Challenges in lipid management

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Challenges in Lipid Management

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A real patient

A 57 year old woman with prior MI, CABG and DM:

- Unable/unwilling to tolerate high intensity statins
- LDL is 3.2 on 2.5 mg rosuvastatin alternate days
- Is started on ezetimibe and then a PCSK9 inhibitor
- LDL falls to 0.6
Overview

• Intolerance to statins
• When to use PCSK9 inhibitors
• Very low LDL
PCSK Family of Proteins

“Each capsule contains your medication, plus a treatment for each of its side effects.”

“I didn’t experience any of the side effects listed in the enclosed literature. Should I be concerned?”
Definition of Statin Intolerance

Goal Inhibiting Statin Intolerance: A clinical syndrome (i.e., there is no specific test yet) that is:

Characterized by inability to use statins for long-term lipid and/or CV risk reduction

Either “complete*” or “partial*”, practically, at least 2 statins

Not due to:
- predictable drug-drug interactions
- either ongoing or inter-current predisposing factors

Due to:
- Significant or alarming symptoms (most commonly muscle pain and/or fatigue) AND/OR
- Biomarker abnormalities attributed temporally and unequivocally to statin use
- As generally determined by re-challenge

*Complete = intolerant to any statin at any dose
*Partial = intolerant to some statins at some doses

Mancini GB et al, Can J Cardiol 2013;29:61553-1568
The Elephant in the Room regarding Goal-Inhibiting Statin Intolerance (GISI)

Mancini et al, DOI: http://dx.doi.org/10.1016/j.cjca.2016.01.003
Management of Elevated CK on Statins

• **MYOSITIS**
  - **SEVERE:** > 50x ULN
  - **MODERATE:** > 10x, < 50x ULN

  - **Mild**
    - **Grade 1:** > 1x, ≤ 5x ULN
    - **Grade 2:** > 5x, ≤ 10x ULN

• **MYALGIA:** pain, no CK elevation

• **Idiopathic/Benign/Chronic elevations (ethnic predisposition)**

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Mancini et al, Can J Cardiol 2011;27:635-662
## CCWG Modification of Statin Associated Muscle Symptom (SAMS) Score

### Clinical symptoms (new or increased unexplained muscle symptoms)

<table>
<thead>
<tr>
<th>Regional distribution/pattern</th>
<th></th>
<th>Regional distribution/pattern</th>
<th></th>
<th>Regional distribution/pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Symmetric hip flexors/thigh aches</td>
<td>3</td>
<td>• Symmetric calf aches</td>
<td>2</td>
<td>• Symmetric upper proximal aches</td>
</tr>
<tr>
<td>• Symmetric calf aches</td>
<td>2</td>
<td>• Non-specific, asymmetric, intermittent</td>
<td>1</td>
<td>• Transient during continued statin use</td>
</tr>
<tr>
<td>• Symmetric upper proximal aches</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Regional distribution/pattern</td>
<td>3</td>
<td>• Symmetric calf aches</td>
<td>2</td>
<td>• Symmetric upper proximal aches</td>
</tr>
<tr>
<td>• Non-specific, asymmetric, intermittent</td>
<td>1</td>
<td>• Transient during continued statin use</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>• Transient during continued statin use</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Temporal Pattern

| Symptom onset | | Symptom onset | | Symptom onset | |
|---------------|---------------|---------------|---------------|---------------|
| ≥ 2 days and < 4 weeks | 3 | 4 – 12 weeks | 2 | > 12 weeks | 1 |
| Symptoms onset > 12 weeks | 1 | Symptom onset < 2# days | 0 | | |

### De-challenge*

<table>
<thead>
<tr>
<th>Improvement upon withdrawal</th>
<th></th>
<th>Improvement upon withdrawal</th>
<th></th>
<th>Improvement upon withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td>(2 days to &lt; 2 weeks)</td>
<td>2</td>
<td>(2 – 4 weeks)</td>
<td>1</td>
<td>(&gt; 4 weeks)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Re-Challenge

<table>
<thead>
<tr>
<th>Symptom onset</th>
<th></th>
</tr>
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<tbody>
<tr>
<td>≥ 2 days and &lt; 4 weeks</td>
<td>3</td>
</tr>
<tr>
<td>4 – 12 weeks</td>
<td>1</td>
</tr>
<tr>
<td>&gt; 4 weeks</td>
<td>0*</td>
</tr>
</tbody>
</table>

### History of Response to Non-lipid Lowering Medications

- Same symptoms as reported with statins | -5 |
- Modified SAMS Score
  - Probable | ≥ 9 |
  - Possible | 7 – 8 |
  - Unlikely | < 7 |

*Intended to distinguish between patients reacting after only one dose compared to multiple, daily doses.

*In rare cases of immune-mediated necrotizing myopathy symptoms may persist or worsen despite statin cessation. Ensure absence of hyperCKemia or markers of inflammation if significant symptoms persist off of statin.


Mancini et al, DOI: [http://dx.doi.org/10.1016/j.cjca.2016.01.003](http://dx.doi.org/10.1016/j.cjca.2016.01.003)
Why bother re-challenging with statin?

92.2 % remained on statin 12 months after the initial statin-related discontinuation

72.5 % were able to tolerate long-term (6-month follow-up) therapy with a stable dosage of statin

Other statins (Simva 40 mg, Lova 80 mg, Prava 40 mg, Fluva 80 mg) may be the only tolerated statins but due to lower potency and ineffectiveness of intermittent dosing schedules, failure to achieve goals solely through trials of these statins would not normally be considered adequate for establishing GISH.

Mancini et al, DOI: http://dx.doi.org/10.1016/j.cjca.2016.01.003
EVOLOCUMAB: GAUSS-3
Study Design

1:1
Uncontrolled LDL-C and intolerant to ≥ 2 statins

Atorvastatin (20 mg daily) → Placebo → Atorvastatin (20 mg daily)

Phase A

Placebo

2:1
Patients with muscle-related adverse effects while taking atorvastatin (42.6%)

Evologcumab (420 mg monthly) → Ezetimibe (10 mg daily)

Phase B

2 weeks washout

24 weeks

4 weeks washout period*

10 weeks

10 weeks

* In which lipid lowering agents were discontinued

Fewer Skeletal Muscle AEs with Alirocumab than with Atorvastatin

Kaplan-Meier estimates for time to first skeletal muscle event†

Cox model analysis:

HR ALI vs ATV = 0.61 (95% CI: 0.38 to 0.99), nominal P=0.042

HR ALI vs EZE = 0.71 (95% CI: 0.47 to 1.06), nominal P=0.096

†Pre-defined category including myalgia, muscle spasms, muscular weakness, musculoskeletal stiffness, muscle fatigue.

ALI, alirocumab; ATV, atorvastatin, EZE, ezetimibe.

Principles for Management of Statin Intolerance: 5 Take Home Points

1. Ensure the patient is fully aware of the expected CV risk reduction benefit from statin therapy

2. Emphasize dietary and health behaviour interventions as a backdrop

3. Use statin-based strategies preferentially if intolerance arises
   – If re-challenge is appropriate but does not work
     • Use lower and/or intermittent statin dosing
     • Use different statin

4. Use non-statins as adjuncts if needed to achieve lipid targets;
   Ezetimibe and PCSK9 inhibitors are reasonable options in high risk patients

5. Do not recommend supplements to alleviate myalgias as none have yet been shown consistently to allow continuation of statins

Adapted from Mancini et al, Can J Cardiol 2011;27:635-662
Overview

• Intolerance to statins

• When to use PCSK9 inhibitors

• Very low LDL
Unmet needs in treating patients with hypercholesterolaemia

![Bar chart showing patient flow](chart)

- Total population: 62.1 million
- Statin Intolerant: 35.7 million
- CHD/CHD Risk Equivalent: 7.6 million
- Diabetes with 0/1 Risk Factor: 11.0 million
- HeFH: 0.2 million
- Eligible population: 21.6 million
- Highest unmet need patients: 2/3 with LDL-C >100mg/dl

**21m Patients Estimated at High CV Risk and Not at Goal for LDL-C**

*(1) CDC, (2) CCRN*
Cardiovascular death, MI, documented unstable angina requiring rehospitalization, coronary revascularization (≥30 days), or stroke

Hazard Ratio, 0.936
(95% CI, 0.89-0.99)
p=0.016

Simvastatin: 34.7% - 2742 events
Mean LDL-C = 1.8 mmol/L

Simvastatin/Ezetimibe: 32.7% - 2572 events
Mean LDL-C = 1.4 mmol/L

NNT* = 50

\( \text{NNT} = \text{Number Needed to Treat} \)
2016 CCS Lipid Guidelines

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

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 can be considered as alternative treatment targets

*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)
PCSK9 inhibitors – 45-60% LDL lowering

**Alirocumab Administration**
- 1 injection SC q2wk, Doses: 75 mg or 150 mg
- Auto-injector

**Evolocumab Administration**
- 1 injection SC q2wk, Dose: 140 mg
- 3 injections SC q4wk Total Dose: 420 mg
- Auto-injector
# Efficacy of PCSK9 Inhibitors

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Analysis</th>
<th>LDL-C</th>
<th>TC</th>
<th>Lp(a)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>vs Placebo</strong></td>
<td>MAb and dose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Alirocumab 75-mg Q2W</td>
<td>-52.63%</td>
<td>-</td>
<td>-14.60%</td>
</tr>
<tr>
<td></td>
<td>Alirocumab 150-mg Q2W</td>
<td>-56.15%</td>
<td>-38.87%</td>
<td>-25.60%</td>
</tr>
<tr>
<td></td>
<td>Evolocumab 140-mg Q2W</td>
<td>-63.46%</td>
<td>-41.18%</td>
<td>-32.31%</td>
</tr>
<tr>
<td></td>
<td>Evolocumab 420-mg Q4W</td>
<td>-57.26%</td>
<td>-36.96%</td>
<td>-26.03%</td>
</tr>
<tr>
<td><strong>vs Ezetimibe</strong></td>
<td>MAb and dose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Alirocumab 75-mg Q2W</td>
<td>-31.67%</td>
<td>-22.20%</td>
<td>-5.40%</td>
</tr>
<tr>
<td></td>
<td>Evolocumab 140-mg Q2W</td>
<td>-39.27%</td>
<td>-25.35%</td>
<td>-26.88%</td>
</tr>
<tr>
<td></td>
<td>Evolocumab 420-mg Q4W</td>
<td>-37.49%</td>
<td>-23.96%</td>
<td>-24.84%</td>
</tr>
</tbody>
</table>

**Background statin**

- Non-intensive
- Intensive

Statin-induced Conditions

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

LDL-C ≥5 mmol/L
(genetic dyslipidemia)

Discuss behavioural modifications

Initiate Statin Treatment: Treat to Target Approach

Confirm adherence and barriers to use

LDL-C <2.0 mmol/L (<1.8 in clinical atherosclerosis pts) or 50% reduction or apoB <0.8 g/L or non-HDL-C <2.6 mmol/L

LDL-C >50% reduction

Target achieved on maximally tolerated dose?

NO

Discuss add-on therapy with patient:
Evaluate reduction in CVD risk vs. additional cost & side effects

ADD-ON

YES

NO ADD-ON

ADD-ON

Add-on Therapy

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

High Risk Patients Who Require Additional LDL-C Reduction

American National Lipid Association

Recommendations for patient-centered management of dyslipidemia

Consider use PCSK9 inhibitors primarily in:

- Patients with CVD
- and
- LDL-C > 100 mg/dl (2.6 mmol/L) or non-HDL-C > 130 mg/dl (3.4 mmol/L) on max. statin ± ezetimibe

- Patients with heterozygous FH without CVD
- and
- LDL-C > 130 mg/dl or non-HDL-C > 160 mg/dl (4.1 mmol/L) on max. statin ± ezetimibe

American National Lipid Association

Recommendations for patient-centered management of dyslipidemia

2. Use of PCSK9 inhibitors *may be considered* in:

- Selected high risk Patients (with e.g. recurrent CVD)
- and
- LDL-C > 70 mg/dl (1.8 mmol/L) or non-HDL-C > 100 mg/dl (2.6 mmol/L) on max. statin ± ezetimibe
- Patients with statin intolerance
Neurocognitive AEs and PCSK9 Inhibitors

- Cumulative evidence does not implicate any correlation between PCSK9i treatment and neurocognitive events
  - Neurocognitive events were uncommon, not associated with on-treatment LDL-C levels and tended to be mild and transient
  - No overall pattern observed in relation to type of event, time to onset, resolution, or outcome

- Ongoing studies are proactively monitoring for cognitive impairment with PCSK9i (Evolocumab FOURIER sub-study EBBINGHAUS)
• **Primary endpoint:**\(^1,2\) Nominal change in PAV from baseline to week 78

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

Amgen Announces Positive Top-Line Results From Phase 3 GLAGOV Imaging Study Of Repatha® (Evolocumab)

First Study to Demonstrate That Lowering LDL Cholesterol With a PCSK9 Inhibitor Impacts Underlying Atherosclerotic Disease on top of Optimized Statin Therapy

Intravascular Ultrasound Study Meets Primary and Secondary Endpoints

Detailed Results to be Presented at AHA Scientific Sessions 2016

THOUSAND OAKS, Calif., Sept. 20, 2016 /PRNewswire/ -- Amgen (NASDAQ:AMGN) today announced that the Phase 3 GLAGOV (GLobal Assessment of Plaque ReGression with a PCSK9 AntibOdy as Measured by IntraVascular Ultrasound) trial evaluating the effect of Repatha® (evolocumab) on coronary artery disease (CAD) met its primary and secondary endpoints. The GLAGOV study is a large serial coronary intravascular imaging trial designed to test whether treatment with the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor Repatha modifies atherosclerotic plaque build-up in the coronary arteries of patients already treated with optimized statin therapy.
PCSK9 Inhibitors – What remains to be learned?
### 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&lt;br&gt;Background: optimal lipid lowering therapy</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) &lt;br&gt;Background: optimized lipid lowering therapy</td>
<td>Bococizumab: 150 mg Q2W&lt;br&gt;Background: lipid lowering therapy</td>
</tr>
<tr>
<td><strong>Population</strong></td>
<td>MI or stroke (≥ last 4 weeks) OR PAD&lt;br&gt; (plus Risk factors for CVD)</td>
<td>Patients hospitalized for ACS&lt;br&gt;(&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&lt;br&gt;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&lt;br&gt;SPIRE-2: LDL-C ≥2.6 mmol/L or non-HDL-C ≥3.4 mmol/L</td>
</tr>
<tr>
<td><strong>Estimated study completion</strong></td>
<td>2017</td>
<td>December 2017</td>
<td>SPIRE-1: June 2018&lt;br&gt;SPIRE-2: March 2018</td>
</tr>
</tbody>
</table>

Overview

• Intolerance to statins

• When to use PCSK9 inhibitors

• Very low LDL
No identified safety concerns with very low LDL-C

- All tissues can synthesize their own cholesterol
- Cholesterol enters the circulation via chylomicrons and VLDL particles
- LDL-C is the final product of remodeling these lipoproteins through interaction with other lipoproteins and the endothelium
- Brain sits behind the blood brain barrier and is independent of circulating lipoproteins
- PCSK9i do not ↓ cholesterol production, they ↑ cholesterol uptake
- Individuals with homozygous PCSK9 deficiency are healthy and have LDL-C between 0.3-0.5 mmol/L

No Association Between Very Low LDL-C and Cancer or Stroke

Cancer

- A meta analysis of 26 statin trials\(^1\) did not associate low LDL-C with cancer
  - Deaths due to cancer or other non-vascular causes (RR 0.97, 95% CI 0.92-1.03; P=0.3)
  - Cancer incidence (RR 1.00, 95% CI 0.96-1.04; P=0.9)

Hemorrhagic Stroke

- No increase in ICH in a meta-analysis of 31 placebo-controlled statin RCTs\(^2\)
  - Intracranial hemorrhage risk was not related to the degree of LDL-C reduction or achieved LDL-C (OR, 1.08; 95% CI, 0.88–1.32; P=0.47)

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## Adverse Events by Achieved LDL-C

<table>
<thead>
<tr>
<th>Evolocumab subjects stratified by minimum achieved LDL-C</th>
<th>All EvoMab (n=2976)</th>
<th>Stnd of Care Alone (n=1489)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;25 mg/dL (n=773)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25 to &lt;40 mg/dL (n=759)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;40 mg/dL (n=1532)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥40 mg/dL (n=1426)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Adverse Events (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>70.0</td>
<td>69.2</td>
</tr>
<tr>
<td>Serious</td>
<td>7.6</td>
<td>7.5</td>
</tr>
<tr>
<td>Muscle-related</td>
<td>4.9</td>
<td>6.4</td>
</tr>
<tr>
<td>Neurocognitive</td>
<td>0.5</td>
<td>0.9</td>
</tr>
<tr>
<td><strong>Lab results (%)</strong></td>
<td></td>
<td></td>
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<tr>
<td>ALT/AST &gt;3×ULN</td>
<td>0.9</td>
<td>1.0</td>
</tr>
<tr>
<td>CK &gt;5×ULN</td>
<td>0.4</td>
<td>0.6</td>
</tr>
</tbody>
</table>
## Two People with Inactivating Mutations in Both PCSK9 Alleles

<table>
<thead>
<tr>
<th>PCSK9 Genotype</th>
<th>PCSK9\textsuperscript{Y142X/\textDelta R97}</th>
<th>PCSK9\textsuperscript{C679X/C679X}</th>
</tr>
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<tbody>
<tr>
<td>Age</td>
<td>32</td>
<td>21</td>
</tr>
<tr>
<td>Sex</td>
<td>F</td>
<td>F</td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>96 mg/dL (2.5 mmol/L)</td>
<td>85mg/dL (2.2 mmol/L)</td>
</tr>
<tr>
<td>LDL</td>
<td>14 mg/dL (0.4 mmol/L)</td>
<td>15 mg/dL (0.4 mmol/L)</td>
</tr>
<tr>
<td>TG</td>
<td>119 mg/dL (1.3 mmol/L)</td>
<td>71 mg/dL (0.8 mmol/L)</td>
</tr>
<tr>
<td>HDL</td>
<td>65 mg/dL (1.7 mmol/L)</td>
<td>54 mg/dL (1.4 mmol/L)</td>
</tr>
<tr>
<td>Plasma [PCS9]</td>
<td>Undetectable</td>
<td>N/A</td>
</tr>
<tr>
<td>Clinical</td>
<td>• Apparent good health</td>
<td>• Apparent good health</td>
</tr>
<tr>
<td></td>
<td>• Normal fertility (mother)</td>
<td>• Normal fertility (mother)</td>
</tr>
<tr>
<td></td>
<td>• No developmental abnl</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• College graduate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Aerobics instructor</td>
<td></td>
</tr>
</tbody>
</table>

Hooper AJ et al.. Atherosclerosis. 2007;193:445-8
SUMMARY

1. A systematic approach to statin intolerance results in the vast majority of patients tolerating at least some statin. Non-statin drugs may be required to achieve target.

2. PCSK9 inhibitors are now recommended as 2\textsuperscript{nd} or 3\textsuperscript{rd} line agents in high risk patients with ASCVD/FH when statins are not enough. Definitive outcome trials are near completion.

3. No toxicity has yet to be identified of achieving very low LDL levels.