Canadian Lipid Guidelines, a Century of Cholesterol and Paul Erlich

Jacques Genest MD

Cardiovascular Research Laboratories
McGill University Health Center

Endocrinology Rounds 19 Nov 2015
Disclosure J. Genest MD 2016

Advisory Board, Speaker’s Bureau, Consultant, Grants, Clinical Trials

- Merck *
- Pfizer
- Novartis *
- AMGEN *
- Cerenis *

- Sanofi/Regeneron *
- Lilly
- Valeant
- Aegerion *
- Ascati

Stock ownership: none;
Off label use: none
* Scientific Advisory

Relevant disclosure: JUPITER, IMPROVE-IT, CANTOS, CAPREE steering Committees; REVEAL, ACCELERATE, AMG145, Lilly Clinical Trials.
Lipids/PCSK9 Inhibitors: New Agents, New Approaches

The conference participants will:

1. Initiate therapy in appropriate patients following the new CCS Lipid guidelines.
2. Discuss the burden of disease of familial hypercholesterolemia (FH)
3. Identify patients in whom novel therapies, especially PCSK9 inhibitors are indicated.
4. Identify the causal role of LDL in ASCVD
Familial Hypercholesterolemia

1- How would you define Familial Hypercholesterolemia (FH)?

2- What are the common genes responsible for FH?

3- What is the prevalence of FH in Canada?

4- What is the risk of CVD in patients with a LDL-C > 5 mmol/L?

5- What is the risk of CVD in patients with a LDL-C > 5 mmol/L and a LDL-receptor mutation?

6- How would you treat a patient with FH?
2016 CCS Lipid Guidelines

Treatment Algorithm
Treatment based on risk (1)

- Adjusted FRS $\geq 20\%$
- Clinical atherosclerosis
- Most diabetics
  - (1) >15y duration + age > 30y
  - (2) Age > 40y
  - (3) Microvascular disease
- High risk hypertension
- Abdominal aortic aneurysm
- Chronic renal disease

High risk patients

Health behaviour modifications
Treatment of modifiable CVD risk factors

Clinical judgement
Patient education/discussion

Statin therapy

*Strong Recommendation, High-Quality Evidence*
Treatment based on risk (2)

Intermediate risk patients
Adjusted FRS ≥ 10% < 20%

LDL-C < 3.5 mmol/L
- ApoB < 1.2 g/L or N-HDL-C < 4.3 mmol/L
  > Optional secondary testing
  > Clinical judgement
  > Patient education/discussion

LDL-C ≥ 3.5 mmol/L
- ApoB ≥ 1.2 g/L or N-HDL-C ≥ 4.3 mmol/L
  > Statin therapy

Health behaviour modifications

Conditional Recommendation, Moderate-Quality Evidence

Strong Recommendation, Moderate-Quality Evidence
Treatment based on risk (3)

Low risk patients
Adjusted FRS < 10%

LDL-C < 5.0 mmol/L
LDL-C ≥ 5.0 mmol/L

Health behaviour modifications

Adjusted FRS 5-9%
Clinical judgement
Patient education/discussion
Optional secondary testing

Clinical judgement
Patient education/discussion
Statin therapy

Strong Recommendation, Moderate-Quality Evidence
Severe Hypercholesterolemia
LDL-C, Familial Hypercholesterolemia
Mutation Status, and Risk for CAD

Amit V. Khera, Hong-Hee Won, Gina M. Peloso,
Sekar Kathiresan, on behalf the
Myocardial Infarction Genetics and CHARGE Consortia
A Century of Cholesterol and Coronaries: From Plaques to Genes to Statins

Joseph L. Goldstein and Michael S. Brown

Department of Molecular Genetics, University of Texas Southwestern Medical Center, Dallas, TX 75390, USA

Table 1. A Century of Cholesterol and Coronaries

First Half—The Early Years
- 1910 Human atherosclerosis
- 1913 High cholesterol
- 1919 Heart attack
- 1933 Feedback
- 1938 Familial
- 1950 Cholesterol
- 1951 High-fat diet
- 1953 Risk factors

Second Half—The Evolution of Understanding
- 1955 LDL identified
- 1973 LDL receptors
- 1976 HMG CoA reductase
- 1981 Statins introduced
- 1987 First statin
- 1994 Statins on market
- 1997 SREBP pathway elucidated
- 2006 PCSK9: Destroyer of LDL receptors

Acetyl CoA
HMG CoA
Reductase
Mevalonate
Cholesterol

LDL receptors

Cell 2015:161; 161-172
**Background:** The Utility of Genetic Testing in Severe Hypercholesterolemia (LDL ≥ 190 mg/dl) is Uncertain

**Study Objectives:**

1. **Diagnostic Yield**
   What proportion of individuals with LDL ≥ 190 have a FH mutation?

2. **Clinical Importance**
   For any given LDL, does coronary risk vary according to FH mutation status?

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**LDL Cholesterol**

- **Monogenic (FH)**
- **Polygenic**
- **Environmental**

7% US Population
Methods: Gene Sequencing of *LDLR*, *APOB*, and *PCSK9* to Identify FH Mutations

1. **Loss of function** variants in *LDLR*:
   a) Premature truncation (nonsense)
   b) Scramble the protein translation (frameshift)
   c) Alter the mRNA splicing process (splice-site)

2. Missense variants in *LDLR* predicted to be **damaging** by each of five computer prediction algorithms

1. Variants in *LDLR*, *APOB*, or *PCSK9*, annotated as “pathogenic” or “likely pathogenic” in ClinVar, a clinical genetics database
Diagnostic Yield: Fewer than 2% of Individuals with LDL ≥ 190 mg/dl have an Identifiable FH Mutation

Severe Hypercholesterolemia
LDL Cholesterol ≥ 190

FH Mutation Positive
24 of 1,386 (1.7%

1,386 of 20,485 (7%)
Clinical Importance: CAD Risk is Substantially Higher in FH Mutation Carriers with LDL ≥ 190

<table>
<thead>
<tr>
<th>LDL ≥ 190 mg/dl</th>
<th>OR for CAD (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FH Mutation − (N = 1,264)</td>
<td></td>
</tr>
<tr>
<td>FH Mutation + (N = 73)</td>
<td></td>
</tr>
<tr>
<td>LDL &lt; 130 &amp; FH Mutation −</td>
<td>Reference</td>
</tr>
</tbody>
</table>

Logistic Regression in Myocardial Infarction Genetics Consortium Studies
Covariates: Gender, Study, 5 principal components of ancestry
Clinical Importance: For a Given Observed LDL, FH Mutation Carriers are at Increased Coronary Risk

Mean LDL 203 mg/dl
Mean LDL 205 mg/dl

Familial Hypercholesterolemia Mutation
- No
- Yes

Odds Ratio for Coronary Artery Disease (95% CI)
Study Limitations

• Our data did not permit stratifying individuals by family history or physical exam features, as recommended by some clinical criteria for familial hypercholesterolemia.

• Large DNA structural variation incompletely captured with current gene sequencing technology.

• Accounting for a 30% LDL reduction with lipid-lowering medication may imperfectly estimate untreated levels.
Summary

1. Diagnostic Yield

Only about 2% of individuals with LDL \( \geq 190 \) have a FH mutation; remainder likely related to polygenic or environmental causes.

2. Clinical Importance

For any given LDL, risk of coronary artery disease is substantially higher among those with a FH mutation, likely due to increased lifelong exposure to circulating LDL.

Additional Details Available in Online Publication
Implications for Clinical Medicine

- **Routine Lipid Testing**: LDL 167
- **Sequencing FH Genes**: FH Mutation Negative
- **Differential Treatment**:
  - FH Mutation Positive
  - Lifestyle Changes
  - Early Pharmacotherapy
  - Cascade Screening
Methods: FH Mutation Prevalence in MIGen

Myocardial Infarction Genetics Consortium

Controls: 48 of 8,577 (0.6%)
Cases: 116* of 5,540 (2.1%)

*One homozygous carrier
Mutations causative of familial hypercholesterolaemia: screening of 98,098 individuals from the Copenhagen General Population Study estimated a prevalence of 1 in 217

Marianne Benn¹,²,³*, Gerald F. Watts⁴, Anne Tybjærg-Hansen²,³,⁵, and Børge G. Nordestgaard²,³,⁶
Title: The Prevalence of Familial Hypercholesterolemia in the 1999-2012 United States National Health and Nutrition Examination Survey (NHANES)

Manuscript number: CIRCULATIONAHA/2015/018791R2

Author(s): Sarah de Ferranti, Children's Hospital Boston

The estimated overall US prevalence of probable/definite FH was 0.40% (95% CI 0.32-0.48) or 1 in 250 (95% CI 1 in 311 to 209); suggesting 834,500 US adults have FH. Prevalence varied by age, being least common in 20-29 year-olds (0.06%, 1 in 1557), and most common in 60-69
Homozygous FH

\[
1/500 \times 1/500 \times 1/4 = 1/106
\]
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

© The Author 2013. Published by Oxford University Press on behalf of the European Society of Cardiology.
Kaplan–Meier curve estimates of cumulative CHD-free survival among individuals with familial hypercholesterolaemia according to statin treatment (P < 0.001 for difference).

Cumulative event-free survival (%) in FH

Follow-up (years)

Nordestgaard B G et al. Eur Heart J 2013;eurheartj.eht273
Monoclonal Antibodies (mAbs) 101
Paul Ehrlich (1854-1915)

- Gram stain
- Arsphenamine (first Rx for Syphilis)
- Anti-serum against dypthergia
- Concept of “magische Kugel” – magic bullet

Nobel Prize 1908
Polyclonal Antibodies

B cell (humoral) immune responses are polyclonal

Polyclonal Abs:
- Recognize multiple epitopes on same antigen
- Usually high affinity

BUT
- Show major batch to batch variability
- Can include relatively non-specific antibodies
Monoclonal Antibodies (MAbs)

Monoclonal Abs:

- High specificity; detect only one epitope on antigen
- High homogeneity; once made, antibodies are constant, all batches identical
- Can be produced in unlimited quantities
How to make a monoclonal Ab

LIMITATIONS to Mouse MAbs

- Inability to trigger human effector functions
- Short ½ life of murine antibodies
- Evoke anti-mouse Ab immune (HAMA) responses
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)**: Humanized, Can be time-consuming to create, e.g., Evolocumab and Alirocumab.
- **4th generation ("Fully" Human)**: "Fully" Human, repeated dosing possible, e.g., Evolocumab and Alirocumab.

**Nomenclature:** Prefix (Pharma) C (Cardiovascular) UMAB
Monoclonal antibodies in the clinic

Over 30 monoclonal antibodies approved for clinical use by European/US regulatory agencies in, for example:

- Asthma
- Autoimmune diseases
- Oncology
- Ophthalmic disorders

Approximately 235 monoclonal antibodies in active trials, for example:

- Alzheimer’s disease
- Cardiovascular disease
- Infectious disease
- Osteoporosis

Cumulative number of human monoclonal antibodies entering clinical study between 1985 and 2008

The biologics explosion

TNF Inhibitors
- Etanercept
- Adalimumab
- Infliximab
- Golimumab
- Certolizumab

Non-TNF Biologics
- Tocilizumab (IL-6)
- Rituximab (B cell CD20)
- Abatacept (B7-CTLA4Ig)
- Anakinra (IL-1)
- Canakinumab (IL-1β)

Emerging non-TNF Biologics
- Sarilimab (IL6R)
- Olokizumab (IL6)
- Clazakizumab (IL6)
- Sirukumab (IL6)
- Secukinumab (IL-17)
- Brodalumab (IL-17R)

Emerging non-MAb Biologics
- Small molecules
  - Tofacitinib (JAK1/3)
- Biosimilars
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

Nature Genetics 34, 154 - 156 (2003)

Dr. Nabil Seidah IRCM
Proprotein Convertase Subtilisin/Kexin Type 9

Evolutionary Conservation: Must be important

Bacillus amyloliquefaciens  saccharomyces cerevisiae  Homo sapiens
A: LDL-R pathway in absence of PCSK9

B: Intracellular PCSK9 route

C: Extracellular PCSK9 route

LDL-R

Endosome

Mature PCSK9

apoB

Degradation

LDL
PCSK9 as a Target

Cohen JC, et al. NEJM 2006;354:1264
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

PCSK9 Directly Binds to the LDLR

Kwon et al. 2008. PNAS. 105:1820
Clinical Data
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 Period</th>
<th>Median LDL-C (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (Parent study)</td>
<td>N=4465</td>
</tr>
<tr>
<td>4 weeks (OSLER)</td>
<td>N=1258</td>
</tr>
<tr>
<td>12 weeks</td>
<td>N=4259</td>
</tr>
<tr>
<td>24 weeks</td>
<td>N=4204</td>
</tr>
<tr>
<td>36 weeks</td>
<td>N=1243</td>
</tr>
<tr>
<td>48 weeks</td>
<td>N=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 Pordy, 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/NEJMoa1501031

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


[Graph showing the reduction in LDL-C levels over time for Alirocumab plus statin therapy versus placebo plus statin therapy.]
ODYSSEY Long-Term: Reduction in the Rate of Cardiovascular Events- Post-hoc Analysis

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

54% RRR

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

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

*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

Ratio of LDL Lowering to CV Event Reduction with PCSK9 Inhibitors Holds True to the “LDL Hypothesis”

Results of Bococizumab, A Monoclonal Antibody Against Proprotein Convertase Subtilisin/Kexin Type 9, from a Randomized, Placebo-Controlled, Dose-Ranging Study in Statin-Treated Subjects With Hypercholesterolemia

Christie M. Ballantyne, MD\textsuperscript{a,b,\textdagger}, Joel Neutel, MD\textsuperscript{c}, Anne Cropp, PharmD\textsuperscript{d}, William Duggan, PhD\textsuperscript{e}, Ellen Q. Wang, PhD\textsuperscript{f}, David Plowchalk, PhD\textsuperscript{g}, Kevin Sweeney, PhD\textsuperscript{g}, Nitin Kaila, PhD\textsuperscript{g}, John Vincent, MD, PhD\textsuperscript{h}, and Harold Bays, MD\textsuperscript{i}

Am J Cardiol 2015;115:1212e1221)
Results of Bococizumab, A Monoclonal Antibody Against Proprotein Convertase Subtilisin/Kexin Type 9, from a Randomized, Placebo-Controlled, Dose-Ranging Study in Statin-Treated Subjects With Hypercholesterolemia

The American Journal of Cardiology, Volume 115, Issue 9, 2015, 1212–1221
Figure 4. Mean percentage change from baseline in LDL-C. Change over time is shown for the (A) Q14 days and (B) Q28 days placebo and bococizumab dose groups.

Ballantyne CM. The American Journal of Cardiology, 2015;115:1212–1221
# Bococizumab: AE

<table>
<thead>
<tr>
<th>Variable</th>
<th>Q14 days</th>
<th></th>
<th>Q28 days</th>
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<tbody>
<tr>
<td></td>
<td>Placebo (n = 49)</td>
<td>50 (n = 50)</td>
<td>100 (n = 51)</td>
<td>150 (n = 49)</td>
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<tr>
<td>AEs</td>
<td>84% [29%]</td>
<td>74% [24%]</td>
<td>84% [31%]</td>
<td>82% [37%]</td>
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<tr>
<td>Serious AEs</td>
<td>14% [0%]</td>
<td>8% [0%]</td>
<td>4% [0%]</td>
<td>8% [2%]</td>
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<tr>
<td>Discontinuation of treatment due to AE</td>
<td>2% [0%]</td>
<td>2% [2%]</td>
<td>4% [0%]</td>
<td>10% [8%]</td>
</tr>
<tr>
<td>Most frequent AEs (≥10%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>12% [0%]</td>
<td>16% [0%]</td>
<td>14% [0%]</td>
<td>10% [0%]</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>14% [0%]</td>
<td>8% [0%]</td>
<td>10% [0%]</td>
<td>6% [2%]</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8% [0%]</td>
<td>6% [0%]</td>
<td>8% [4%]</td>
<td>10% [2%]</td>
</tr>
</tbody>
</table>
FDA approves Praluent to treat certain patients with high cholesterol

PCSK9 mAb

Praluent®
alirocumab

FDA

Praluent®
alirocumab

Green button

Body

Window

Yellow safety cover
Needle inside

Blue cap

For single use only

Repatha™
evolumab

Repatha™
evolumab

Now Approved in the EU

Read More
Praluent is approved for use in addition to diet and maximally tolerated statin therapy in adult patients with heterozygous familial hypercholesterolemia (HeFH) or patients with clinical atherosclerotic cardiovascular disease such as heart attacks or strokes, who require additional lowering of LDL cholesterol.

Repatha is approved for use in addition to diet and maximally-tolerated statin therapy in adult patients with heterozygous familial hypercholesterolemia (HeFH), homozygous familial hypercholesterolemia (HoFH), or clinical atherosclerotic cardiovascular disease, such as heart attacks or strokes, who require additional lowering of LDL cholesterol.
Anti-drug Antibodies (ADA)
Anti-drug antibodies (ADA): the challenge

**Immunogenicity:**
- The potential for an antigen to induce an immune response
- Immunogenicity against therapeutic proteins that are not in the normal human repertoire is a normal immune response.
- Reaction to neo-antigens
  - Proteins are non-human
  - Fusion proteins create new epitopes
  - Unusual glycosylation
Anti-PCSK9 Antibodies

The detection of anti-drug binding antibody formation is highly dependent on the sensitivity and specificity of the assay. Comparison of the incidence of antibodies to evolocumab with incidence of antibodies to other products may be misleading.

<table>
<thead>
<tr>
<th>Evolocumab</th>
<th>Alirocumab</th>
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</thead>
<tbody>
<tr>
<td>• Overall incidence of anti-evolocumab binding antibodies after at least one dose of evolocumab was 0.3% (13 of 4915)</td>
<td>• Observed in 4.8% of patients following alirocumab treatment vs. 0.6% of patients in control group</td>
</tr>
<tr>
<td>• Responses were of low-titer, most were transient</td>
<td>• Most responses were of low-titer, non-neutralizing, and/or transient</td>
</tr>
<tr>
<td>• No neutralizing antibodies have been detected</td>
<td>• Neutralizing antibodies were reported in 1.2% of patients treated with alirocumab</td>
</tr>
<tr>
<td>• No impact of binding antibodies on safety, pharmacokinetics, or pharmacodynamics</td>
<td></td>
</tr>
</tbody>
</table>

Effect of an RNA interference drug on the synthesis of proprotein convertase subtilisin/kexin type 9 (PCSK9) and the concentration of serum LDL cholesterol in healthy volunteers: a randomised, single-blind, placebo-controlled trial.
PCSK9 mAb Clinical Indications

Familial Hypercholesterolemia

ASCVD (Atherosclerotic Cardiovascular Disease) not at goal despite maximally tolerated lipid-lowering therapy

Statin intolerant
PCSK9 mAb: Whom, When?

Numbers (Guess)

- CAD* Approx 1.5 M CDN
- 250,000
- CAD* Not @ Goal
- Hi Risk Not @ Goal
- FH Not @ Goal
- FH + CAD
- 20-30 HoFH
PCSK9 and Diabetes
Background: Statin Treatment and Increased Risk of T2DM

<table>
<thead>
<tr>
<th>Statin treatment</th>
<th>Case</th>
<th>Non-case</th>
<th>Control</th>
<th>Case</th>
<th>Non-case</th>
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</thead>
<tbody>
<tr>
<td>Placebo-controlled or standard care-controlled</td>
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</tr>
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<td>SSSS</td>
<td>198</td>
<td>1918</td>
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<td>WOSCOPS</td>
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<td>GISSI Prevenzione</td>
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<td>1647</td>
<td>105</td>
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<td>ALLHAT-LLT</td>
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<td>1435</td>
<td>215</td>
<td>1503</td>
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<tr>
<td><strong>Subtotal</strong></td>
<td><strong>2409</strong></td>
<td><strong>45741</strong></td>
<td><strong>2181</strong></td>
<td><strong>46087</strong></td>
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(\(I^2=29.6\%, p=0.134\))

<table>
<thead>
<tr>
<th>Statin treatment</th>
<th>Case</th>
<th>Non-case</th>
<th>Control</th>
<th>Case</th>
<th>Non-case</th>
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<tbody>
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<td>Intensive vs moderate dose</td>
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<td>PROVE-IT TIMI22</td>
<td>101</td>
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<td>A to Z</td>
<td>65</td>
<td>1703</td>
<td>47</td>
<td>1689</td>
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<tr>
<td>TNT</td>
<td>418</td>
<td>3380</td>
<td>358</td>
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<td>3497</td>
<td>209</td>
<td>3515</td>
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<tr>
<td>SEARCH</td>
<td>625</td>
<td>4773</td>
<td>587</td>
<td>4812</td>
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<tr>
<td><strong>Subtotal</strong></td>
<td><strong>1449</strong></td>
<td><strong>14959</strong></td>
<td><strong>1300</strong></td>
<td><strong>15044</strong></td>
<td></td>
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</table>

(\(I^2=0.0\%, p=0.598\))

<table>
<thead>
<tr>
<th>Statin treatment</th>
<th>Case</th>
<th>Non-case</th>
<th>Control</th>
<th>Case</th>
<th>Non-case</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>3858</td>
<td>60700</td>
<td>3481</td>
<td>61131</td>
<td></td>
</tr>
</tbody>
</table>

(\(I^2=16.2\%, p=0.253\))

CI, confidence interval; OR, odds ratio; T2DM, type 2 diabetes mellitus.
Case = developed T2DM. Non-case = did not develop T2DM.
Efficacy and Safety of Alirocumab: Pooled Analyses of 1051 Individuals with Diabetes Mellitus from Five Placebo-Controlled Phase 3 Studies of at least 52 weeks’ duration

Henry N Ginsberg¹, Michel Farnier², Jennifer G Robinson³, Christopher P Cannon⁴, Naveed Sattar⁵, Marie T Baccara-Dinet⁶, Christelle Lorenzato⁷, Maja Bujas-Bobanovic⁸, Michael J Louie⁹, Helen M Colhoun¹⁰

¹Columbia University, New York, NY; ²Point Medical, Dijon, France; ³University of Iowa, Iowa City, IA; ⁴Harvard Clinical Res Inst, Boston, MA; ⁵University of Glasgow, Glasgow, UK; ⁶Sanofi, Montpellier, France; ⁷Sanofi, Chilly-Mazarin, France; ⁸Sanofi, Paris, France; ⁹Regeneron Pharmaceuticals, Tarrytown, NY; ¹⁰University of Dundee, Dundee, UK.

This study was funded by Sanofi and Regeneron Pharmaceuticals, Inc.
Mean Fasting Plasma Glucose Over Time (Safety Population)

- Alirocumab with DM
- Alirocumab without DM
- Placebo with DM
- Placebo without DM

Alirocumab 75/150 mg Q2W

Alirocumab 150 mg Q2W

†75 mg Q2W increased to 150 mg Q2W at W12 if LDL-C levels at Week 8 were ≥70 mg/dL (1.81 mmol/L).

FPG, fasting plasma glucose.
Mean HbA$_{1c}$ Over Time (Safety Population)

- **Alirocumab with DM**
- **Placebo with DM**
- **Alirocumab without DM**
- **Placebo without DM**

**Alirocumab 75/150 mg Q2W**

- 5.5
- 6
- 6.5
- 7
- 7.5
- 8
- 8.5
- 9
- 9.5
- 10

**Alirocumab 150 mg Q2W**

- 5.5
- 6
- 6.5
- 7
- 7.5
- 8
- 8.5
- 9
- 9.5
- 10

**Week**

- 0
- 12
- 24
- 52

HbA1c, glycated hemoglobin.

†75 mg Q2W increased to 150 mg Q2W at Week 12 if LDL-C levels at Week 8 were ≥70 mg/dL (1.81 mmol/L).
Evaluation of the One-Year Efficacy, Safety and Glycaemic Effects of Evolocumab (AMG 145) in 4,802 Subjects With, at High Risk for, or at Low Risk for, Diabetes Mellitus

Naveed Sattar,1 David Preiss,1 Dirk Blom,2 C. Stephen Djedjos,3 Mary Elliott,4 Andrea Pellacani,3 Scott M Wasserman,3 Michael Koren,5 Rury Holman6

1BHF Cardiovascular Research Centre, University of Glasgow, UK; 2Division of Lipidology, Department of Medicine, University of Cape Town, South Africa; 3Amgen Inc., Thousand Oaks, CA, USA; 4Amgen Limited, Cambridge, UK; 5Jacksonville Center for Clinical Research, Jacksonville, FL, USA; 6Diabetes Trials Unit, OCDEM, University of Oxford, UK

European Association for the Study of Diabetes
Stockholm, Sweden
17 September, 2015 – Session OP 27
Results: Median Fasting Plasma Glucose Over One Year*

*48 weeks of open-label treatment

Error bars represent SE of the median

SoC, standard of care; T2DM, type 2 diabetes mellitus
Results: Median HbA$_{1c}$ Over One Year*

*48 weeks of open-label treatment

Error bars represent SE of the median

HbA$_{1c}$, glycated haemoglobin; SoC, standard of care; T2DM, type 2 diabetes mellitus
Conclusion

• In patients with T2DM, or people at high or low risk of T2DM, one year of treatment with evolocumab or alirocumab:
  – markedly reduced LDL-C in all groups
  – showed encouraging safety
  – showed no measurable effect on glycaemic parameters including new-onset T2DM vs SoC alone

• Clinical trials are ongoing to examine the effects of evolocumab on patients with T2DM, and on the incidence of new-onset T2DM
• PCSK9 inhibitors (evolocumab, alirocumab*) to lower LDL-C for patients with heterozygous FH whose LDL-C remains above target despite maximally tolerated statin therapy (*Conditional recommendation, moderate quality evidence).

• We suggest that Evolocumab be added to background therapy in patients with homozygous familial hypercholesterolemia and continued if LDL-C lowering is documented (*Conditional recommendation, moderate quality evidence).
We suggest that PCSK9 inhibitors be considered to lower LDL-C for patients with atherosclerotic cardiovascular disease in those not at LDL-C goal despite maximally tolerated statin +/- ezetimibe therapy. (*Conditional recommendation, moderate quality evidence*).
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>Median LDL-C (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (Parent study)</td>
<td>120 (N=4465)</td>
</tr>
<tr>
<td>4 weeks (OSLER)</td>
<td>120 (N=1258)</td>
</tr>
<tr>
<td>12 weeks</td>
<td>60 (N=4259)</td>
</tr>
<tr>
<td>24 weeks</td>
<td>60 (N=4204)</td>
</tr>
<tr>
<td>36 weeks</td>
<td>40 (N=1243)</td>
</tr>
<tr>
<td>48 weeks</td>
<td>40 (N=3727)</td>
</tr>
</tbody>
</table>

An Academic Research Organization of Brigham and Women’s Hospital and Harvard Medical School
Cardiovascular Outcomes

Composite Endpoint: Death, MI, UA → hosp, coronary revasc, stroke, TIA, or CHF → hosp

- Standard of care alone (N=1489)
  - HR 0.47
  - 95% CI 0.28-0.78
  - P=0.003
  - Cumulative Incidence 2.18%

- Evolocumab plus standard of care (N=2976)
  - Cumulative Incidence 0.95%

Days since Randomization
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 Krempef, 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 Pordy, 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/NEJMoia1501031

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


No. of patients with data available

<table>
<thead>
<tr>
<th>Week</th>
<th>Placebo</th>
<th>Alirocumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>780</td>
<td>1530</td>
</tr>
<tr>
<td>4</td>
<td>754</td>
<td>1473</td>
</tr>
<tr>
<td>8</td>
<td>747</td>
<td>1458</td>
</tr>
<tr>
<td>12</td>
<td>746</td>
<td>1436</td>
</tr>
<tr>
<td>16</td>
<td>716</td>
<td>1412</td>
</tr>
<tr>
<td>24</td>
<td>708</td>
<td>1386</td>
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<tr>
<td>36</td>
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<td>52</td>
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<td>64</td>
<td>659</td>
<td>1324</td>
</tr>
<tr>
<td>78</td>
<td>652</td>
<td>1269</td>
</tr>
</tbody>
</table>

Median LDL-C (mmol/L)

<table>
<thead>
<tr>
<th>Week</th>
<th>Placebo + statin therapy at maximum tolerated dose ± other LLT</th>
<th>Alirocumab + statin therapy at maximum tolerated dose ± other LLT</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>3.08 mmol/L</td>
<td>1.25 mmol/L</td>
</tr>
<tr>
<td>4</td>
<td>3.17 mmol/L</td>
<td>1.50 mmol/L</td>
</tr>
<tr>
<td>8</td>
<td>3.60 mmol/L</td>
<td>1.80 mmol/L</td>
</tr>
<tr>
<td>12</td>
<td>3.00 mmol/L</td>
<td>2.40 mmol/L</td>
</tr>
<tr>
<td>16</td>
<td>2.40 mmol/L</td>
<td>1.80 mmol/L</td>
</tr>
<tr>
<td>24</td>
<td>3.60 mmol/L</td>
<td>2.40 mmol/L</td>
</tr>
<tr>
<td>36</td>
<td>3.00 mmol/L</td>
<td>2.00 mmol/L</td>
</tr>
<tr>
<td>52</td>
<td>3.00 mmol/L</td>
<td>2.00 mmol/L</td>
</tr>
<tr>
<td>64</td>
<td>2.40 mmol/L</td>
<td>1.60 mmol/L</td>
</tr>
<tr>
<td>78</td>
<td>3.00 mmol/L</td>
<td>1.60 mmol/L</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

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

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

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

*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

Ratio of LDL Lowering to CV Event Reduction with PCSK9 Inhibitors Holds True to the “LDL Hypothesis”

PCSK9 in ASCVD
## PCSK9 Outcome Trials

<table>
<thead>
<tr>
<th></th>
<th>Alirocumab</th>
<th>Evolocumab</th>
<th>Bococizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trial</strong></td>
<td>ODYSSEY Outcomes (secondary prevention)</td>
<td>FOURIER (secondary prevention)</td>
<td>SPIRE1 (secondary prevention)</td>
</tr>
<tr>
<td><strong>No of patients</strong></td>
<td>18000</td>
<td>27000</td>
<td>19000</td>
</tr>
<tr>
<td><strong>Dosage</strong></td>
<td>s/c, Q2W</td>
<td>s/c, Q2W or Q4W</td>
<td>s/c, Q2W</td>
</tr>
<tr>
<td><strong>Expected End date</strong></td>
<td>Mar 2018</td>
<td>Q4 2016?</td>
<td>Aug 2017</td>
</tr>
<tr>
<td><strong>Primary endpoint</strong></td>
<td>• CHD death</td>
<td>• CV death</td>
<td>• CV death</td>
</tr>
<tr>
<td></td>
<td>• non-fatal MI</td>
<td>• MI</td>
<td>• non-fatal MI</td>
</tr>
<tr>
<td></td>
<td>• fatal and non-fatal ischemic stroke</td>
<td>• Stroke</td>
<td>• non-fatal stroke</td>
</tr>
<tr>
<td></td>
<td>• high risk UA requiring hospitalization</td>
<td>• hospitalization for UA</td>
<td>• hospitalization for UA needing urgent revascularization</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>Up to Month 64</td>
<td>Up to 5 years</td>
<td>Up to Month 60</td>
</tr>
<tr>
<td><strong>Population</strong></td>
<td>Patients 4 to 52 wks post ACS</td>
<td>History of clinically evident CVD: MI, stroke or symptomatic PAD and ≥1 major RF or ≥ 2 minor RFs</td>
<td>High risk patients</td>
</tr>
<tr>
<td></td>
<td>• LDL-C ≥70 (1.8)</td>
<td>• LDL-C ≥70 (1.8) or</td>
<td>• LDL-C ≥70 (1.8) or</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;100 (2.6) or</td>
<td></td>
</tr>
</tbody>
</table>

73,000 patients
Lipid efficacy of CETP inhibitors (% change from baseline)

<table>
<thead>
<tr>
<th>CETP inhibitor</th>
<th>Dose mg/d</th>
<th>HDL-C %</th>
<th>LDL-C %</th>
<th>TG %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Torcetrapib</td>
<td>600</td>
<td>61</td>
<td>-24</td>
<td>-2</td>
</tr>
<tr>
<td>Dalcetrapib</td>
<td>600</td>
<td>31</td>
<td>-2</td>
<td>-3</td>
</tr>
<tr>
<td>Anacetrapib</td>
<td>100</td>
<td>138</td>
<td>-40</td>
<td>-7</td>
</tr>
<tr>
<td>Evacetrapib</td>
<td>500</td>
<td>129</td>
<td>-36</td>
<td>-17</td>
</tr>
</tbody>
</table>

Adapted from Cannon C, JAMA 306:2154; 2011
Familial Hypercholesterolemia

1- How would you define Familial Hypercholesterolemia (FH)?

2- What are the common genes responsible for FH?

3- What is the prevalence of FH in Canada?

4- What is the risk of CVD in patients with a LDL-C > 5 mmol/L?

5- What is the risk of CVD in patients with a LDL-C > 5 mmol/L and a LDL-receptor mutation?

6- How would you treat a patient with FH?