Dyslipidemia Management in 2016

Michael Heffernan
MD PhD FRCPC FACC
Faculty/Presenter Disclosure

• **Faculty:** Dr. Michael Heffernan
• **Title of Talk:** 2016 Dyslipidemia Update

• **Relationships with commercial interests:**
  • Grants/Research Support: Bayer, Boehringer Ingelheim, Esai, AstraZeneca
  • Speakers Bureau/Honoraria: AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Pfizer, Amgen, Servier, Sanofi
  • Consulting Fees: Bayer, AstraZeneca, Boehringer Ingelheim, Amgen, Sanofi
  • Other: None
Objectives

At the end of this presentation, the participant will be able to:

- **Identify** patients not at LDL-C goal despite current treatment and discuss why they would benefit from further LDL-C reduction

- **Appraise** clinical data and new treatment strategies to lower LDL-C in the high risk patient

- **Discuss** clinical management of the high risk patient not at goal and implementation of new treatment strategies
The Case: John

- 56y male
- HTN, dyslipidemia
- Previous MI and angioplasty at age 48y
- Family history of premature CAD

- Non-smoker
- Exercises 100 min/week
- Attended cardiac rehab and adheres to dietary guidelines
The Case

- **Medications**
  - ASA 81 mg once daily
  - Atorvastatin 20 mg
  - Bisoprolol 5 mg once daily
  - Ramipril 10 mg once daily

- **Lipid Profile**
  - TC: 5.9 mmol/L
  - TG: 1.4 mmol/L
  - HDL-C: 1.4 mmol/L
  - **LDL-C: 3.6 mmol/L (current)**
  - non-HDL-C: 4.3 mmol/L

- He has tried rosuvastatin but was unable to tolerate it (myalgias)
- He was on 40 mg of atorvastatin however this also provoked myalgias
- He can tolerate 20 mg of atorvastatin
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What is John’s Target and Why Do We Want to Get Him There?
The Cholesterol Hypothesis Originated with Observational Studies

Epidemiologic Data – Serum Cholesterol Levels and CHD

MRFIT trial: age-adjusted CHD death rate and serum cholesterol in 361,662 US men (aged 35–57 years)

Each 1% Increase in Total Cholesterol Level is associated with a 2% Increase in CHD Risk

These trials have demonstrated that LDL-C lowering is associated with greater reduction of CHD events.
Amount of LDL-C Reduction is Associated with Proportional Reduction in CV Events

The IMPROVE-IT Study

The IMPROVE-IT Study investigated the effects of different cholesterol-lowering treatments on LDL cholesterol levels over time since randomization. The graph shows the mean LDL-C levels (in mg/dL) for two treatment groups: Simvastatin and Simvastatin + Ezetimibe.

- **Simvastatin**: The graph demonstrates a significant reduction in LDL-C levels, with a mean LDL-C level of 1.8 mmol/L at the end of the study.
- **Simvastatin + Ezetimibe**: This group also shows a substantial decrease in LDL-C levels, with a mean LDL-C level of 1.4 mmol/L at the end of the study.

The study duration spanned from randomization (R) to 96 months. The results provide evidence for the effectiveness of combined therapy in lowering LDL cholesterol levels compared to monotherapy.

**Reference:**
Effect of Lower LDL-C on the Risk of CHD Appears to be Independent of the Mechanism by which LDL-C is Lowered

Non-statin lipid-lowering studies suggest coronary event reduction is due to LDL-C reduction, independent of method.

Change in Progression of IVUS Percent Atheroma Volume versus LDL-C in IVUS Trials

On-Treatment LDL-C (mmol/L)

Median Change In Percent Atheroma Volume (%)

r² = 0.95
p < 0.001

ASTEROID
rosvastatin

CAMELOT
placebo

REVERSAL
pravastatin

REVERSAL
atorvastatin

ACTIVATE
placebo

A-Plus
placebo
Epidemiologic data indicates a direct relationship between total cholesterol levels and CV outcomes.

Clinical trials to date indicate that decrease in total cholesterol or LDL-C with statin therapy or other measures leads to a proportionate decrease in CV outcomes.

The IMPROVE-IT trial has reaffirmed the lipid hypothesis by demonstrating that non-statin therapy can achieve an LDL-C decrease that translates into a similar CV risk reduction as that previously observed with statins.

LDL values well below 2.0 appear to confer additional benefit.
Lower is Better – How Do We Get John to Target?

a) Double statin dose
b) Add-on ezetimibe
c) Add-on fibrate
d) Add-on PCSK9 inhibitor
# 2012 Canadian Cardiovascular Society Dyslipidemia Guidelines

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Initiate Therapy if</th>
<th>Primary LDL-C Target</th>
<th>Alternate Target</th>
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</thead>
<tbody>
<tr>
<td>LOW FRS &lt; 10%</td>
<td>➢ LDL-C &gt; 5.0 mmol/L&lt;br&gt; ➢ Familial hypercholesterolemia</td>
<td>≥50% reduction in LDL-C</td>
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<tr>
<td>INTERMEDIATE FRS 10 – 19%</td>
<td>➢ LDL-C &gt; 3.5 mmol/L&lt;br&gt; ➢ For LDL-C &lt; 3.5 mmol/L consider if: Apo B &gt; 1.2 g/L or Non-HDL-C &gt; 4.3 mmol/L</td>
<td>≤2 mmol/L or ≥50% decrease in LDL-C (Strong, Moderate)</td>
<td>➢ Apo B ≤0.8 g/L&lt;br&gt; ➢ Non-HDL-C ≤2.6 mmol/L</td>
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<tr>
<td>HIGH* FRS ≥ 20%</td>
<td>Consider treatment in all</td>
<td>≤2 mmol/L or ≥50% decrease in LDL-C (Strong, High)</td>
<td>➢ Apo B ≤0.8 g/L&lt;br&gt; ➢ Non-HDL-C ≤2.6 mmol/L</td>
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Anderson et al Can J Cardiol 2013;29151-67:
Statin Therapy Has Been Effective in Reducing LDL-C, however, Even Maximal Statin Therapy is Insufficient for Some Patients

Doubling the statin dose results in only 6% LDL reduction

<table>
<thead>
<tr>
<th>Statin</th>
<th>5 mg</th>
<th>10 mg</th>
<th>20 mg</th>
<th>40 mg</th>
<th>10 mg</th>
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<th>40 mg</th>
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<td>Rosuvastatin</td>
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<td>Pravastatin</td>
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<td>Lovastatin</td>
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</table>

*As per Canadian Product Monographs
Add-On Therapy has had Moderate Benefit in Further Lowering LDL-C

<table>
<thead>
<tr>
<th>Add-On Therapy</th>
<th>LDL-C Lowering</th>
<th>Other Lipid Effects</th>
<th>Outcome Data (Add-on to statin)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Niacin4-6</td>
<td>20%</td>
<td>↑ HDL by 30% ▼ TG by 40%</td>
<td>No benefit as add-on to statin7,8</td>
</tr>
<tr>
<td>Fibrates9,10</td>
<td>5 – 20%</td>
<td>↑ HDL-C (10-50%) ▼ TG (20-50%)</td>
<td>No benefit as add-on to statin</td>
</tr>
<tr>
<td>Bile Acid Sequestrants11</td>
<td>15 – 20%</td>
<td>Limited</td>
<td></td>
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<tr>
<td>Ezetimibe1</td>
<td>15 – 25%</td>
<td></td>
<td>IMPROVE-IT ~6.5% reduction in CV events (CVD/MI/stroke)2†</td>
</tr>
</tbody>
</table>

‡In high risk ACS population

Current Therapy Options May Not Get Some of Our High Risk Patients to LDL-C Goal

- Niacin
- BAS
- Fibrates
- Statins 1st Gen
- Statins 2nd Gen
- Ezetimibe
- IMPROVE-IT

LDL-C Lowering (%)

-10% -20% -40% -60% -80%


Fibrates

Statins 1st Gen

Statins 2nd Gen

Ezetimibe

IMPROVE-IT

reduction on top of statin

Despite Guideline Targets Many High-risk Canadian Patients Treated with Statins Are Not at LDL-C Goal

45% Canadian high-risk patients are NOT at LDL-C target\(^1\) (\(\leq 2\) mmol/L)
- 88% of patients received a ‘potent’ statin with suboptimal dose
- 14% of patients received additional lipid-lowering agent

43% Canadian patients with diabetes are NOT at LDL-C target\(^2\) (\(\leq 2\) mmol/L)
- 82% of patients were on a lipid-lowering agent

\(^1\)High risk = coronary artery disease, peripheral arterial disease, cerebrovascular disease, diabetes mellitus or Framingham 10-year risk score \(\geq 20\%\). DYSIS Study = 2,436 patients, 1913 high risk patients.
\(^2\)N = 5,069

New Therapies and New Guidelines
The French Connections

- Catherine Boileau at the Necker-Enfants Malades Hospital in Paris had been following families with FH
  - Her lab had identified a mutation on chromosome 1 carried by some of these families, but had been unable to identify the relevant gene

- In February 2003, Nabil Seidah at the Clinical Research Institute of Montreal discovered a novel human proprotein convertase on chromosome 1
  - Proprotein convertase subtilisin/kexin type 9 (PCSK9)
Discovery of PCSK9

• The labs collaborated and by the end of 2003 they published the connection between PCSK9 mutations and familial hypercholesterolemia

• This was the third gene involved in autosomal-dominant familial hypercholesterolemia along with mutations in the LDL and ApoB genes

• A gain of function mutation destroys LDL receptors and therefore increases LDL resulting in familial hypercholesterolemia (FH) and premature CAD

• PCSK9 became an obvious target for drug development
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**Statin Influence on LDL-C Metabolism and PCSK9**

- **Acetyl-CoA + acetoacetyl-CoA**
- **HMG-CoA**
- **Intracellular Cholesterol Biosynthesis**
- **Hepatocyte Cholesterol Content**
- **LDL-R**
- **LDL Protein at Cell Surface**
- **PCSK9 Protein**
- **SREBP Activation**
- **Nucleus**
- **Endoplasmic Reticulum (ER)**
- **Plasma**
**PCSK9 Inhibitors: Targeted Therapy**

- LDL
- LDL-R
- Endocytosis
- Recycling Endosome
- LDL Degradation
- LDL, LDL-R and PCSK9 Degradation

**PCSK9 Inhibitors: Targeted Therapy**

Targeting and inhibiting PCSK9 activity leads to an increase in LDL receptor levels, which increases removal of LDL-C

- PCSK9 inhibitors (PCSK9i)
  - Evolocumab
  - Alirocumab*
  - Bococizumab*

* Investigational product, not approved by Health Canada

PCSK9 = Proprotein Convertase Subtilisin Kexin Type 9
Patients with Less PCSK9 due to Loss-of-function Mutations have Lower Serum LDL-C and Significantly Lower Incidence of CHD

No nonsense mutation (n = 3,278)

PCSK9$^{142x}$ or PCSK9$^{679x}$ (n=85)

A Race To Bring PCSK9 Therapy To Patients
PROFICIO Program Evaluates Reduction in LDL, Atherosclerosis, and CV Risk with Evolocumab

Phase 2
- Combo-therapy with statin
- Mono-therapy
- Statin-intolerant
- HeFH with LDLR mutations
- HoFH with mutations in both LDLR alleles
- Long-term safety and efficacy
- Open-label extension
- Plaque imaging study
- Secondary prevention

Phase 3
- LAPLACE-2 (N=1,896)
- MENDEL-2 (N=614)
- GAUSS2 (N=329) | GAUSS3 (N=100)
- RUTHERFORD-2 (N=307)
- TESLA/TAUSSIG (N<250)
- DES CARTES (N=901)
- OSLER-2 (N>3,800)
- GLAGOV (N=950)
- FOURIER (N=27,500)
## ODISSEY Program Evaluates Reduction in LDL, Atherosclerosis, and CV Risk with Alirocumab

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Population Description</th>
<th>N</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>PII PRIMARY/SECONDARY PREVENTION</td>
<td>N=77; 12 weeks</td>
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<tr>
<td>HeFH population</td>
<td>Add-on to max tolerated statin (+/- other LMT)</td>
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<tr>
<td>ODISSEY FH I</td>
<td>N=471; 18 months</td>
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<tr>
<td>ODISSEY FH II</td>
<td>N=250; 18 months</td>
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<tr>
<td>ODISSEY HIGH FH</td>
<td>N=107; 18 months</td>
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<tr>
<td>PIII PRIMARY HYPERLipoproteinemia</td>
<td>N=92; 8 weeks</td>
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<tr>
<td>HC in high CV risk population</td>
<td>HC in high CV risk population (+/- other LMT)*</td>
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<tr>
<td>ODISSEY COMBO I</td>
<td>N=314; 12 months</td>
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<tr>
<td>ODISSEY COMBO II</td>
<td>N=720; 24 weeks</td>
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<tr>
<td>ODISSEY CHOICE I</td>
<td>N=803; 24 weeks</td>
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<tr>
<td>ODISSEY LONG TERM</td>
<td>N=2,341; 18 months</td>
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<tr>
<td>ODISSEY OUTCOMES</td>
<td>N=18,000; &gt;5 years</td>
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</tbody>
</table>

Additional populations:

- **ODISSEY MONO**
  - Patient on no background LMT
  - N=103; 24 weeks

- **ODISSEY ALTERNATIVE**
  - Patients with defined statin intolerance
  - N=314; 24 weeks

- **ODISSEY CHOICE II**
  - Patients with hypercholesterolemia on non-statin LMT or diet
  - N=200; 6 months

- **ODISSEY OPTIONS I**
  - Patients not at goal with moderate dose atorvastatin
  - N=355; 6 months

- **ODISSEY OPTIONS II**
  - Patients not at goal with moderate dose rosuvastatin
  - N=305; 6 months

LMT = lipid modifying therapy

*For the ODISSEY COMBO II other LMT not allowed at entry

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Interesting Concept, But Will It Help John?
OSLER: Evolocumab Plus Standard of Care Achieved a 61% Reduction in LDL-C over Standard of Care at 12 Weeks

61% reduction (95%CI 59-63%), P<0.0001

Absolute reduction: 1.9 mmol/L

Median LDL-C (mmol/L)

Baseline (Parent study) N=4465
4 weeks (OSLER) N=1258
12 weeks N=4259
24 weeks N=4204
36 weeks N=1243
48 weeks N=3727

0 0.52 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5

Evolocumab plus standard of care
Standard of care alone

ODYSSEY Long-Term: Alirocumab Achieved a 62% Reduction in LDL-C vs Placebo at 24 weeks

Mean Calculated LDL-C (mmol/L)

Week

0 4 8 12 16 24 36 52 64 78

Placebo + statin therapy at maximum tolerated dose ± other LLT

Alirocumab + statin therapy at maximum tolerated dose ± other LLT

No. of patients with data available

Placebo 780 754 747 746 716 708 694 676 659 652

Alirocumab 1530 1473 1458 1436 1412 1386 1359 1349 1324 1269

62% reduction, P<0.001

Absolute reduction: 1.2 mmol/L

**OSLER: Reduction in the Rate of CV Events Among Patients Receiving Evolocumab**

- **Composite Endpoint:** Death, MI, UA → hospitalization, coronary revasc, stroke, TIA, or CHF → hospitalization
- **HR:** 0.47
  - **95% CI:** 0.28-0.78
  - **P:** 0.003

*Pre-specified exploratory analysis from open-label extension studies OSLER 1 and 2 of adjudicated cardiovascular events.*

**ODYSSEY Long-Term: Reduction in the Rate of CV Events Among Patients Receiving Alirocumab**

Kaplan-Meier Estimates for Time to First Adjudicated Major CV Event*

**Safety Analysis†**
- Cox model analysis
- HR 0.46
- 95% CI: 0.26 to 0.82
- P<0.01

- **Alirocumab + max-tolerated statin ± other LLT (150 mg q2w)**
- **Placebo + max-tolerated statin ± other LLT**

54% RRR

**No. at Risk**
- **Placebo**
  - 788
  - 776
  - 731
  - 703
  - 682
  - 667
  - 321
  - 127
- **Alirocumab**
  - 1550
  - 1534
  - 1446
  - 1393
  - 1352
  - 1335
  - 642
  - 252

* Major CV events based on 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
† ≥ 52 weeks for all patients continuing treatment, incl. 607 patients who completed W78 visit

LDL-C

Achieve an LDL-C of 1.4 mmol/L (60% reduction from 3.6 mmol/L)

Improved tolerability in comparison to a statin in his circumstance

A suggestion of a significant decrease in future CV events – proof is pending
Ratio of LDL Lowering to CV Event Reduction with PCSK9 Inhibitors Holds True to the “LDL Hypothesis”

* Based on exploratory endpoints from Phase 3 trials

**PCSK9i Demonstrate a Further Reduction in LDL-C and an Impact on CV Events**

**LDL-C Reduction:** PCSK9i achieve a 50-60% further reduction in LDL-C when added to statin therapy

**Safety of PCSK9i:** no safety signals to date

**Safety of very low LDL-C:** Little to no evidence to show that very low LDL-C has cause for concern (genetic, statin data, PCSK9i data)

**CV risk:** Initial outcome data with PCSK9i to date have suggested CV event reduction (prospective outcome trials are underway).
PCSK9i Can Achieve a Further 60% Reduction of LDL-C

<table>
<thead>
<tr>
<th>Year</th>
<th>Niacin</th>
<th>BAS</th>
<th>Fibrates</th>
<th>Statins 1st Gen</th>
<th>Statins 2nd Gen</th>
<th>Ezetimibe</th>
<th>PCSK9i</th>
<th>BACKGROUND LLT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1970’s</td>
<td>-20%</td>
<td>-20%</td>
<td>-10%</td>
<td>-40%</td>
<td>-60%</td>
<td>-20%</td>
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<td>1980’s</td>
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LDL-C Lowering (%)

-20% -10% -20% -40% -60% -80% -100% -120%

Reduction on top of statin

Summary

- Observational, genetic, and clinical trial data support the LDL hypothesis
  - A lower LDL provides CV benefit

- Many high risk patients do not achieve the target LDL

- New emerging therapies may benefit high risk patients that are unable to achieve the LDL goal on a statin plus ezetimibe

- The 2016 Canadian Dyslipidemia Guidelines will be released soon
  - There will be a target LDL
  - How low will we go?
Thank You