Cholesterol Summit
CCS Dyslipidemia Guidelines
- 2016 and beyond -

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Disclosures

• **Research grants**: Ionis Pharma, Servier Canada, NIH, CIHR, HSFC

• **Industry relations**: Sanofi, Amgen, Ionis, Servier, Boehringer-Ingelheim
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Learning Objectives

1. To provide an overview of the 2016 CCS dyslipidemia guidelines

2. To understand the utility of lipoprotein measurement in preventive care

3. To highlight the evidence that (1) earlier treatment may be better and (2) that lower LDL-C is better
Outline

• 2016 Dyslipidemia Guidelines – overview

• Primary prevention in 2019 – what’s new
  • Earlier is better!
  • Risk modifiers -> apoB, Lp(a), CAC

• Secondary prevention
  • Lower is better!

• Future guidelines??

• Questions/Discussion
Society Guidelines

2016 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult

Todd J. Anderson, MD, a,* Jean Grégoire, MD, b,* Glen J. Pearson, PharmD, c,* Arden R. Barry, PharmD, d Patrick Couture, MD, e Martin Dawes, MD, f Gordon A. Francis, MD, g Jacques Genest, Jr, MD, h Steven Grover, MD, i Milan Gupta, MD, j,k Robert A. Hegele, MD, l David C. Lau, MD, PhD, m Lawrence A. Leiter, MD, k Eva Lonn, MD, n G.B. John Mancini, MD, f Ruth McPherson, MD, PhD, o Daniel Ngui, MD, f Paul Poirier, MD, PhD, p John L. Sievenpiper, MD, PhD, k James A. Stone, MD, PhD, a George Thanassoulis, MD, h and Richard Ward, MD q
Who should I screen for dyslipidemia?

Which of the following is false:
(a) All men and women starting at 40 years of age
(b) Screening should start earlier in Native Canadians and individuals of South Asian descent
(c) Screening at any age with atherosclerosis
(d) Screening at any age with inflammatory conditions
(e) Screening is not required in women with prior pre-eclampsia
Who should I screen for dyslipidemia?

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(d) Screening at any age with inflammatory conditions
(e) Screening is not required in women with prior pre-eclampsia
Who should I screen?

<table>
<thead>
<tr>
<th>WHO TO SCREEN</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men ≥40 years of age; women ≥40 years of age (or postmenopausal)</strong></td>
</tr>
<tr>
<td>Consider earlier in ethnic groups at increased risk such as South Asian or First Nations individuals</td>
</tr>
</tbody>
</table>

| All patients with the following conditions regardless of age: |
| - Clinical evidence of atherosclerosis |
| - Abdominal aortic aneurysm |
| - Diabetes |
| - Arterial hypertension |
| - Current cigarette smoking |
| - Stigmata of dyslipidemia (arcus cornea, xanthelasma or xanthoma) |
| - Family history of premature CVD* |
| - Family history of dyslipidemia |
| - Chronic kidney disease |
| - Obesity (BMI ≥30 kg/m²) |
| - Inflammatory bowel disease |
| - HIV infection |
| - Erectile dysfunction |
| - Chronic obstructive pulmonary disease |
| - Hypertensive diseases of pregnancy |
What tests do I need?

When performing a CV risk assessment what are the standard tests required?

(a) Fasting Standard lipid panel (± apoB)
(b) Glucose
(c) eGFR (± urine albumin/Cr ratio)
(d) All of the above
(e) None of the above
What tests do I need?

When performing a CV risk assessment what are the standard tests required?

(a) Fasting Standard lipid panel (± apoB)
(b) Glucose
(c) eGFR (± urine albumin/Cr ratio)
(d) All of the above
(e) None of the above
How to screen?

For all:
- History and physical examination
- Standard lipid panel (TC, LDL-C, HDL-C, TG)
- Non-HDL-C (will be calculated from profile)
- Glucose
- eGFR

Optional:
- ApoB
- Urine albumin:creatinine ratio
  (if eGFR <60 mL/min/1.73m², hypertension or diabetes)

NON-FASTING LIPID TESTING IS ACCEPTABLE
Who requires treatment?

In which of the following patients is statin treatment generally recommended?

(a) 47 M with prior MI
(b) 54 M with incidental abdominal aorta measuring 3.2 cm
(c) 62 F with diabetes
(d) 52 F with moderate chronic kidney disease (eGFR < 60 ml/min/1.73 m²)
(e) 28 F with LDL-C 6.1 mmol/L and 2 first degree relatives with premature MI
(f) All of the above
Who requires treatment?

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(a) 47 M with prior MI
(b) 54 M with incidental abdominal aorta measuring 3.2 cm
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(d) 52 F with moderate chronic kidney disease (eGFR < 60 ml/min/1.73 m²)
(e) 28 F with LDL-C 6.1 mmol/L and 2 first degree relatives with premature MI
(f) **All of the above**
Statin-indicated conditions

**CLINICAL ATHEROSCLEROSIS**
- Myocardial infarction, acute coronary syndromes
- Stable angina, documented coronary disease by angiography (>10% stenoses)
- Stroke, TIA, documented carotid disease
- Peripheral artery disease, claudication and/or ABI < 0.9

**ABDOMINAL AORTIC ANEURYSM**
- Abdominal aorta > 3.0 cm or
- Previous aneurysm surgery

**DIABETES MELLITUS**
- ≥ 40 years of age or
- > 15 years duration and age ≥ 30 years or
- Microvascular complications

**CHRONIC KIDNEY DISEASE**
- > 3 months duration and
- ACR > 3.0 mg/mmol or
- eGFR < 60 ml/min/1.73m²

**LDL-C ≥ 5.0 MMOL/L**
- LDL-C ≥ 5.0 mmol/L or
- Document familial hypercholesterolemia
- Excluded 2nd causes
What LDL-C should I aim for?

Adequacy of statin therapy is determined by:
(a) LDL-C < 2.0 mmol/L
(b) apoB < 0.8 mg/L
(c) Non-HDL-C < 2.6 mmol/L
(d) LDL-C decrease by > 50%
(e) Any of the above
What LDL-C should I aim for?

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(a) LDL-C < 2.0 mmol/L
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(d) LDL-C decrease by > 50%
(e) Any of the above
### Treatment targets

<table>
<thead>
<tr>
<th>Category</th>
<th>Consider initiating pharmacotherapy if</th>
<th>Target</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary prevention</td>
<td>High FRS (≥ 20%)</td>
<td>LDL-C &lt; 2.0 mmol/L or &gt; 50% ↓</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>All</td>
<td>Or ApoB &lt; 0.8 g/L</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Intermediate FRS (10%-19%)</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>LDL-C ≥ 3.5 mmol/L</td>
<td>Or non-HDL-C ≥ 4.3 mmol/L</td>
<td></td>
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<tr>
<td></td>
<td>or ApoB ≥ 1.2 g/L</td>
<td>Or non-HDL-C &lt; 2.6 mmol/L</td>
<td></td>
</tr>
<tr>
<td></td>
<td>or men ≥ 50 and women ≥ 60 years and 1 additional CVD RF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statin-induced conditions</td>
<td>Clinical atherosclerosis</td>
<td></td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>Abdominal aortic aneurysm</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diabetes mellitus</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Age ≥ 40 years</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>15-Year duration for age ≥ 30 years (DM 1)</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Microvascular disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chronic kidney disease (age ≥ 50 years)</td>
<td>eGFR &lt; 60 ml/min/1.73 m² or ACR &gt; 3 mg/mmol</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LDL-C ≥ 5.0 mmol/L</td>
<td>&gt; 50% ↓ in LDL-C</td>
<td></td>
</tr>
</tbody>
</table>

ACR, albumin:creatinine ratio; ACS, acute coronary syndrome; apoB, apolipoprotein B; CVD, cardiovascular disease; DM 1, type 1 diabetes mellitus; eGFR, estimated glomerular filtration rate; FRS, modified Framingham Risk Score; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NNT, number needed to treat; RF, risk factor.

* Statins indicated as initial therapy.

† Consider LDL-C < 1.8 mmol/L for subjects with ACS within past 3 months.
2016 CCS dyslipidemia summary

**RISK ASSESSMENT, STRATIFICATION & TREATMENT CONSIDERATION**

Calculate risk (unless statin-indicated condition) using the Framingham Risk Score (FRS) or Cardiovascular Life Expectancy Model (CLEM). 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%
    - LDL-C ≥3.5 mmol/L
    - 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

- **Statin-indicated Conditions**
  - Clinical atherosclerosis
  - Abdominal aortic aneurysm
  - Most diabetes including:
    - Age ≥40 y
    - Age ≥30 y & 15 y duration (type 1 DM)
  - Microvascular disease
  - Chronic kidney disease
  - LDL-C ≥5 mmol/L (genetic dyslipidemia)

**Health Behavioural Modifications**

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

**Initiate Statin Treatment: Treat to Target Approach**

- Confirm adherence and barriers to use
- LDL-C <2.0 mmol/L or ≥50% reduction or
- apoB <0.8 g/L or non-HDL-C <2.6 mmol/L
- LDL-C ≥50% reduction

**YES**

Target achieved on maximally tolerated dose?

**NO**

**NO ADD-ON**

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

- ADD-ON
  - Ezetimibe as 1st line (BAS as alternative)

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

- ADD-ON
  - Ezetimibe (or BAS) or PCSK9 inhibitors

**Monitor**

- Response to statin Rx
- Health behaviours
What’s new in 2019 and beyond?
Case 1: Mr. Hy Risc
Mr. Hy. Risc

44 years old, non-smoker

- BMI = 26 kg/m²
- BP 135/80 mm Hg
- No diabetes
- Total cholesterol = 5.9 mmol/L
- HDL cholesterol = 1.0 mmol/L
- TG = 1.7
- LDL-C = 4.1
New for 2019
Earlier LDL treatment is better
Mr. Hy Risc

Estimation of 10-year risk of total cardiovascular disease in men (Framingham Heart Study)

<table>
<thead>
<tr>
<th>POINTS</th>
<th>Age</th>
<th>HDL-C</th>
<th>Total Cholesterol</th>
<th>SBP Not Treated</th>
<th>SBP Treated</th>
<th>Smoker</th>
<th>Diabetic</th>
</tr>
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<tbody>
<tr>
<td>-2</td>
<td>44</td>
<td>&gt;1.6</td>
<td>&lt;120</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-1</td>
<td>44</td>
<td>1.3-1.6</td>
<td>&lt;120-129</td>
<td>&lt;120</td>
<td>NO</td>
<td>NO</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>44</td>
<td>1.3-1.6</td>
<td>&lt;120-129</td>
<td>130-139</td>
<td></td>
<td></td>
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<tr>
<td>1</td>
<td>44</td>
<td>&gt;1.6</td>
<td>&lt;120-129</td>
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<tr>
<td>2</td>
<td>44</td>
<td>&gt;1.6</td>
<td>&lt;120-129</td>
<td>130-139</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>44</td>
<td>&gt;1.6</td>
<td>&lt;120-129</td>
<td>130-139</td>
<td></td>
<td></td>
<td>YES</td>
</tr>
<tr>
<td>4</td>
<td>44</td>
<td>&gt;1.6</td>
<td>&lt;120-129</td>
<td>130-139</td>
<td></td>
<td></td>
<td>YES</td>
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44 M

BMI = 26 kg/m²
BP 135/80 mm Hg
No diabetes

Total cholesterol = 5.9 mmol/L
HDL cholesterol = 1.0 mmol/L
TG = 1.7

What’s his risk?
Mr. Hy Risc

Estimation of 10-year risk of total cardiovascular disease in men (Framingham Heart Study)

Points | Age | HDL-C | Total Cholesterol | SBP Not Treated | SBP Treated | Smoker | Diabetic |
--- | --- | --- | --- | --- | --- | --- | --- |
-2 | 1-3 | <1.6 | <120 | | | | |
-1 | 4-5 | 1.5-1.6 | | | | | |
0 | 5-6 | 22-34 | 1.2-1.3 | 120-129 | <120 | NO | NO |
1 | 7-8 | 35-39 | <1.2 | 120-129 | <120 | NO | NO |
2 | 9-10 | 40-49 | 1.2-1.6 | 120-129 | <120 | NO | NO |
3 | 11-12 | 50-59 | 1.2-1.7 | 120-129 | <120 | NO | NO |
4 | 13-14 | 60-69 | 1.2-1.8 | 120-129 | <120 | NO | NO |
5 | 15-16 | 70-79 | 1.2-1.9 | 120-129 | <120 | NO | NO |
6 | 17-18 | 80-89 | 1.2-2.0 | 120-129 | <120 | NO | NO |
7 | 19-20 | 90-99 | 1.2-2.1 | 120-129 | <120 | NO | NO |
8 | 21-22 | 100-109 | 1.2-2.2 | 120-129 | <120 | NO | NO |
9 | 23-24 | 110-119 | 1.2-2.3 | 120-129 | <120 | NO | NO |
10 | 25-26 | 120-129 | 1.2-2.4 | 120-129 | <120 | NO | NO |
11 | 27-28 | 130-139 | 1.2-2.5 | 120-129 | <120 | NO | NO |
12 | 29-30 | 140-149 | 1.2-2.6 | 120-129 | <120 | NO | NO |
13 | 31-32 | 150-159 | 1.2-2.7 | 120-129 | <120 | NO | NO |
14 | 33-34 | 160-169 | 1.2-2.8 | 120-129 | <120 | NO | NO |
15 | 35-36 | 170-179 | 1.2-2.9 | 120-129 | <120 | NO | NO |

Adapted from reference 33, HDL-C High-density lipoprotein cholesterol; SBP Systolic blood pressure.

44 M

BMI = 26 kg/m²
BP 135/80 mm Hg
No diabetes

Total cholesterol = 5.9 mmol/L
HDL cholesterol = 1.0 mmol/L
TG = 1.7

What’s his risk?

10 pts = 9% risk of CV event in 10 years (low risk)
What would you do?

a) Congratulations! You’re at low risk.
b) You need to work on your lifestyle
c) You need to start on ECASA
d) You need to start on statins
e) You need to start on blood pressure medications
What would you do?

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b) You need to work on your lifestyle
c) You need to start on ECASA
d) You need to start on statins
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Low Short-term but High Lifetime Risk
What to do?

• A large proportion have **low short-term BUT high lifetime risk**
  • Counselling
  • Focus on lifestyle change
    • Target optimal risk factors
  • Consider EARLY preventative treatment?
Earlier is better

What % of myocardial infarctions occur before the age of 65 years?

a) 65% in men and 50% in women
b) 50% in men and 33% in women
c) 33% in men and 20% in women
d) 15% in men and 10% in women
e) 5% in men and 2% in women
Earlier is better

Figure. Event Rates, Population at Risk, and Event Numbers by Sex and Age Groups


Sniderman et al JAMA-Cardiology 2017
Earlier is better

What % of myocardial infarctions occur before the age of 65 years?

a) 65% in men and 50% in women
b) 50% in men and 33% in women
c) 33% in men and 20% in women
d) 15% in men and 10% in women
e) 5% in men and 2% in women
Earlier is better: Epidemiologic evidence
LDL is worse when young

Prospective Studies Collaboration Lancet 2007
Earlier is better: Genetic evidence
Life-long lipids and Risk of CHD

Cohen JC et al, NEJM 2008
Life-long lipids and Risk of CHD

88% risk reduction in CHD

Cohen JC et al, NEJM 2008
Earlier is better: RCT evidence
Cholesterol Treatment Trialists

CTT collaboration *Lancet* 2010
How much benefit?

Epidemiology and Prevention

Individualized Statin Benefit for Determining Statin Eligibility in the Primary Prevention of Cardiovascular Disease

George Thanassoulis, MD, MSc; Ken Williams, MSc, PStat; Kathleen Kimler Altopelli, MS; Michael J. Pencina, PhD; Christopher P. Cannon, MD; Allan D. Sniderman, MD

Circulation 2016
How much benefit?

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• 9% risk at 10-year
• Atorvastatin 40 mg -> LDL-C from 4.1 to 2.5 mmol/L
• $\text{ARR} = 9\% \times (0.66)^{1.6} = 4.6\%$
• $\text{NNT} = 1/\text{ARR} = 21.7$

Circulation 2016
How much benefit?

MUHC-Duke Statin Benefit Calculator

Age
50

Ethnicity
--- Select ---

Sex
Male
Female

Blood Pressure
120 / 80

Are you currently being treated for hypertension?
Yes
No

Do you currently smoke?
Yes
No

Are you diabetic?
Yes
No

Cholesterol:
Total

LDL-C

HDL-C

Units
mmol/L

Are you currently taking statins?
Yes
No

https://github.com/tgetgood/statin-benefit
How much benefit?

• What is the NNT for 30 years?
How much benefit?

A Long-term Benefit Approach vs Standard Risk-Based Approaches for Statin Eligibility in Primary Prevention

George Thanassoulis, MD, MSc, FRCPC; Allan D. Sniderman, MD; Michael J. Pencina, PhD

CONCLUSIONS AND RELEVANCE  A long-term benefit approach to statin eligibility identifies nearly 1 in 6 individuals as having a high degree of expected long-term benefit of statins, with a number needed to treat of less than 7. This approach identifies younger individuals with higher LDL-C levels who would not be currently recommended for treatment and may provide a more optimal approach for determining statin eligibility in primary prevention.
What about apolipoprotein B?
Which of the following is true?

a) Each atherogenic particle contains 1 apoB molecule
b) Risk tracks apoB more closely than LDL-C
c) Differences in apoB and LDL-C occur in ~15% of individuals
d) Benefit of therapy is best predicted by change in apoB
e) All of the above
ApoB

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e) All of the above
Apolipoprotein B

- apoB measures the number of LDL particles
High apoB = danger
Risk tracks ApoB - always

Framingham Offspring Study

- LDL<130, ApoB<100
- LDL≥130, ApoB<100
- LDL<130, ApoB≥100
- LDL≥130, ApoB≥100
Benefit also tracks ApoB - always

Figure 4. Association of Genetic Variants With Naturally Occurring Discordance Between Changes in Concentrations of LDL-C and apoB and the Risk of CHD Among CARDioGRAMplusC4D Consortium Participants

<table>
<thead>
<tr>
<th></th>
<th>Effect per 10-mg/dL lower LDL-C</th>
<th>Effect per 10-mg/dL lower apoB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discordant variants score (21 variants)</td>
<td>0.916 (0.890-0.943)</td>
<td>0.772 (0.701-0.844)</td>
</tr>
<tr>
<td>LDL-C score (36 variants)</td>
<td>0.831 (0.816-0.847)</td>
<td>0.788 (0.769-0.807)</td>
</tr>
</tbody>
</table>

P Value for Difference | MR-Egger OR (95% CI)
-----------------------|----------------------
2.9 x 10^-8            | 0.909 (0.826-0.992)  |
                      | 0.839 (0.811-0.867)  |
                      | 0.747 (0.585-0.967)  |
                      | 0.785 (0.751-0.821)  |

Analyses are based on summary data from up to 62,240 participants with coronary heart disease (CHD) and 127,299 control participants from the Coronary Artery Disease Genome Wide Replication and Meta-analysis plus the Coronary Artery Disease Genetics (CARDioGRAMplusC4D) Consortium. Effect sizes are standardized per 10-mg/dL lower level of low-density lipoprotein cholesterol (LDL-C) or 10-mg/dL lower level of apolipoprotein B (apoB). MR-Egger regression estimates are presented for sensitivity analyses. Data markers indicate point estimates of effect; error bars, 95% confidence intervals.

Ference BA et al JAMA 2017
Benefit also tracks ApoB - always

Ference BA et al *JAMA* 2018
Mr. Hy. Risc

- 44 years old, non-smoker
- BMI = 26 kg/m²
- BP 135/80 mm Hg
- No diabetes
- Total cholesterol = 5.9 mmol/L
- HDL cholesterol = 1.2 mmol/L
- TG = 1.7
- LDL-C = 4.1
Mr. Hy. Risc

• 44 years old, non-smoker
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• BP 135/80 mm Hg
• No diabetes
• Total cholesterol = 5.9 mmol/L
• HDL cholesterol = 1.2 mmol/L
• TG = 1.7
• LDL-C = 4.1
• Apo B 1.4
What about Lipoprotein(a)?
Elevated Lp(a) is a likely cause of the following:

a) Myocardial infarction (frequently premature)
b) Stroke (including in children)
c) Aortic stenosis
d) Recurrent ACS
e) All of the above
Lp(a)

Elevated Lp(a) is a likely cause of the following:

  a) Myocardial infarction (frequently premature)
  b) Stroke (including in children)
  c) Aortic stenosis
  d) Recurrent ACS
  e) All of the above
What is Lp(a)?

• ApoB+apo(a) $\rightarrow$ Lp(a)

• Lp(a) levels are almost entirely mediated by genetics

• Highly atherogenic, pro-calcific

• Most common genetic dyslipidemia
  • 6 million Canadians have high Lp(a)
Lp(a) is atherogenic
Lp(a) and recurrent events

Figure 3
Meta-Analysis of Published Studies of Lp(a) in Secondary Prevention
Lp(a) and aortic stenosis
Lp(a) and AS progression

High Lp(a) associated with faster disease progression and increased incidence of AVR

Capoulade R J Am Coll Cardiol. 2015
Who should I screen for Lp(a)?

(i) premature CVD,
(ii) familial hypercholesterolaemia,
(iii) a family history of premature CVD and/or elevated Lp(a),
(iv) recurrent CVD despite statin treatment,
(v) ≥3% 10-year risk of fatal CVD according to the European guidelines,
(vi) ≥10% 10-year risk of fatal and/or non-fatal CHD according to the US guidelines.
Who should I screen for Lp(a)?

(i) premature CVD,
(ii) familial hypercholesterolaemia,
(iii) a family history of premature CVD and/or elevated Lp(a),
(iv) recurrent CVD despite statin treatment,
(v) \( \geq 3\% \) 10-year risk of fatal CVD according to the European guidelines,\(^{35}\)
and
(vi) \( \geq 10\% \) 10-year risk of fatal and/or non-fatal CHD according to the US guidelines\(^{36}\)

vii. Premature aortic valve calcification or aortic stenosis
Management

• Individuals with high Lp(a)
  • Lifestyle change
  • Treat LDL-C (and all risk factors) much more aggressively
  • Consider ECASA
  • Consider extended-release niacin
Future therapy

Antisense therapy targeting apolipoprotein(a): a randomised, double-blind, placebo-controlled phase 1 study

Sotirios Tsimikas, Nicholas J Viney, Steven G Hughes, Walter Singleton, Mark J Graham, Brenda F Baker, Jennifer L Burkey, Qingqing Yang, Santica M Marcovina, Richard S Geary, Rosanne M Crooke, Joseph L Witztum
Case 2: Mr. Tremblay
Case: Mr. Tremblay

- 54 yrs old, non-smoker, 1 month post-ACS, stented pLAD and pCirc
- BMI = 27 kg/m^2
- BP 130/80
- No diabetes
- TC = 4.2 mmol/L
- HDL-C = 1.2 mmol/L
- TG = 1.7 mmol/L
- LDL-C = 2.2 mmol/L (on atorvastatin 80 mg daily)
Question

What % of post-ACS patients achieve CCS guideline based LDL-C targets in Canada?

a) 60-80%

b) 40-60%

c) 20-40%

d) 0-20%
Question

What % of post-ACS patients achieve CCS guideline based LDL-C targets in Canada?

a) 60-80%
b) 40-60%
c) 20-40%
d) 0-20%
Case: Mr. Tremblay

What would you do?

a) Cardiac rehabilitation for improvement in lifestyle and exercise
b) Switch atorvastatin 80 mg to rosuvastatin 40 mg
c) Add ezetimibe
d) Add niacin
e) Add PCSK9i
### Lifestyle, diet and exercise

<table>
<thead>
<tr>
<th>Diet Type</th>
<th>Effect on CVE</th>
<th>Effect on LDL-C</th>
<th>Effect on HDL-C</th>
<th>Effect on TG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mediterranean diet</td>
<td>↓ 28-30 %</td>
<td>Ideal efficacy</td>
<td>↓ 11 %</td>
<td>↓ 28-30 %</td>
</tr>
<tr>
<td>Portfolio diet</td>
<td>↓ 11 %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DASH diet (Dietary Approaches to Stop Hypertension)</td>
<td>↓ 20 %</td>
<td></td>
<td></td>
<td>↓ LDL-C by 3 %</td>
</tr>
</tbody>
</table>

**Weight loss and reduction in abdominal obesity**

5-10 % reduction in BMI

<table>
<thead>
<tr>
<th>Effect on BMI</th>
<th>Effect on WC</th>
<th>Effect on LDL-C</th>
<th>Effect on HDL-C</th>
<th>Effect on TG</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ 6 %</td>
<td>↓ 9% for a ~5 unit change</td>
<td>↓ 11%</td>
<td>↑ 5-10%</td>
<td>↓ 32%</td>
</tr>
<tr>
<td>↓ 12.6 cm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Physical exercise**

30-60 min/d moderate to high intensity

<table>
<thead>
<tr>
<th>Effect on CVE</th>
<th>Effect on HDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ 20-30%</td>
<td>↑ 5-10%</td>
</tr>
</tbody>
</table>

**Smoking cessation**

<table>
<thead>
<tr>
<th>Effect on CVE</th>
<th>Effect on HDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ 52%</td>
<td>↑ 7-12%</td>
</tr>
</tbody>
</table>

**Combined lifestyle changes**

<table>
<thead>
<tr>
<th>Effect on CVE (and mortality)</th>
<th>Effect on CVE</th>
<th>Effect on HDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ 75%</td>
<td></td>
<td>↑ 7-12%</td>
</tr>
</tbody>
</table>

**CCS Dyslipidemia Guidelines 2016**
## Lifestyle, diet and exercise

<table>
<thead>
<tr>
<th>Diet/Exercise</th>
<th>Effect on CVE (% reduction)</th>
<th>Effect on LDL-C (% reduction)</th>
<th>Effect on HDL-C (% increase)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mediterranean diet</td>
<td>↓ 28-30% (ARR 0.6-1% [NNT = 100-167])</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Portfolio diet</td>
<td>↓ 11%</td>
<td>Ideal efficacy ↓ LDL-C by 21-29% (comparable to lovastatine 20 mg)</td>
<td>↑ HDL-C by 5-10%</td>
</tr>
<tr>
<td>DASH diet ((\text{Dietary Approaches to Stop Hypertension})^{97,98})</td>
<td>↓ 20%</td>
<td>Ideal efficacy ↓ LDL-C by 21-29% (comparable to lovastatine 20 mg)</td>
<td>↑ HDL-C by 7-12%</td>
</tr>
</tbody>
</table>

### Physical exercise
- **30-60 min/d moderate to high intensity**
- ↓ CVE 20-30%  
  ↑ HDL-C by 5-10%

### Smoking cessation
- ↓ CVE by 52%  
  ↑ HDL-C by 7-12%

### Combined lifestyle changes
- ↓ CVE (and mortality) by 75%

---

Refer all patients to Cardiac Rehabilitation Programs!!!

---

CCS Dyslipidemia Guidelines 2016

---
# Lipid-lowering post-ACS

<table>
<thead>
<tr>
<th></th>
<th>LDL lowering</th>
<th>Other effects</th>
<th>Results</th>
<th>Side effects</th>
</tr>
</thead>
</table>
| **Niacin** | 20%         | ↑ HDL 30%  
↓ TG 40%   | No benefit   | Vasomotor symptoms, itchiness, nausea |
| **Fibrates** | 5-20%       | ↑ HDL (10-50%  
↓ TG (20-50%) | No benefit   | Nausea, muscle pains             |
| **Bile acid sequestrants** | 15-20%   | Limited data | IMROVE-IT MACE reduction 6.5% | GI intolerance, myalgias          |
| **ezetimibe** | 15-25% | | | Muscle pains |
Case: Mr. Tremblay

What would you do?

a) Cardiac rehabilitation for improvement in lifestyle and exercise
b) Switch atorvastatin 80 mg to rosuvastatin 40 mg
c) Add ezetimibe
d) Add niacin
e) Add PCSK9i
Very low LDL-C: Is there a benefit?
Very low LDL-C: Is there a benefit?
Very low LDL-C: Is there a benefit?

Efficacy and Safety of Further Lowering of Low-Density Lipoprotein Cholesterol in Patients Starting With Very Low Levels
A Meta-analysis

Marc S. Sabatine, MD, MPH; Stephen D. Wiviott, MD; KyungAh Im, PhD; Sabina A. Murphy, MPH; Robert P. Giugliano, MD, SM
Very low LDL-C: Is there a benefit?

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. of Participants</th>
<th>Type of Intervention</th>
<th>Drug</th>
<th>Achieved LDL-C, mmol/L</th>
<th>Median Duration of Follow-up, y</th>
<th>Overall No. of Major Vascular Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTTC (&lt;2 mmol/L)</td>
<td>NR</td>
<td>HMGCR inhibitor (statin)</td>
<td>Various</td>
<td>1.7&lt;sup&gt;a&lt;/sup&gt;</td>
<td>NR</td>
<td>4.9&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>IMPROVE-IT</td>
<td>18 144</td>
<td>NPC1L1 inhibitor</td>
<td>Ezetimibe</td>
<td>1.8&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.4</td>
<td>6.0</td>
</tr>
<tr>
<td>FOURIER (&lt;1.8 mmol/L)</td>
<td>2034</td>
<td>PCSK9 inhibitor</td>
<td>Evolocumab</td>
<td>1.7&lt;sup&gt;d&lt;/sup&gt;</td>
<td>0.5</td>
<td>2.1</td>
</tr>
<tr>
<td>REVEAL</td>
<td>30 449</td>
<td>CETP inhibitor</td>
<td>Anacetrapib</td>
<td>1.6&lt;sup&gt;e&lt;/sup&gt;</td>
<td>1.4</td>
<td>4.1</td>
</tr>
</tbody>
</table>
Very low LDL-C: Is there a benefit?

**Meta-analysis of effect of 1-mmol/L LDL-C lowering on the risk of major vascular events**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Events, % per annum</th>
<th>LDL-C Lowering Better</th>
<th>LDL-C Lowering Worse</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Experimental Arm</td>
<td>Control Arm</td>
<td>RR (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Statins</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTTC &lt;2 mmol/L subgroup</td>
<td>910 (4.1)</td>
<td>1012 (4.6)</td>
<td>0.78 (0.65-0.94)</td>
<td></td>
</tr>
<tr>
<td>Nonstatin LDL-C lowering</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IMPROVE-IT</td>
<td>2455 (4.5)</td>
<td>2649 (4.9)</td>
<td>0.79 (0.67-0.93)</td>
<td>P &lt; .001</td>
</tr>
<tr>
<td>FOURIER &lt;1.8 mmol/L subgroup</td>
<td>81 (3.7)</td>
<td>103 (4.9)</td>
<td>0.80 (0.61-1.04)</td>
<td></td>
</tr>
<tr>
<td>REVEAL</td>
<td>2068 (3.3)</td>
<td>2214 (3.5)</td>
<td>0.77 (0.63-0.96)</td>
<td></td>
</tr>
<tr>
<td>Summary</td>
<td>4604</td>
<td>4966</td>
<td>0.79 (0.70-0.88)</td>
<td>P &lt; .001</td>
</tr>
<tr>
<td>Overall summary</td>
<td>5514</td>
<td>5978</td>
<td>0.79 (0.71-0.87)</td>
<td>P &lt; .001</td>
</tr>
</tbody>
</table>
Very low LDL-C: Is there a benefit?
Very low LDL-C: Is there HARM?
Very low LDL-C: Is there HARM?

Table 2. Safety Outcomes in Trials of Nonstatin Therapy

<table>
<thead>
<tr>
<th>Safety Outcome</th>
<th>Patients With Event, No.</th>
<th>Meta-analysis Data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Experimental Arm</td>
<td>Control Arm</td>
</tr>
<tr>
<td>Any serious adverse event</td>
<td>12,809</td>
<td>12,836</td>
</tr>
<tr>
<td>Myalgias or myopathy</td>
<td>116</td>
<td>135</td>
</tr>
<tr>
<td>Aminotransferase elevation</td>
<td>488</td>
<td>510</td>
</tr>
<tr>
<td>New-onset diabetes</td>
<td>1,272</td>
<td>1,320</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>132</td>
<td>118</td>
</tr>
<tr>
<td>Cancer</td>
<td>1,747</td>
<td>1,715</td>
</tr>
</tbody>
</table>
Case: Mr. Tremblay

- 54 yrs old, non-smoker, 1 month post-ACS, stented pLAD + pCIRC

- BMI = 27 kg/m²
- BP 130/80
- No diabetes
- TC = 4.0 mmol/L
- HDL-C = 1.2 mmol/L
- TG = 1.7 mmol/L
- LDL-C = 2.0 mmol/L (on atorvastatin 80 mg + ezetimibe daily)
Case: Mr. Tremblay

• What do you do?

  a) Nothing
  b) Add niacin
  c) Add fibrate
  d) Add PCSK9i
  e) Add omega-3 fatty acids
Case: Mr. Tremblay

- What do you do?
  a) Nothing
  b) Add niacin
  c) Add fibrate
  d) Add PCSK9i
  e) Add omega-3 fatty acids
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
The ODYSSEY OUTCOMES Trial: Topline Results

Alirocumab in Patients After Acute Coronary Syndrome

Gregory G. Schwartz, Michael Szarek, Deepak L. Bhatt, Vera Bittner, Rafael Diaz, Jay Edelberg, Shaun G. Goodman, Corinne Hanotin, Robert Harrington, J. Wouter Jukema, Guillaume Lecorps, Angèle Moryusef, Robert Pordy, Matthew Roe, Harvey D. White, Andreas Zeiher,

Ph. Gabriel Steg

On behalf of the ODYSSEY OUTCOMES Investigators and Committees

American College of Cardiology – 67th Scientific Sessions
March 10, 2018

ClinicalTrials.gov: NCT01663402
Conclusions

• In primary prevention:
  • Earlier is better, especially when LDL-C is high
  • Consider using risk modifiers: apoB, Lp(a)

• In secondary prevention:
  • Lower is better, especially in high risk patients → < 1.8 mmol/L
  • Aggressive lowering of LDL-C (and/or apoB) is recommended often requiring ezetimibe ± PCSK9i

• Future guidelines:
  • Benefit vs risk-based approach
  • Treatment targets vs intensification thresholds?
  • How low should we go?
Questions
## Types de résultats CV

<table>
<thead>
<tr>
<th>Paramètre d’évaluation</th>
<th>Évolocumab (N = 13 784)</th>
<th>Placebo (N = 13 780)</th>
<th>RRI (IC à 95 %)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Taux de Kaplan-Meier après 3 ans</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Décès CV, IM ou AVC</td>
<td>7,9</td>
<td>9,9</td>
<td>0,80 (0,73-0,88)</td>
</tr>
<tr>
<td>Décès CV</td>
<td>2,5</td>
<td>2,4</td>
<td>1,05 (0,88-1,25)</td>
</tr>
<tr>
<td>Décès causé par un IM aigü</td>
<td>0,26</td>
<td>0,32</td>
<td>0,84 (0,49-1,42)</td>
</tr>
<tr>
<td>Décès causé par un AVC</td>
<td>0,29</td>
<td>0,30</td>
<td>0,94 (0,58-1,54)</td>
</tr>
<tr>
<td>Autre décès CV</td>
<td>1,9</td>
<td>1,8</td>
<td>1,10 (0,90-1,35)</td>
</tr>
<tr>
<td>IM</td>
<td>4,4</td>
<td>6,3</td>
<td>0,73 (0,65-0,82)</td>
</tr>
<tr>
<td>AVC</td>
<td>2,2</td>
<td>2,6</td>
<td>0,79 (0,66-0,95)</td>
</tr>
</tbody>
</table>
Réduction plus importante du C-LDL et décès CV

Aucun avantage manifeste sur les décès CV

<table>
<thead>
<tr>
<th>Essai</th>
<th>Année</th>
<th>Groupe recevant le traitement le plus intense</th>
<th>Groupe recevant le traitement le moins intense</th>
<th>RRI (IC à 95 %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROVE-IT TIMI 22</td>
<td>2004</td>
<td>27</td>
<td>36</td>
<td>0,74 (0,45-1,22)</td>
</tr>
<tr>
<td>A2Z</td>
<td>2004</td>
<td>86</td>
<td>111</td>
<td>0,76 (0,57-1,01)</td>
</tr>
<tr>
<td>TNT</td>
<td>2005</td>
<td>101</td>
<td>127</td>
<td>0,80 (0,61-1,03)</td>
</tr>
<tr>
<td>IDEAL</td>
<td>2005</td>
<td>223</td>
<td>218</td>
<td>1,03 (0,85-1,24)</td>
</tr>
<tr>
<td>SEARCH</td>
<td>2010</td>
<td>565</td>
<td>572</td>
<td>0,99 (0,88-1,11)</td>
</tr>
<tr>
<td>IMPROVE-IT</td>
<td>2015</td>
<td>538</td>
<td>537</td>
<td>1,00 (0,89-1,13)</td>
</tr>
<tr>
<td>Résumé</td>
<td></td>
<td>1540</td>
<td>1601</td>
<td>0,96 (0,90-1,03)</td>
</tr>
</tbody>
</table>

NEJM 2004;350:1495-504  
JAMA 2004;292:1307-16  
NEJM 2005;352:1425-35  
JAMA 2005;294:2437-45  
Lancet 2010;376:1658-69  
NEJM 2015;372:2387-97
Réduction du C-LDL et des décès CV

Les bienfaits sur la mortalité n’étaient pas manifestes tôt dans l’essai même dans les essais pour lesquels il s’agissait du paramètre d’évaluation principal

ÉTUDE 4S

ÉTUDE LIPID

• Environ 2 ans pour une séparation des courbes
  • 4S et LIPID: 20% de fatality rate
  • FOURIER: 5% de fatality rate

Lancet 1994;344:1383-89
NEJM 1998;339:1349-57
### Sous-groupes clés

<table>
<thead>
<tr>
<th>Sous-groupe</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>27 564</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type de maladie</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>IM seul</td>
<td>19 113</td>
</tr>
<tr>
<td>AVC seul</td>
<td>3 366</td>
</tr>
<tr>
<td>MAP seule</td>
<td>1 505</td>
</tr>
<tr>
<td>Maladie polyvasculaire</td>
<td>3 563</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>C-LDL au départ</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1 (&lt; 2,07 mmol/L)</td>
<td>6 961</td>
</tr>
<tr>
<td>Q2 (2,07-&lt; 2,38 mmol/L)</td>
<td>6 886</td>
</tr>
<tr>
<td>Q3 (2,38-2,82 mmol/L)</td>
<td>6 887</td>
</tr>
<tr>
<td>Q4 (&gt; 2,82 mmol/L)</td>
<td>6 829</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Intensité du traitement par statines au départ</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Élevée</td>
<td>19 103</td>
</tr>
<tr>
<td>Non élevée</td>
<td>8 461</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ézétimibe</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oui</td>
<td>1 440</td>
</tr>
<tr>
<td>Non</td>
<td>26 124</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Schéma posologique au départ</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toutes les 2 semaines</td>
<td>24 774</td>
</tr>
<tr>
<td>Une fois par mois</td>
<td>2 790</td>
</tr>
</tbody>
</table>

Les paramètres d'évaluation principal et secondaire clé sont représentés graphiquement. Les valeurs de p pour les interactions sont NS (non significatives).
Analyse déterminante

RRR : 16 %
RRI : 0,84 (IC à 95 % : 0,74-0,96)
\( p = 0,008 \)

RRR : 25 %
RRI : 0,75 (IC à 95 % : 0,66-0,85)
\( p < 0,00001 \)
Réductions absolues du risque

Dans le contexte de la prévention secondaire d’une maladie stable

<table>
<thead>
<tr>
<th>Essai</th>
<th>Contexte de l’essai</th>
<th>↓ absolue selon les EICVM</th>
<th>Suivi</th>
<th>NNT sur 5 ans</th>
</tr>
</thead>
<tbody>
<tr>
<td>CARE</td>
<td>Statine c. placebo chez des patients dont le C-LDL est moyen</td>
<td>3,0-4,2%</td>
<td>5,0 ans</td>
<td>24-34</td>
</tr>
<tr>
<td>LIPID</td>
<td>Statine c. placebo chez des patients dont le C-LDL est moyen</td>
<td>3,6-4,4%</td>
<td>6,1 ans</td>
<td>28-34</td>
</tr>
<tr>
<td>TNT</td>
<td>Ordonnance de doses de statines fortes c. modérées</td>
<td>2,2 %</td>
<td>4,9 ans</td>
<td>45</td>
</tr>
<tr>
<td>FOURIER</td>
<td>iPCSK9 c. placebo chez des patients ayant reçu une ordonnance de statines</td>
<td>2,0 %</td>
<td>3,0 ans</td>
<td>25-30</td>
</tr>
</tbody>
</table>

EICVM défini comme une combinaison du décès d’origine coronarienne ou CV, un IM ou un AVC.
Fourchette fournie lorsque les essais n’ont pas signalé une triple combinaison.
Dans le cas de l’essai FOURIER, la fourchette inférieure du NNT est fondée sur l’extrapolation du RRR des EICVM après la première année et les années subséquentes.

All Patients

Randomization to Alleles at Conception

PCSK9 /-/-

PCSK9 +/-

↓ LDL

↓ No change

↓ Measure Outcomes over Time

#2. Variations génétiques
#2. Variations génétiques

Similaire à une étude randomisée...

**All Patients**

Randomization to Statin

**STATIN**
- LDL

**No STATIN**
- No change

Measure Outcomes over Time
# Low Dose Omega-3 Mixtures Show No Significant Cardiovascular Benefit

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of Events (%)</th>
<th>Rate Ratios (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treatment</td>
<td>Control</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>1121 (2.9)</td>
<td>1155 (3.0)</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>1301 (3.3)</td>
<td>1394 (3.6)</td>
</tr>
<tr>
<td>Any</td>
<td>3085 (7.9)</td>
<td>3188 (8.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic</td>
<td>574 (1.9)</td>
<td>554 (1.8)</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>117 (0.4)</td>
<td>109 (0.4)</td>
</tr>
<tr>
<td>Unclassified/other</td>
<td>142 (0.4)</td>
<td>135 (0.3)</td>
</tr>
<tr>
<td>Any</td>
<td>870 (2.2)</td>
<td>843 (2.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Revascularization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary</td>
<td>3044 (9.3)</td>
<td>3040 (9.3)</td>
</tr>
<tr>
<td>Noncoronary</td>
<td>305 (2.7)</td>
<td>330 (2.9)</td>
</tr>
<tr>
<td>Any</td>
<td>3290 (10.0)</td>
<td>3313 (10.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any major vascular event</td>
<td>5930 (15.2)</td>
<td>6071 (15.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adapted with permission* from Aung T, Halsey J, Kromhout D, et al. Associations of omega-3 fatty acid supplement use with cardiovascular disease risks: Meta-analysis of 10 trials involving 77917 individuals. *JAMA Cardiol*. 2018;3:225-234. [*https://creativecommons.org/licenses/by-nc/4.0/*]
## Prespecified Hierarchical Testing

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Hazard Ratio (95% CI)</th>
<th>Icosapent Ethyl n/N (%)</th>
<th>Placebo n/N (%)</th>
<th>RRR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Composite (ITT)</td>
<td></td>
<td>705/4089 (17.2%)</td>
<td>901/4090 (22.0%)</td>
<td>0.75 (0.68–0.83)</td>
<td>25%▼</td>
</tr>
<tr>
<td>Key Secondary Composite (ITT)</td>
<td></td>
<td>459/4089 (11.2%)</td>
<td>606/4090 (14.8%)</td>
<td>0.74 (0.65–0.83)</td>
<td>26%▼</td>
</tr>
<tr>
<td>Cardiovascular Death or Nonfatal Myocardial Infarction</td>
<td></td>
<td>392/4089 (9.6%)</td>
<td>507/4090 (12.4%)</td>
<td>0.75 (0.66–0.86)</td>
<td>25%▼</td>
</tr>
<tr>
<td>Fatal or Nonfatal Myocardial Infarction</td>
<td></td>
<td>250/4089 (6.1%)</td>
<td>355/4090 (8.7%)</td>
<td>0.69 (0.58–0.81)</td>
<td>31%▼</td>
</tr>
<tr>
<td>Urgent or Emergent Revascularization</td>
<td></td>
<td>216/4089 (5.3%)</td>
<td>321/4090 (7.8%)</td>
<td>0.65 (0.55–0.78)</td>
<td>35%▼</td>
</tr>
<tr>
<td>Cardiovascular Death</td>
<td></td>
<td>174/4089 (4.3%)</td>
<td>213/4090 (5.2%)</td>
<td>0.80 (0.66–0.98)</td>
<td>20%▼</td>
</tr>
<tr>
<td>Hospitalization for Unstable Angina</td>
<td></td>
<td>108/4089 (2.6%)</td>
<td>157/4090 (3.8%)</td>
<td>0.68 (0.53–0.87)</td>
<td>32%▼</td>
</tr>
<tr>
<td>Fatal or Nonfatal Stroke</td>
<td></td>
<td>98/4089 (2.4%)</td>
<td>134/4090 (3.3%)</td>
<td>0.72 (0.55–0.93)</td>
<td>28%▼</td>
</tr>
<tr>
<td>Total Mortality, Nonfatal Myocardial Infarction, or Nonfatal Stroke</td>
<td></td>
<td>549/4089 (13.4%)</td>
<td>690/4090 (16.9%)</td>
<td>0.77 (0.69–0.86)</td>
<td>23%▼</td>
</tr>
</tbody>
</table>

**Total Mortality**

- Icosapent Ethyl: 274/4089 (6.7%)
- Placebo: 310/4090 (7.6%)

RRR denotes relative risk reduction

Bhatt DL. AHA 2018, Chicago. Icosapent Ethyl Better

## Effects on Biomarkers from Baseline to Year 1

<table>
<thead>
<tr>
<th>Biomarker*</th>
<th>Icosapent Ethyl (N=4089) Median</th>
<th>Placebo (N=4090) Median</th>
<th>Median Between Group Difference at Year 1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Year 1</td>
<td>Baseline</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>216.5</td>
<td>175.0</td>
<td>216.0</td>
</tr>
<tr>
<td>Non-HDL-C (mg/dL)</td>
<td>118.0</td>
<td>113.0</td>
<td>118.5</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>74.0</td>
<td>77.0</td>
<td>76.0</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>40.0</td>
<td>39.0</td>
<td>40.0</td>
</tr>
<tr>
<td>Apo B (mg/dL)</td>
<td>82.0</td>
<td>80.0</td>
<td>83.0</td>
</tr>
<tr>
<td>hsCRP (mg/L)</td>
<td>2.2</td>
<td>1.8</td>
<td>2.1</td>
</tr>
<tr>
<td>Log hsCRP (mg/L)</td>
<td>0.8</td>
<td>0.6</td>
<td>0.8</td>
</tr>
<tr>
<td>EPA (μg/mL)</td>
<td>26.1</td>
<td>144.0</td>
<td>26.1</td>
</tr>
</tbody>
</table>

*Apo B and hsCRP were measured at Year 2.

Most Frequent Treatment-Emergent Adverse Events: ≥5% in Either Treatment Group and Significantly Different

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Icosapent Ethyl (N=4089)</th>
<th>Placebo (N=4090)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>367 (9.0%)</td>
<td>453 (11.1%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>267 (6.5%)</td>
<td>203 (5.0%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Constipation</td>
<td>221 (5.4%)</td>
<td>149 (3.6%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>215 (5.3%)</td>
<td>159 (3.9%)</td>
<td>0.003</td>
</tr>
<tr>
<td>Anemia</td>
<td>191 (4.7%)</td>
<td>236 (5.8%)</td>
<td>0.03</td>
</tr>
</tbody>
</table>