Fat, Cholesterol and Genetics 2019

Jacques Genest MD

Cardiovascular Health Across the Lifespan
McGill University Health Center

ACC-Rockies 12 March 2019
Disclosure J. Genest MD 2019

Scientific Advisory Board, Consultant
- Pfizer
- Novartis
- AMGEN *
- Cerenis*

Grants, Clinical Trials
- Sanofi/Regeneron *
- Lilly*
- RengenXBio

Laboratory
- We share all our reagents, cells, animal models freely, without expectation of Authorship or remuneration

Expertise
- CADTH, CDR
- INESSS
- EAS, IAS
- DSMB: RE-Energize trial

- Stock ownership: none;
- Off label use: none
Fat, Cholesterol and Genetics 2019… for the uninterested

1. Triglycerides
   - Chylomicronemia
   - Severe hyper Tg
2. Lipoprotein Lp(a)
3. LDL-C, Genetics and Guidelines

HDL-C
Primary and Secondary Lipoprotein Determinants

Recommendations

• Non HDL-C or apoB represent atherogenic lipoproteins
  *Strong Recommendation, High Quality Evidence*
Triglycerides

2-10 mmol/L: moderate
>10 mmol/L: severe
Definition of Hypertriglyceridemia

Figure 1: Redefinition of hypertriglyceridaemic states on the basis of new genetic data

Lancet DM 2014
Chylomicronemia
Triglycerides > 10 mmol/L (885 mg/dL)

Familial Chylomicronemia Syndrome (FCS)
(Type I Hyperlipidemia)
Orphan disease
- Prevalence: 1/10^6
- LPL deficiency
- Rare (GPIHBP1, APOC2, APOA5, LMF1)
- Young age
- Women > Men
- BMI normal
- Risk of pancreatitis

Labs:
- ApoB

Type V Hyperlipidemia
- Prevalence 1/600
- Polygenic
- Obesity, Met syn; BMI ↑
- Diabetes
- HTA
- Alcohol excess
- Risk of ASCVD ↑

Labs:
- ApoB
- Elevated transaminases

Alothman L. Atheroscler 2019
Hypertriglyceridemia
Triglycerides 2-10 mmol/L (170-885 mg/dL)

Type IV Hyperlipidemia
- Prevalence v. common
- Polygenic +
- Obesity, Met syn; BMI ↑
- Diabetes
- HTA
- Alcohol excess
- Risk of ASCVD ↑

Labs:
- Non-HDL-C ↑
- ApoB↑

Chylomicrons/remnants
  VLDL
  IDL
  Lp(a)
  LDL
  HDL

Treatment
- Diet
- Lifestyle
- Weight reduction
- Exercise
- Diabetes control
- Statins
Harmonization of US Cholesterol Guidelines 2018

Grundy SM, et al.
2018 Cholesterol Clinical Practice Guidelines: Executive Summary

2018
AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA
Guideline on the Management of Blood Cholesterol: Executive Summary

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines

Grundy SM. JACC in press
## Recommendations for Hypertriglyceridemia

Referenced studies that support recommendations are summarized in Online Data Supplement 30, 31, and 32.

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
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<tbody>
<tr>
<td>I</td>
<td>B-NR</td>
<td>1. In adults 20 years of age or older with moderate hypertriglyceridemia (fasting or nonfasting triglycerides 175-499 mg/dL [1.9-5.6 mmol/L]), clinicians should address and treat lifestyle factors (obesity and metabolic syndrome), secondary factors (diabetes mellitus, chronic liver or kidney disease and/or nephrotic syndrome, hypothyroidism), and medications that increase triglycerides (S4.5.2-1).</td>
</tr>
<tr>
<td>IIa</td>
<td>B-R</td>
<td>2. In adults 40 to 75 years of age with moderate or severe hypertriglyceridemia and ASCVD risk of 7.5% or higher, it is reasonable to reevaluate ASCVD risk after lifestyle and secondary factors are addressed and to consider a persistently elevated triglyceride level as a factor favoring initiation or intensification of statin therapy (see Section 4.4.2.) (S4.5.2-2–S4.5.2-6).</td>
</tr>
</tbody>
</table>
2. Lp(a)
Lp(a) Excess
- Prevalence: 1:5 ?
- Genetically determined (APOA gene polymorphisms)
- Risk of ASCVD ↑

**Treatment:**
- None accepted
- Statins ineffective
- PCSK9 ↓25-30%
- asRNA
Lipoprotein (a)

LIPOPROTEIN (A)

❖ Lipoprotein (a) [Lp (a)] is a heterogeneous macromolecule associated with early myocardial infarction, coronary artery disease, and stroke.

❖ The structure of Lp (a) consists of an apolipoprotein (a) molecule linked to apolipoprotein B-100 on a lipid-rich LDL core.

❖ The level of Lp(a) is genetically controlled.

❖ Apo (a) has a strong structural homology to plasminogen, and their genes are adjacent on chromosome 6.
Lp(a) and ASCVD Risk

Typical distributions of lipoprotein(a) levels in the general population. These graphs are based on non-fasting fresh serum samples from 3000 men and 3000 women from the Copenhagen General Population Study collected from 2003 through 2004. Green color indicates levels below the 80th percentile, whereas red color indicates levels above the 80th percentile.

Nordesgaard BG et al. Eur Heart J. 2010 Dec;31(23):2844-53
Antisense $APO(a)$ mRNA for elevated Lp(a)

Viney NJ. Lancet 2016; 388: 2239
3. LDL-C

Familial Hypercholesterolemia

- Xanthelasma
- Corneal Arcus
- Xanthomas
- Xanthomas
LDL-C > 5.0 mmol/L

- Prevalence: 0.05
- Familial Hypercholesterolemia
- 0.004
- Risk of ASCVD

**Treatment:**
- Statins
- Ezetimibe
- PCSK9
- PCSK9 asRNA
Meta-analysis of Familial Hypercholesterolemia Prevalence

Prevalence: 0.004 or 1/250

1/125 in Cath Lab patients
Genetic testing for FH – impact of ASCVD risk

CCS Guidelines 2016

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
Grundy SM, et al.
2018 Cholesterol Clinical Practice Guidelines: Executive Summary

Figure 2. Primary Prevention

**Primary Prevention:**
Assess ASCVD Risk in Each Age Group
Emphasize Adherence to Healthy Lifestyle

- **Age 0-19 y**
  - Lifestyle to prevent or reduce ASCVD risk
  - Diagnosis of Familial Hypercholesterolemia → statin

- **Age 20-39 y**
  - Estimate lifetime risk to encourage lifestyle to reduce ASCVD risk
  - Consider statin if family history premature ASCVD and LDL-C ≥160 mg/dL (≥4.1 mmol/L)

- **Age 40-75 y and LDL-C ≥70-<190 mg/dL (≥1.8-<4.9 mmol/L) without diabetes mellitus**
  - 10-year ASCVD risk percent begins risk discussion

- **Age >75 y**
  - Clinical assessment, Risk discussion

- **LDL-C ≥190 mg/dL (≥4.9 mmol/L)**
  - No risk assessment; High-intensity statin (Class I)

- **Diabetes mellitus and age 40-75 y**
  - Moderate-intensity statin (Class I)

- **Diabetes mellitus and age 40-75 y**
  - Risk assessment to consider high-intensity statin (Class IIa)
Top 10 Take-Home Messages to Reduce Risk of Atherosclerotic Cardiovascular Disease Through Cholesterol Management

4. In patients with severe primary hypercholesterolemia (LDL-C level ≥190 mg/dL [≥4.9 mmol/L]), without calculating 10-year ASCVD risk, begin high-intensity statin therapy without calculating 10-year ASCVD risk. If the LDL-C level remains ≥100 mg/dL (≥2.6 mmol/L), adding ezetimibe is reasonable. If the LDL-C level on statin plus ezetimibe remains ≥100 mg/dL (≥2.6 mmol/L) and the patient has multiple factors that increase subsequent risk of ASCVD events, a PCSK9 inhibitor may be considered, although the long-term safety (>3 years) is uncertain and economic value is low at mid-2018 list prices.
Training/Practice
Contemporary Issues in Cardiology Practice

Simplified Canadian Definition for Familial Hypercholesterolemia

Isabelle Ruel, PhD, Diane Brisson, PhD, Sumayah Aljenedil, MD, Zuhier Awan, MD, PhD, Alexis Baass, MD, MSc, Alexandre Bélanger, BSc, Jean Bergeron, MD, MSc, David Bewick, MD, James M. Brophy, MD, PhD, Liam R. Brunham, MD, PhD, Patrick Couture, MD, PhD, Robert Dufour, MD, MSc, Gordon A. Francis, MD, Jiri Frohlich, MD, Claude Gagné, MD, Daniel Gaudet, MD, PhD, Jean C. Grégoire, MD, Milan Gupta, MD, Robert A. Hegele, MD, G.B. John Mancini, MD, Brian W. McCrindle, MD, Jing Pang, PhD, Paolo Raggi, MD, PhD, Jack V. Tu, MD, PhD, Gerald F. Watts, DSc, MD, and Jacques Genest, MD
New Canadian Definition for Familial Hypercholesterolemia

**LDL-C ≥ 5.0 mmol/L (≥ 40 yr)**
* LDL-C ≥ 4.5 mmol/L (18-39 yr); ≥ 4.0 mmol/L (<18 yr)

**DNA Mutation**
** OR **
Tendon xanthomas
** OR **
LDL-C ≥ 8.5 mmol/L

** Definite FH **

1st-degree relative with high LDL-C
** OR **
Proband or 1st-degree relative with ASCVD (<55 yr men; <65 yr women)

** Probable FH **

Severe Hypercholesterolemia

Ruel I. *Can J Cardiol.* 2018;34(9):1210-1214
LDL-C 95% Percentile

Comparison in 95th percentile of LDL between males and females cohort: GDML lab data

Overall, the 95th percentile for the population was 5.0 mmol/L in men and in women

n=3,336,046 patients
Imputation of Baseline LDL Cholesterol Concentration in Patients with Familial Hypercholesterolemia on Statins or Ezetimibe


DOI: 10.1373/clinchem.2017.279422 Published January 2018
Results: baseline vs. imputed baseline LDL-C

- There were no statistically significant differences ($P > 0.002$) observed except for ezetimibe ($P < 0.001$)

- the mean±SEM baseline LDL-C was $6.28±0.06$ mmol/L

- the mean±SEM imputed baseline LDL-C was $6.31±0.07$ mmol/L

- ($P=0.48$)

- There was no difference in response with regard to the patient’s sex
Other initiatives: CardioRisk Calculator

http://www.circl.ubc.ca

iTunes Store CardioRisk Calculator  Free!
DNA Diagnosis for FH MUHC CMDL

[Image of a form with fields for Patient Information, including Name, Birthdate, Name of Referring Physician, and Physician's Specialty.]

[Form content discussing Familial Hypercholesterolemia Panel – Testing Eligibility Criteria Form with criteria for diagnosis and minor criteria.]

- Untreated elevated LDL-cholesterol levels (not due to secondary causes).
- Minimum criteria required for testing to be appropriate are listed below. Please complete and provide any relevant familial and clinical information. If the patient does not fulfill the criteria and you still feel that testing should be performed, please contact the CMDL or www.FHCanada.net to discuss testing of the sample.

Confirm diagnosis (indications and minimum criteria required for testing):

- Untreated LDL-cholesterol levels ≥ 5.0 mmol/L for age 40 yr and over – Specify level: _______ mmol/L
- Untreated LDL-cholesterol levels ≥ 4.5 mmol/L for age between 18 yr and 39 yr – Specify level: _______ mmol/L
- Untreated LDL-cholesterol levels ≥ 4.0 mmol/L for age under 18 yr – Specify level: _______ mmol/L

AND at least one of the following:

Major Criteria (definite FH)
- Tendon xanthomas in proband.
- Known FH-causing DNA mutation in a first-degree relative.
- High LDL-cholesterol in proband (≥ 8.5 mmol/L).

Minor Criteria (probable FH)
- First-degree relative with high LDL-cholesterol (not due to secondary causes).*
- Proband or first-degree relative with early onset atherosclerotic cardiovascular disease (men under 55 yr; women under 65 yr).

*Secondary causes of high LDL-cholesterol should be ruled out (severe or untreated hypothyroidism, nephrotic syndrome, hepatic disease [primary biliary cirrhosis], or medication especially antiretroviral agents).
Society Position Statement

Canadian Cardiovascular Society Position Statement on Familial Hypercholesterolemia: Update 2018

Primary Panel: Liam R. Brunham, MD, PhD, Isabelle Ruel, PhD, Sumayah Aljenedil, MD, Jean-Baptiste Rivière, PhD, Alexis Baass, MD, MSc, Jack V. Tu, MD, PhD, G.B. John Mancini, MD, Paolo Raggi, MD, PhD, Milan Gupta, MD, Patrick Couture, MD, PhD, Glen J. Pearson, PharmD, Jean Bergeron, MD, MSc, Gordon A. Francis, MD, Brian W. McCrindle, MD, MPH, Katherine Morrison, MD, Julie St-Pierre, MD, PhD, Mélanie Henderson, MD, PhD, Robert A. Hegele, MD, (Co-chair), Jacques Genest, MD, (Co-chair), Secondary Panel: Jeannette Goguen, MD, Daniel Gaudet, MD, MSc, Guillaume Paré, MD, MSc, Jacques Romney, MD, Thomas Ransom, MD, MSc, Sophie Bernard, MD, PhD, Pamela Katz, MD, Tisha R. Joy, MD, David Bewick, MD, and James Brophy, MD, PhD
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.
<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Initiate therapy if</th>
<th>Primary Target LDL-C</th>
<th>Alternate Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>High FRS ≥ 20%</td>
<td>Consider treatment in all (Strong, High)</td>
<td>≤ 2 mmol/L or ≥50% decrease in LDL-C (Strong, High)</td>
<td>▪ Apo B ≤ 0.8 g/L  ▪ Non HDL-C ≤ 2.6 mmol/L</td>
</tr>
<tr>
<td>Intermediate FRS 10-19%</td>
<td>LDL-C ≥ 3.5 mmol/L (Strong, Moderate) For LDL-C &lt; 3.5 consider if: Apo B ≥ 1.2 g/L or Non-HDL-C ≥ 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  ▪ Non HDL-C ≤ 2.6 mmol/L</td>
</tr>
<tr>
<td>Low FRS &lt;10%</td>
<td>➢ LDL-C ≥ 5.0 mmol/L ➢ Familial hypercholesterolemia (Strong, Moderate)</td>
<td>≥50% reduction in LDL-C (Strong, Moderate)</td>
<td></td>
</tr>
</tbody>
</table>
LDL-C
• Total cholesterol
• Non-HDL-C
• Apo B
• LDL particle size
• LDL particle number
• Apo A-I / Apo B
• Apo AI / Remnant Chol.
• $\log_{10} Tg/HDL-C$

Note that the clinical trial data used LDL-C as a measurement

Lower is Better $\rightarrow$ Lowest is Best
CHD-free survival in HeFH according to statin Rx

(P < 0.001 for difference)

Nordestgaard B G et al. Eur Heart J 2013;34:3478-3490
Scandinavian Simvastatin Survival Study (1994)

Primary End Point: Total Mortality

-30%

Total mortality $P=.0003$

Secondary End Point: Major Coronary Events

-34%

Major coronary events $P=.00001$

Mean LDL – 4.9 mmol/l

4S=Scandinavian Simvastatin Survival Study Group.
Primary end point of trial was total mortality. Secondary end point was first major coronary event defined as coronary death, nonfatal definite or probable myocardial infarction (MI), silent MI, or resuscitated cardiac arrest.

Primary Endpoint

Hazard ratio 0.85
(95% CI, 0.79-0.92)
P<0.0001
CV Death, MI, or Stroke

<table>
<thead>
<tr>
<th>LDL-C (mM)</th>
<th>Adj HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.5</td>
<td>0.69 (0.56-0.85)</td>
</tr>
<tr>
<td>0.5-1.3</td>
<td>0.75 (0.64-0.86)</td>
</tr>
<tr>
<td>1.3-1.8</td>
<td>0.87 (0.73-1.04)</td>
</tr>
<tr>
<td>1.8-2.6</td>
<td>0.90 (0.78-1.04)</td>
</tr>
<tr>
<td>≥2.6</td>
<td>referent</td>
</tr>
</tbody>
</table>

P = 0.0001
Primary Efficacy Endpoint: MACE

MACE: CHD death, non-fatal MI, ischemic stroke, or unstable angina requiring hospitalization

ARR* 1.6%

HR 0.85
(95% CI 0.78, 0.93)
P=0.0003

*Based on cumulative incidence
## Evaluation of Cognition

<table>
<thead>
<tr>
<th>CANTAB Tests</th>
<th>$P_{\text{trend}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Executive function</td>
<td>0.11</td>
</tr>
<tr>
<td>Working memory</td>
<td>0.61</td>
</tr>
<tr>
<td>Episodic memory</td>
<td>0.61</td>
</tr>
<tr>
<td>Reaction Time</td>
<td>0.47</td>
</tr>
<tr>
<td><strong>Global Score</strong></td>
<td><strong>0.30</strong></td>
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<tr>
<th>Everyday Cognition Self Survey</th>
<th>$P_{\text{trend}}$</th>
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</thead>
<tbody>
<tr>
<td>Memory</td>
<td>0.11</td>
</tr>
<tr>
<td>Executive function</td>
<td>0.12</td>
</tr>
<tr>
<td>Planning</td>
<td>0.27</td>
</tr>
<tr>
<td>Organization</td>
<td>0.98</td>
</tr>
<tr>
<td>Divided attention</td>
<td>0.038</td>
</tr>
<tr>
<td><strong>Total Score</strong></td>
<td><strong>0.017</strong></td>
</tr>
</tbody>
</table>

Better scores at lower achieved LDL-C

Giugliano RP, ESC Congress 2017, Barcelona 8/28/2017
Alirocumab Reduces Total Nonfatal Cardiovascular and Fatal Events in the ODYSSEY OUTCOMES Trial


On behalf of the ODYSSEY OUTCOMES Investigators and Committees

American Heart Association – 2018 Scientific Sessions
November 11, 2018
Alirocumab Reduced Total Events

5,425 total nonfatal CV events or deaths; 77% greater than first events

Among patients with a first nonfatal CV event:

- 82%* of alirocumab patients and 85% of placebo patients were on assigned treatment; all but 4 alirocumab patients and 3 placebo patients continued treatment after first event
- 1,261 (48%) had at least one additional event
Conclusions

Genetic Lipoprotein disorders and ASCVD

1. Hyper Tg is rare and mostly driven by poor lifestyle, diabetes and polygenic predisposition.

2. Elevated Lp(a) is frequent and our best guess is to further lower LDL-C. New therapies are coming...

3. Familial Hypercholesterolemia is more frequent than previously thought. Opportunity for cascade screening

4. PCSK9 inhibition with evolocumab and alirocumab significantly & safely ↓ major cardiovascular events when added to statin therapy
2016 CCS Lipid Guidelines Recommend: PCSK9 inhibitors for ASCVD and FH

PCSK9 INHIBITORS
ASCVD with sub-optimal LDL-C despite taking maximally tolerated statin ± ezetimibe

PCSK9 INHIBITORS
Heterozygous FH with sub-optimal LDL-C despite taking maximally tolerated statin ± ezetimibe

ASCVD, atherosclerotic cardiovascular disease; CCS, Canadian Cardiovascular Society, FH, familial hypercholesterolemia, PCSK9, proprotein convertase subtilisin/kexin type 9
Merci