PCSK9 Inhibitors
and
Canadian Cardiovascular Lipid Guidelines

Robert C. Welsh, MD, FRCPC
Professor of Medicine, University of Alberta
Zone Clinical Department Head, Cardiac Sciences
Faculty Disclosure (12 months):

- **Research and Clinical Trials**: Abbott Vascular, Astra Zeneca, Bayer, BMS, Boehringer Ingelheim, CIHR, CSL Behring LLC, Edwards Lifesciences, Eli Lilly, Jansen, Johnson and Johnson, Pfizer, Population Health Research Institute, University of Alberta Hospital Foundation
- **Consulting Fees/Honoraria**: Amgen, Astra Zeneca, Bayer, Bristol Myers-Squibb/Pfizer, Canadian Cardiovascular Society
- **Other**: University of Alberta (employee), Alberta Health Services (Clinical privileges) and President, The Canadian Centre for Clinicians and Scientists
Objectives

1. Discuss the development of PCSK9 inhibitors
   1. Demonstrate the effect of PCSK9 inhibitors on LDL levels
   2. Review current evidence regarding PCSK9 inhibitors impact on atherosclerosis and clinical outcomes

2. Review current CCS lipid guidelines and the role of PCSK9 inhibitors
PCSK9: A Canadian Discovery

Mutations in PCSK9 cause autosomal dominant hypercholesterolemia

Marianne Abifadel, Mathilde Varret, Jean-Pierre Rabès, Delphine Allard, Khadija Ouguerram, Martine Devillers, Corinne Cruaud, Suzanne Benjannet, Louise Wickham, Danièle Erlich, Aurélie Derré, Ludovic Villéger, Michel Farnier, Isabel Beucler, Eric Bruckert, Jean Chambaz, Bernard Chanu, Jean-Michel Lecerf, Gerald Luc, Philippe Moulin, Jean Weissenbach, Annick Prat, Michel Krempf, Claudine Junien, Nabil G Seidah & Catherine Boileau

Dr. Nabil Seidah IRCM

Nature Genetics 34, 154 - 156 (2003)
PCSK9 - Rapid Progress from Bench to Clinic in Less than a Decade

Antibody technology has evolved over past decades.

- **1st generation** (Fully Mouse):
  - Highly Immunogenic
  - e.g. Abciximab

- **2nd generation** (Chimeric):
  - Chimeric
  - Still very immunogenic
  - e.g. Bococizumab

- **3rd generation** (Humanized):
  - Can be time-consuming to create
  - e.g. Evolocumab and Alirocumab

- **4th generation** (“Fully” Human):
  - repeated dosing possible
  - e.g. Evolocumab and Alirocumab

**Nomenclature:** Prefix (Pharma) C (Cardiovascular) UMAB
Patients with Genetically Lower LDL have Correspondingly Better CV Event Reduction

Greater effect than Pharmacologically Lower LDL:
- Possibly due to Lifetime Lower LDL levels

Genetically Lower LDL-C

Pharmacologically Lower LDL-C

Proportional Risk Reduction (SE) log scale

Lower LDL-C (mmol/L)

PCSK9 46L rs11591147

NPC1L1 LDL-C Score
HMGCR LDL-C Score

LDLR rs2228671

LDLR rs6511720

Combined NPC1L1 & HMGCR LDL-C Score

NPC1L1 LDL-C Score

HMGCR LDL-C Score

ABCG5/8 rs4299376
HMGCR rs12916

PCSK9 rs2479409

NPC1L1 rs217386

HMGCR LDL-C Score
NPC1L1 LDL-C Score

A to Z

GISSI-P

SEARCH

IMPROVE-IT

ALLHAT-LLT

PCSK9 Directly Binds to the LDLR

Kwon et al. 2008, PNAS, 105:1820
LDL Receptor Function and Life Cycle

For illustration purposes only
The Role of PCSK9 in the Regulation of LDL Receptor Expression
Impact of PCSK9 Inhibition on LDL Receptor Expression
PCSK9 mAb
Effect of the PCSK9 Inhibitor Evolocumab on Cardiovascular Outcomes

MS Sabatine, RP Giugliano, SD Wiviott, FJ Raal, CM Ballantyne, R Somaratne, J Legg, SM Wasserman, R Scott, MJ Koren, and EA Stein for the OSLER Investigators

American College of Cardiology – 64th Annual Scientific Session
Late-Breaking Clinical Trial
March 15, 2015
**LDL Cholesterol**

**Standard of care alone**

- 61% reduction (95% CI 59-63%), P < 0.0001
- Absolute reduction: 73 mg/dL (95% CI 71-76%)

**Evolocumab plus standard of care**

<table>
<thead>
<tr>
<th>Time</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (Parent study)</td>
<td>4465</td>
</tr>
<tr>
<td>4 weeks (OSLER)</td>
<td>1258</td>
</tr>
<tr>
<td>12 weeks</td>
<td>4259</td>
</tr>
<tr>
<td>24 weeks</td>
<td>4204</td>
</tr>
<tr>
<td>36 weeks</td>
<td>1243</td>
</tr>
<tr>
<td>48 weeks</td>
<td>3727</td>
</tr>
</tbody>
</table>
Cardiovascular Outcomes

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)
2.18%

Evolocumab plus standard of care (N=2976)
0.95%
Efficacy and Safety of Alirocumab in Reducing Lipids and Cardiovascular Events

Jennifer G. Robinson, M.D., M.P.H., Michel Farnier, M.D., Ph.D., Michel Krempf, M.D., Jean Bergeron, M.D., Gérald Luc, M.D., Maurizio Averna, M.D., Erik S. Stroes, M.D., Ph.D., Gisle Langslet, M.D., Frederick J. Raal, M.D., Ph.D., Mahfouz El Shahawy, M.D., Michael J. Koren, M.D., Norman E. Lepor, M.D., Christelle Lorenzato, M.Sc., Robert Pardy, M.D., Umesh Chaudhari, M.D., and John J.P. Kastelein, M.D., Ph.D. for the ODYSSEY LONG TERM Investigators

March 15, 2015 | DOI: 10.1056/NEJMo1501031

Comments open through March 22, 2015
ODYSSEY Long-Term: Alirocumab Plus Statin
Achieved a 62% Reduction in LDL-C over Placebo+Statin at 24 weeks


Median LDL-C (mmol/L)

<table>
<thead>
<tr>
<th>Week</th>
<th>0</th>
<th>4</th>
<th>8</th>
<th>12</th>
<th>16</th>
<th>24</th>
<th>36</th>
<th>52</th>
<th>64</th>
<th>78</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>3.60</td>
<td>3.08</td>
<td>3.17</td>
<td>3.17</td>
<td>3.08</td>
<td>3.08</td>
<td>3.08</td>
<td>3.08</td>
<td>3.08</td>
<td>3.08</td>
</tr>
<tr>
<td>Alirocumab</td>
<td>3.60</td>
<td>2.43</td>
<td>2.22</td>
<td>2.01</td>
<td>1.80</td>
<td>1.69</td>
<td>1.58</td>
<td>1.47</td>
<td>1.36</td>
<td>1.25</td>
</tr>
</tbody>
</table>

62% reduction, P<0.001
Absolute reduction: 1.2 mmol/L
ODYSSEY Long-Term: Reduction in the Rate of Cardiovascular Events - Post-hoc Analysis

*Primary endpoint for the ODYSSEY OUTCOMES trial: CHD death, Non-fatal MI, Fatal and non-fatal ischemic stroke, Unstable angina requiring hospitalization. LLT, lipid-lowering therapy

Effect of Evolocumab on Progression of Coronary Disease in Statin-Treated Patients: The GLAGOV Randomized Clinical Trial

Stephen J Nicholls MBBS PhD, Rishi Puri MBBS PhD, Todd Anderson MD, Christie M Ballantyne MD, Leslie Cho MD, John JP Kastelein MD PhD, Wolfgang Koenig MD, Ransi Somaratne MD, Helina Kassahun MD, Jingyuan Yang PhD, Scott M Wasserman MD, Robert Scott MD, Imre Ungi MD PhD, Jakub Podolec MD PhD, Antonius Oude Ophuis MD PhD, Jan H Cornel MD PhD, Marilyn Borgman RN BSN, Danielle M Brennan MS and Steven E Nissen MD

1South Australian Health and Medical Research Institute, University of Adelaide, Australia; 2Department of Cardiovascular Medicine and Cleveland Clinic Coordinating Center for Clinical Research, Cleveland, OH; 3Lobin Cardiovascular Institute, University of Calgary, Canada; 4Section of Cardiovascular Research, Baylor College of Medicine and the Methodist DeBakey Heart and Vascular Center, Houston, TX; 5Department of Vascular Medicine, Academic Medical Center, University of Amsterdam, the Netherlands; 6Deutsches Herzzentrum München, Technische Universität München, Munich, DZHK (German Centre for Cardiovascular Research), partner site Munich Heart Alliance, Munich, Department of Internal Medicine, University of Ulm Medical Center, Ulm, Germany; 7Amgen Inc, Thousand Oaks, CA; 8Department of Cardiology, University of Szeged, Hungary; 9Department of Interventional Cardiology, Jagiellonian University, Cardiology Institute, College of Medicine and the John Paul II Hospital, Krakow, Poland; 10Department of Cardiology Canisius Wilhelmina Hospital, Nijmegen, The Netherlands; 11Department of Cardiology, Noordwest Ziekenhuisgroep, Alkmaar, the Netherlands

Background

- Intravascular ultrasound (IVUS) trials have studied the effect of statins on coronary atherosclerosis and demonstrated a linear relationship between achieved LDL-C levels and reduction in atheroma burden.
- Monoclonal antibodies against PCSK9 lower LDL-C when administered alone or in combination with statins. Initial studies have demonstrated the feasibility of using the combination of statins and PCSK9 inhibitors to achieve much lower LDL-C levels than previously studied.
- No trials to date have explored whether LDL-C lowering beyond that achievable with statins with a PCSK9 inhibitor results in incremental benefits on coronary artery disease compared with statins alone.

GLAGOV: Study Design

Nominal change refers to the actual number, as opposed to percent change.

D = day; IVUS = intravascular ultrasound; PAV = percentage atheroma volume; SC = subcutaneously; TAV = total atheroma volume; W = week.

GLAGOV: Baseline Characteristics of Randomized Patients

<table>
<thead>
<tr>
<th>Parameter*</th>
<th>Placebo (N = 484)</th>
<th>Evolocumab (N = 484)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td>59.8±8.8</td>
<td>59.8±9.6</td>
</tr>
<tr>
<td><strong>Men, n (%)</strong></td>
<td>350 (72.3)</td>
<td>349 (72.1)</td>
</tr>
<tr>
<td><strong>White, n (%)</strong></td>
<td>452 (93.4)</td>
<td>456 (94.2)</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td>29.5±5.0</td>
<td>29.4±5.0</td>
</tr>
<tr>
<td><strong>Hypertension, n (%)</strong></td>
<td>405 (83.7)</td>
<td>398 (82.2)</td>
</tr>
<tr>
<td><strong>Previous PCI, n (%)</strong></td>
<td>188 (38.8)</td>
<td>189 (39.0)</td>
</tr>
<tr>
<td><strong>Previous MI, n (%)</strong></td>
<td>171 (35.3)</td>
<td>169 (34.9)</td>
</tr>
<tr>
<td><strong>Smoking, n (%)</strong></td>
<td>113 (23.3)</td>
<td>124 (25.6)</td>
</tr>
<tr>
<td><strong>Diabetes, n (%)</strong></td>
<td>104 (21.5)</td>
<td>98 (20.2)</td>
</tr>
<tr>
<td><em><em>Baseline statin use,</em> n (%)</em>*</td>
<td>476 (98.3)</td>
<td>478 (98.8)</td>
</tr>
<tr>
<td><strong>High intensity , n (%)</strong></td>
<td>290 (59.9)</td>
<td>280 (57.9)</td>
</tr>
<tr>
<td><strong>Moderate intensity, n (%)</strong></td>
<td>185 (38.2)</td>
<td>196 (40.5)</td>
</tr>
<tr>
<td><strong>Low intensity, n (%)</strong></td>
<td>1 (0.2)</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td><em><em>Baseline ezetimibe use,</em> n (%)</em>*</td>
<td>9 (2.1)</td>
<td>9 (2.1)</td>
</tr>
</tbody>
</table>

**Baseline medications**

<table>
<thead>
<tr>
<th>Parameter*</th>
<th>Placebo (N = 484)</th>
<th>Evolocumab (N = 484)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anti-platelet therapy, n (%)</strong></td>
<td>465 (96.1)</td>
<td>454 (93.8)</td>
</tr>
<tr>
<td><strong>Beta-blocker, n (%)</strong></td>
<td>370 (76.4)</td>
<td>362 (74.8)</td>
</tr>
<tr>
<td><strong>ACE inhibitor, n (%)</strong></td>
<td>264 (54.5)</td>
<td>260 (53.7)</td>
</tr>
<tr>
<td><strong>ARB, n (%)</strong></td>
<td>92 (19.0)</td>
<td>87 (18.0)</td>
</tr>
</tbody>
</table>

Age and BMI expressed as mean ± standard deviation. *Baseline statin and ezetimibe use is defined as subject treated with statin or ezetimibe therapy at the end of the lipid stabilization period at randomization. †High intensity statin as defined by ACC/AHA criteria

Mean Absolute Change in LDL-C

Absolute change for evolocumab-statin group: -56.3 (-59.4 to -53.1); $p < 0.001$

Data shown are Mean (95% CI) *Time-weighted LDL-C; LDL-C = low-density lipoprotein cholesterol
Primary Endpoint: Nominal Change in Percent Atheroma Volume From Baseline to Week 78

Data shown are least-squares mean (95% CI). PAV = Percent Atheroma Volume

*Comparison versus baseline
Secondary Endpoint: Nominal Change in Total Atheroma Volume From Baseline to Week 78

Data shown are least-squares mean (95% CI). TAV = Total Atheroma Volume
*Comparison versus baseline
Exploratory Analysis: Achieved LDL-C and Change in Percent Atheroma Volume in All Patients

Local regression (LOESS) curve illustrating the association (with 95% CI) between achieved LDL-C levels and change in PAV in all patients undergoing serial IVUS evaluation.

Exploratory Subgroup: LDL-C Change from Baseline in Patients with LDL-C < 70 mg/dL at Baseline

Patients with LDL-C < 70 mg/dL at Baseline (n = 144)

- Statin monotherapy
- Statin + evolocumab

Mean LDL-C 70.6 mg/dL
Change from baseline 16.4%

Mean LDL-C 24.0 mg/dL
Change from baseline -58.3%

Exploratory Subgroup: Change in PAV & Regression in Patients with LDL-C < 70 mg/dL at Baseline

Patients with LDL-C < 70 mg/dL at Baseline (n = 144)

**Percent Atheroma Volume**

- **Statin Monotherapy:** -0.35%
- **Statin + Evolocumab:** -1.97%

*P < 0.001*

**Fraction Showing Regression**

- **Statin Monotherapy:** 48%
- **Statin + Evolocumab:** 81.2%

*P < 0.001*

*Between-treatment group comparison*

FOURIER

Further cardiovascular Outcomes Research with PCSK9 Inhibition in subjects with Elevated Risk

MS Sabatine, RP Giugliano, AC Keech, N Honarpour, SM Wasserman, PS Sever, and TR Pedersen, for the FOURIER Steering Committee & Investigators

American College of Cardiology – 66th Annual Scientific Session
Late-Breaking Clinical Trial
March 17, 2017
Trial Design

27,564 high-risk, stable patients with established CV disease (prior MI, prior stroke, or symptomatic PAD)

Screening, Lipid Stabilization, and Placebo Run-in

High or moderate intensity statin therapy (± ezetimibe)

LDL-C ≥70 mg/dL or non-HDL-C ≥100 mg/dL

RANDOMIZED DOUBLE BLIND

Evolocumab SC
140 mg Q2W or 420 mg QM

Placebo SC
Q2W or QM

Follow-up Q 12 weeks

Endpoints

• **Efficacy**
  – Primary: CV death, MI, stroke, hosp. for UA, or coronary revasc
  – Key secondary: CV death, MI or stroke

• **Safety**
  – AEs/SAEs
  – Events of interest incl. muscle-related, new-onset diabetes, neurocognitive
  – Development of anti-evolocumab Ab (binding and neutralizing)

• **TIMI Clinical Events Committee (CEC)**
  – Adjudicated all efficacy endpoints & new-onset diabetes
  – Members unaware of treatment assignment & lipid levels

### Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years, mean (SD)</strong></td>
<td>63 (9)</td>
</tr>
<tr>
<td><strong>Male sex (%)</strong></td>
<td>75</td>
</tr>
<tr>
<td><strong>Type of cardiovascular disease (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>81</td>
</tr>
<tr>
<td>Stroke (non-hemorrhagic)</td>
<td>19</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>

Median time from most recent event ~3 yrs

Pooled data; no differences between treatment arms.
### 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) – mg/dL</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.
## 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><strong>3-yr Kaplan-Meier rate</strong></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>2.5</td>
<td>2.4</td>
<td>1.05 (0.88-1.25)</td>
</tr>
<tr>
<td>Death due to acute MI</td>
<td>0.26</td>
<td>0.32</td>
<td>0.84 (0.49-1.42)</td>
</tr>
<tr>
<td>Death due to stroke</td>
<td>0.29</td>
<td>0.30</td>
<td>0.94 (0.58-1.54)</td>
</tr>
<tr>
<td>Other CV death</td>
<td>1.9</td>
<td>1.8</td>
<td>1.10 (0.90-1.35)</td>
</tr>
<tr>
<td><strong>MI</strong></td>
<td>4.4</td>
<td>6.3</td>
<td>0.73 (0.65-0.82)</td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
<td>2.2</td>
<td>2.6</td>
<td>0.79 (0.66-0.95)</td>
</tr>
</tbody>
</table>
Lower LDL-C Is Better

Patients divided by quartile of baseline LDL-C and by treatment arm

\[ P < 0.0001 \]
## Safety

<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>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>
<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><em>none</em></td>
<td>n/a</td>
</tr>
</tbody>
</table>

New-onset diabetes assessed in patients without diabetes at baseline; adjudicated by CEC
Summary for Evolocumab

• ↓ LDL-C by 59%
  – Consistent throughout duration of trial
  – Median achieved LDL-C of 30 mg/dl (IQR 19-46 mg/dl)

• ↓ 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
Patients stabilized post ACS ≤ 10 days:
LDL-C 1.3 – 3.2 mmol/L (or 1.3 – 2.6 mmol/L if prior lipid-lowering Rx)

N=18,144

Standard Medical & Interventional Therapy

- Simvastatin 40 mg*
  *uptitrated to 80 mg if LDL-C >2.0 mmol/L

- Ezetimibe / Simvastatin 10 / 40 mg*

Duration: Minimum 2 ½-year follow-up (5314 events)

Primary Endpoint: CV death, MI, hospital admission for UA, coronary revascularization (≥ 30 days after randomization), or stroke

Cannon CP AHJ 2008;156:826-32; Califf RM NEJM 2009;361:712-7; Blazing MA AHJ 2014;168:205-12
Primary Endpoint — ITT (2014)

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

Simva — 34.7%
2742 events

EZ/Simva — 32.7%
2572 events

NNT = 50
Conditions for which pharmacotherapy with statins is indicated.

<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% stenoses)</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>Document familial hypercholesterolemia</td>
</tr>
<tr>
<td>Excluded 2nd causes</td>
</tr>
</tbody>
</table>

ABI, ankle-brachial index; ACR, albumin:creatinine ratio; eGFR, estimated glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol; TIA, transient ischemic attack.
**Risk Assessment, Stratification & Treatment Consideration**

Calculate risk (unless statin-indicated condition) using the Framingham Risk Score (FRS)\(^1\) or Cardiovascular Life Expectancy Model (CLEM)\(^1\).

Repeat screening every 5 years for FRS <5% or every year for FRS ≥5%.

### No Pharmacotherapy

- **Low Risk**
  - FRS <10%

### Primary Prevention Conditions

- **Intermediate Risk**
  - FRS 10-19% and
  - LDL-C ≥3.5 mmol/L or
  - Non-HDL-C ≥4.3 mmol/L or
  - apoB ≥1.2 g/L or
  - Men ≥50 and women ≥60 with one additional risk factor: low HDL-C, impaired fasting glucose, high waist circumference, smoker, hypertension

- **High Risk**
  - FRS ≥20% or alternative method

### Statin-indicated Conditions\(^2\)

- Clinical atherosclerosis
- Abdominal aortic aneurysm
- Most diabetes including:
  - Age ≥40y
  - Age ≥30y & 15y duration (type 1 DM)
  - Microvascular disease
- Chronic kidney disease

### Health Behavioural Modifications

- Smoking cessation
- Diet:
  - It is recommended all individuals adopt a health dietary pattern\(^1\).
- Exercise:
  - It is recommended adults should accumulate at least 150 minutes per week of moderate-vigorous intensity aerobic physical activity

### Discuss behavioural modifications

### Initiate Statin Treatment: Treat to Target Approach

**Confirm adherence and barriers to use**

<table>
<thead>
<tr>
<th>LDL-C &lt;2.0 mmol/L or &gt;50% reduction or apoB &lt;0.8 g/L or non-HDL-C &lt;2.6 mmol/L</th>
<th>LDL-C &gt;50% reduction</th>
</tr>
</thead>
</table>

### Target achieved on maximally tolerated dose?

<table>
<thead>
<tr>
<th>NO</th>
<th>NO</th>
<th>NO</th>
</tr>
</thead>
</table>

### Discuss add-on therapy with patient:\(^3\)

- Evaluate reduction in CVD risk vs. additional cost & side effects
- ADD-ON

### Add-on Therapy

- **Ezetimibe as 1st line** (BAS as alternative)
- **Ezetimibe 1st line** (BAS as alternative)
- **PCSK9 inhibitors as 2nd line** (add on to other drugs)**
- Ezetimibe (or BAS) or PCSK9 inhibitors

### Monitor

- Response to statin Rx
- Health behaviours
Reviewed Objectives

1. Discuss the development of PCSK9 inhibitors
   1. PCSK9 inhibitors are associated with a 55%-60% reduction in LDL
   2. PCSK9 inhibitors are well tolerated
   3. PCSK9 inhibitors are associated with coronary artery plaque regression and improved clinical outcomes

2. PCSK9 inhibitors are currently second line or add on therapy in the CCS lipid
MAZANKOWSKI
ALBERTA HEART INSTITUTE

PCSK9 Inhibitors and Canadian Cardiovascular Lipid Guidelines

Robert C. Welsh, MD, FRCPC
Professor of Medicine, University of Alberta
Zone Clinical Department Head, Cardiac Sciences
LDL cholesterol burden in individuals with or without familial hypercholesterolaemia as a function of the age of initiation of statin therapy.

Nordestgaard B G et al. Eur Heart J 2013;eurheartj.eht273
Prognostic Value of fasting versus nonfasting LDL-C levels on long-term mortality. Insight from the

Figure 2. Kaplan–Meier curve for fasting vs nonfasting low-density lipoprotein cholesterol (LDL-C) levels and all-cause mortality.
Statin intolerance and monitoring

TOLERANCE (70 - 80 %)

CONFIRMED INTOLERANCE (5 - 6 %)

SUSPECTED INTOLERANCE (20 - 30 %)

STATIN TREATED PATIENTS 100%
PCSK9 Inhibitors -

Numbers (Guess)

FH + CAD
10,000

FH Not @ Goal
10,000

CAD* Not @ Goal
250,000

High Risk Not @ Goal
>250,000

CAD* Approx 1.5 M CDN

20-30 HoFH