Content

LDL-C

PCSK9 Secretion

LDL-C Protein at Cell Surface

LDL-R

PCSK9 Protein

PCSK9 Expression

SREBP Activation

Lipid metabolism processes and interactions with statins and PCSK9 in the context of LDL-C metabolism.
Why is There Significant Lipid Lowering With PCSK9i?

PCSK9i offer enhanced LDL-C lowering due to targeted removal of LDL-C through increased availability of LDL-R and decreased presence of PCSK9, whose function it is to target LDL-R for degradation.

Direct inhibition of PCSK9 avoids the feedback loop caused by statins which increase production of both LDL-R and PCSK9, creating a competition between LDL-R production and degradation.

PCSK9 inhibitors

- very potent LDL-C reduction: 55-75%
- non-statin mechanism
- mAbs: sc q2 or q4 wk
- competitive environment
- signal for 50% reduced MCVE
Terminology of Monoclonal Antibodies

Mouse (0% human)

Chimeric (65% human)

Humanized (> 90% human)

Human (100% human)

Source (% human protein)

Generic suffix: -omab -ximab -zumab -umab

High Potential for immunogenicity Low

PCSK9 Inhibition in Patients With Hypercholesterolemia Receiving Statin Therapy

<table>
<thead>
<tr>
<th>PCSK9 Inhibitor</th>
<th>Arilocumab&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Bococizumab&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Evolocumab&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose (mg)</td>
<td>100 150 200 300</td>
<td>150 300</td>
<td>105 140 280 350 420</td>
</tr>
<tr>
<td>Change from Baseline in LDL-C vs Placebo at Week 12 (%)</td>
<td>-64.2 -72.4</td>
<td>-53.4 -60.2</td>
<td>-50.0 -50.3</td>
</tr>
</tbody>
</table>

P <.0001 for each comparison.

PCSK9 Inhibition in Patients With Hypercholesterolemia Receiving Statin Therapy

Change From Baseline in LDL-C vs Placebo at Week 12, %

- Arilocumab:
  - 100 mg: -64.2%
  - 150 mg: -72.4%
  - 200 mg: -66.1%
  - 300 mg: -60.2%

- Bococizumab:
  - 150 mg: -53.1%
  - 300 mg: -41.8%

- Evolocumab:
  - 105 mg: -50.0%
  - 140 mg: -50.3%
  - 280 mg: -50.0%
  - 350 mg: -50.3%
  - 420 mg: -50.3%

P < .0001 for each comparison.

Evolocumab: effect on LDL-C

LDL-C 3.1 mmol/L

LDL-C 1.24 mmol/L

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>Standard therapy</th>
<th>Evolocumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>1489</td>
<td>2976</td>
</tr>
<tr>
<td>4 weeks</td>
<td>394</td>
<td>864</td>
</tr>
<tr>
<td>12 weeks</td>
<td>1388</td>
<td>2871</td>
</tr>
<tr>
<td>24 weeks</td>
<td>1376</td>
<td>2828</td>
</tr>
<tr>
<td>36 weeks</td>
<td>402</td>
<td>841</td>
</tr>
<tr>
<td>48 weeks</td>
<td>1219</td>
<td>2508</td>
</tr>
</tbody>
</table>

Absolute reduction (mg/dl) | 60.4 | 73.4 | 70.4 | 72.7 | 70.5
Percentage reduction | 45.3 | 60.9 | 58.8 | 54.0 | 58.4
P value | <0.001 | <0.001 | <0.001 | <0.001 | <0.001

Sabatine M et al. NEJM 2015; 372:1500-9
Evolocumab: CVD reduction

Hazard ratio, 0.47 (95% CI, 0.28–0.78)
P=0.003

No. at Risk
Standard therapy  1489  1486  1481  1473  1467  1463  1458  1454  1447  1438  1428  1361  407
Evolocumab       2976  2970  2962  2949  2938  2930  2920  2910  2901  2885  2871  2778  843

Sabatine M et al. *NEJM* 2015; 372:1500-9
### Table 3. Adverse Events and Laboratory Results.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Evolocumab Group (N = 2976)</th>
<th>Standard-Therapy Group (N = 1489)</th>
<th>no. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse events</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>2060 (69.2)</td>
<td>965 (64.8)</td>
<td></td>
</tr>
<tr>
<td>Serious</td>
<td>222 (7.5)</td>
<td>111 (7.5)</td>
<td></td>
</tr>
<tr>
<td>Leading to discontinuation of evolocumab</td>
<td>71 (2.4)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Muscle-related</td>
<td>190 (6.4)</td>
<td>90 (6.0)</td>
<td></td>
</tr>
<tr>
<td>Injection-site reaction</td>
<td>129 (4.3)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Neurocognitive event†</td>
<td>27 (0.9)</td>
<td>4 (0.3)</td>
<td></td>
</tr>
<tr>
<td>Other‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>137 (4.6)</td>
<td>48 (3.2)</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>106 (3.6)</td>
<td>32 (2.1)</td>
<td></td>
</tr>
<tr>
<td>Limb pain</td>
<td>99 (3.3)</td>
<td>32 (2.1)</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>83 (2.8)</td>
<td>15 (1.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Laboratory results</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alanine or aspartate aminotransferase &gt;3 × ULN at any visit after baseline</td>
<td>31 (1.0)</td>
<td>18 (1.2)</td>
<td></td>
</tr>
<tr>
<td>Creatine kinase &gt;5 × ULN at any visit after baseline</td>
<td>17 (0.6)</td>
<td>17 (1.1)</td>
<td></td>
</tr>
</tbody>
</table>

*Based on data from the clinical trial, Sabatine M et al. NEJM 2015; 372:1500-9.
Alirocumab: effect on LDL-C

Alirocumab: CVD reduction

Placebo + maximally tolerated statin ± other LLT
Alirocumab + maximally tolerated statin ± other LLT

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

No. at risk
Placebo 788 776 731 700 670 653 644 597
Alirocumab 1550 1533 1445 1392 1342 1306 1266 1170

Meta-analysis: PCSK9i

17 RCTs with 13 083 patients

### All-Cause Mortality

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>PCSK9 Events</th>
<th>Total</th>
<th>Placebo Events</th>
<th>Total</th>
<th>Weight</th>
<th>M-H, Random, 95% CI</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
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<tr>
<td><strong>1.3.1 Follow-up &lt;6 months</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAPLACE</td>
<td>1</td>
<td>158</td>
<td>0</td>
<td>155</td>
<td>4.1%</td>
<td>2.96 [0.12, 73.27]</td>
<td></td>
</tr>
<tr>
<td>LAPLACE-2</td>
<td>0</td>
<td>1117</td>
<td>1</td>
<td>558</td>
<td>4.1%</td>
<td>0.17 [0.01, 4.09]</td>
<td></td>
</tr>
<tr>
<td>McKenney</td>
<td>0</td>
<td>59</td>
<td>0</td>
<td>31</td>
<td></td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td>MENDEL</td>
<td>0</td>
<td>90</td>
<td>0</td>
<td>90</td>
<td></td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td>MENDEL-2</td>
<td>0</td>
<td>306</td>
<td>0</td>
<td>154</td>
<td></td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td>RUTHERFORD</td>
<td>0</td>
<td>56</td>
<td>0</td>
<td>56</td>
<td></td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td>RUTHERFORD 2</td>
<td>0</td>
<td>220</td>
<td>0</td>
<td>109</td>
<td></td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td>Stein</td>
<td>0</td>
<td>31</td>
<td>0</td>
<td>15</td>
<td></td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td>YUKAWA</td>
<td>0</td>
<td>105</td>
<td>0</td>
<td>102</td>
<td></td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td></td>
<td>2142</td>
<td></td>
<td>1270</td>
<td>8.2%</td>
<td>0.70 [0.04, 11.79]</td>
<td></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td></td>
<td>1</td>
<td></td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Heterogeneity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tau²: 1.47; Chi²: 1.55, df = 1 (P = 0.21); I²: 36%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Test for overall effect</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Z = 0.25 (P = 0.80)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>1.3.2 Follow-up ≥6 months</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DESCARTESES</td>
<td>2</td>
<td>599</td>
<td>0</td>
<td>302</td>
<td>4.5%</td>
<td>2.53 [0.12, 52.89]</td>
<td></td>
</tr>
<tr>
<td>ODYSSEY COMBO I</td>
<td>2</td>
<td>207</td>
<td>3</td>
<td>107</td>
<td>12.9%</td>
<td>0.34 [0.06, 2.06]</td>
<td></td>
</tr>
<tr>
<td>ODYSSEY LONG TERM</td>
<td>8</td>
<td>1550</td>
<td>10</td>
<td>788</td>
<td>48.2%</td>
<td>0.40 [0.16, 1.03]</td>
<td></td>
</tr>
<tr>
<td>OSLER 2</td>
<td>4</td>
<td>2976</td>
<td>6</td>
<td>1489</td>
<td>26.2%</td>
<td>0.33 [0.09, 1.18]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td></td>
<td>5332</td>
<td></td>
<td>2686</td>
<td>91.8%</td>
<td>0.41 [0.21, 0.80]</td>
<td></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td></td>
<td>16</td>
<td></td>
<td>19</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Heterogeneity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tau²: 0.00; Chi²: 1.54, df = 3 (P = 0.67); I²: 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Test for overall effect</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Z = 2.60 (P = 0.009)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Total (95% CI)**

- **7474 [3956, 100.0%]**
- **17 [20, 100.0%]**

**Heterogeneity**

- Tau²: 0.00; Chi²: 3.31, df = 5 (P = 0.65); I²: 0%
- Test for overall effect: Z = 2.58 (P = 0.010)
- Test for subgroup differences: Chi² = 0.13, df = 1 (P = 0.72), I² = 0%

Event rate reduction

Proportional reduction in event rate (SE)

Reduction in LDL cholesterol (mmol/L)

-10% 0%  10%  20%  30%  40%  50%  60%  70%

ezetimibe

statins

PCSK9i

ODYSSEY Long-Term†

OSLER†

†Exploratory analysis from Phase 3 studies.

Individuals who may require lipid–lowering strategies beyond statins

**Clinical ASCVD**
- According to the CCS Lipid Guidelines and AHA/ACC Guidelines, ASCVD may include one or more of the following:

  **Coronary heart disease**
  - Acute coronary syndrome
  - History of myocardial infarction
  - Stable or unstable angina
  - Documented coronary disease
  - Coronary or other arterial revascularization

  **Cerebrovascular disease or transient ischemic attack**

  **Peripheral arterial disease**

  **Abdominal aortic aneurysm**

**Familial Hypercholesterolemia (FH)**
- Inherited conditions characterized by elevated LDL-C and resulting from mutations in genes involved in LDL-C metabolism

  **Heterozygous FH**
  - LDL-C >4.9 mmol/L†
  - Identification
    - Elevated LDL-C with physical findings or a family history
    - DNA-based evidence

  **Homozygous FH**
  - Untreated LDL-C >13 mmol/L†‡
  - CVD diagnosis on average at 20 years³

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*ASCVD, termed “clinical atherosclerosis” per CCS guidelines; †typical levels when untreated; ‡LDL-C level indicative, lower levels do not exclude HoFH.

ACC, American College of Cardiology; AHA, American Heart Association; CCS, Canadian Cardiovascular Society; CVD, cardiovascular disease; LDL-C, low-density lipoprotein cholesterol

Pfizer Discontinues Global Development of Bococizumab, Its Investigational PCSK9 Inhibitor

Company will record a charge to GAAP and Adjusted earnings in the fourth quarter of 2016 estimated to be approximately $0.04 per share

November 01, 2016 06:30 AM Eastern Daylight Time

NEW YORK--(BUSINESS WIRE)--Pfizer Inc. announced today the discontinuation of the global clinical development program for bococizumab, its investigational Proprotein Convertase Subtilisin Kexin type 9 inhibitor (PCSK9i). The totality of clinical information now available for bococizumab, taken together with the evolving treatment and market landscape for lipid-lowering agents, indicates that bococizumab is not likely to provide value to patients, physicians, or shareholders. As a result, Pfizer has decided to discontinue the development program, including the two ongoing cardiovascular
GLAGOV study

<table>
<thead>
<tr>
<th></th>
<th>placebo</th>
<th>evolocumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>484</td>
<td>484</td>
</tr>
<tr>
<td>male</td>
<td>72.3%</td>
<td>72.1%</td>
</tr>
<tr>
<td>BMI</td>
<td>29.5</td>
<td>29.4</td>
</tr>
<tr>
<td>smoking</td>
<td>23.3%</td>
<td>25.6%</td>
</tr>
<tr>
<td>diabetes</td>
<td>21.5%</td>
<td>20.2%</td>
</tr>
<tr>
<td>statin use</td>
<td>98.3%</td>
<td>98.8%</td>
</tr>
<tr>
<td>baseline LDL-C</td>
<td>2.39</td>
<td>2.39</td>
</tr>
<tr>
<td>treated LDL-C</td>
<td>2.32</td>
<td>0.75</td>
</tr>
<tr>
<td>change in PAV</td>
<td>+0.05</td>
<td>-0.95</td>
</tr>
<tr>
<td>change in TAV</td>
<td>-0.09</td>
<td>-5.8</td>
</tr>
<tr>
<td>progression</td>
<td>53.7%</td>
<td>35.7%</td>
</tr>
<tr>
<td>regression</td>
<td>47.3%</td>
<td>64.3%</td>
</tr>
</tbody>
</table>

When treated LDL-C was 0.6 mmol/L, 81.2% had regression

Nissen et al. JAMA 2016; Nov 15 online.
Inclisiran single dose

A Change in PCSK9 Level in Single-Dose Cohorts

Cohort
- Placebo (N=6)
- Inclisiran, 25 mg (N=3)
- Inclisiran, 100 mg (N=3)
- Inclisiran, 300 mg (N=3)
- Inclisiran, 500 mg (N=3)
- Inclisiran, 800 mg (N=6)

A Change in LDL Cholesterol Level in Single-Dose Cohorts

Cohort
- Placebo (N=6)
- Inclisiran, 25 mg (N=3)
- Inclisiran, 100 mg (N=3)
- Inclisiran, 300 mg (N=3)
- Inclisiran, 500 mg (N=3)
- Inclisiran, 800 mg (N=6)
Primary Endpoint: Percent Atheroma Volume

Change in Percent Atheroma Volume (%)

- Statin monotherapy: 0.05% increase
  - $P = \text{NS}$
- Statin-evolocumab: -0.95% decrease
  - $P < 0.0001$
Exploratory Subgroup: Baseline LDL-C < 1.8 mmol/L

Percent Atheroma Volume

- Change in PAV (%)
  - Statin monotherapy: -0.35
  - Statin-evolocumab: -1.97
  - P < 0.0001

Fraction Showing Regression

- Percentage Regressing (%)
  - Statin monotherapy: 48.0%
  - Statin-evolocumab: 81.2%
  - P = NS
### Non-pharmacological LDL-lowering

<table>
<thead>
<tr>
<th>Compound</th>
<th>Dose</th>
<th>% LDL lowering</th>
<th>Evidence level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoflavones (soy protein powder)</td>
<td>50-100 mg</td>
<td>3-11%</td>
<td>A-I</td>
</tr>
<tr>
<td>Soluble fibre</td>
<td>5-15 g</td>
<td>5-20%</td>
<td>A-I</td>
</tr>
<tr>
<td>Oatmeal</td>
<td>60 g</td>
<td>2-6%</td>
<td>A-I</td>
</tr>
<tr>
<td>Plant sterols</td>
<td>1.3 g</td>
<td>4-13%</td>
<td>A-I</td>
</tr>
<tr>
<td>AHA Step 2 diet</td>
<td></td>
<td>5-10%</td>
<td>A-I</td>
</tr>
<tr>
<td>Mediterranean diet</td>
<td></td>
<td>5-10%</td>
<td>A-I</td>
</tr>
<tr>
<td>Portfolio diet</td>
<td></td>
<td>10-20%</td>
<td>A-I</td>
</tr>
<tr>
<td>Almonds</td>
<td>50-80 g</td>
<td>5%</td>
<td>B-I</td>
</tr>
<tr>
<td>Green tea extract</td>
<td>1.2 g</td>
<td>10%</td>
<td>B-I</td>
</tr>
<tr>
<td>High carb diet</td>
<td>60% of calories</td>
<td>5-10%</td>
<td>B-I</td>
</tr>
<tr>
<td>High protein diet</td>
<td>25% of calories</td>
<td>5-10%</td>
<td>B-I</td>
</tr>
<tr>
<td>Red yeast rice</td>
<td>1-2 g</td>
<td>7-20%</td>
<td>A-IIa</td>
</tr>
<tr>
<td>Guggulipid</td>
<td>100 mg</td>
<td>12%</td>
<td>A-IIb</td>
</tr>
</tbody>
</table>

Huang et al. *Can J Cardiol* 2011: 488-505
Take home points

1. Guidelines: - LDL-centric; non-fasting lipids OK

2. Statins: - use first

3. Non-statins: - use ezetimibe next

4. PCSK9i: - alirocumab and evolocumab approved
- HeFH and ASCVD not controlled
- regression studies positive
- outcome studies pending
- long acting form in development