What’s New in Dyslipidemia

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Disclosures

- I have participated on advisory boards or have been a paid speaker for:
  - Bayer
  - BI Canada,
  - Pfizer/BMS Alliance,
  - Servier
  - Sanofi

- I am a member of the Heart and Stroke Canada Secondary Prevention of Stroke Guidelines Primary Panel
Learning Objectives

▪ To highlight emerging information in the management of dyslipidemia since publication of the 2016 CCS Guidelines including:
  ▪ Canadian FH Guidelines
  ▪ Outcome data with PCSK9 inhibitors
  ▪ Emerging Importance of Triglycerides and associated management strategies

▪ To provide guidance in application of this data
2016 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult Canadian Journal of Cardiology
CJC: 2016;32(11); 1263-1282

Risk Assessment, Stratification & Treatment Considerations

Calculate risk (unless statin-indicated condition) using the Framingham Risk Score (FRS)1 or Cardiovascular Life Expectancy Model (CLEM)2.
Repeat screening every 5 years for FRS ≥10% or every year for FRS ≥1%

No Pharmacotherapy

Low Risk
FRS <10%

Primary Prevention Conditions

Intermediate Risk
FRS 10-10%
and
LDL-C ≥3.5 mmol/L
or
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

High Risk
FRS ≥20%
or
alternative method

Statin-indicated Conditions3

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

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

Discuss behavioral modifications

Health Behavioural Modifications

• Smoking cessation
• Diet:
  - Recommended all individuals adopt a health dietary pattern
• Exercise:
  - Recommended adults should accumulate at least 150 minutes per week of moderate-intensity aerobic physical activity

Initiate Statin Treatment: Treat to Target Approach

Confirm adherence and barriers to use

<table>
<thead>
<tr>
<th>LDL-C ≥2.0 mmol/L or ≥50% reduction or apoB ≥1.2 g/L or non-HDL-C ≥2.6 mmol/L</th>
<th>LDL-C ≥50% reduction</th>
</tr>
</thead>
</table>

Target achieved on maximally tolerated dose?

NO

Discuss add-on therapy with patient4

Evaluate reduction in CVD risk vs. additional cost & side effects

NO

ADD-ON

Ezetimibe as 2nd line (EAS as alternative)

ADD-ON

Ezetimibe (or BAS) on PCSK9 inhibitors

ADD-ON

Ezetimibe (or BAS) or PCSK9 inhibitors
Familial Dyslipidemia

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, Tanya J. Lee, MD, David Patrick, MD, Pamela Pauker, MD, PhD
Familial Hypercholesterolemia (FH)

- Autosomal co-dominant disorder
  - Elevated LDL concentrations
    - Heterozygous: 2-3 times greater than normal (> 5 – 10 mmol/L)
    - Homozygous: Up to 10 times greater than normal (> 10 – 13 mmol/L)
    - 3 – 13 times greater risk of premature atherosclerotic CVD

- Heterozygous affects ~1/200-600 individuals

- Homozygous originally believed to affect 1/1,000,000 people
  - Likely 3 times more prevalent than previously thought

- Originally believed to be due only to large gene variants, but now shown to be affected by small-effect gene variants
  - Discovered due to patients with heterozygous FH presenting with LDL concentrations typical for homozygous, and vice versa
Figure 1. Canadian definition for the clinical diagnosis of familial hypercholesterolemia (FH). ASCVD, atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol. * Secondary causes of high LDL-C should be ruled out (severe or untreated hypothyroidism, nephrotic syndrome, hepatic disease [biliary cirrhosis], medication, especially antiretroviral agents); LDL-C ≥ 4.0 mmol/L for age younger than 18 years; and LDL-C ≥ 4.5 mmol/L for age 18 years to younger than 40 years. ** Causal DNA mutation refers to the presence of a known FH-causing variant in the LDLR, APOB, or PCSK9 gene on the basis of the presence of the variant in ClinVar, The Human Gene Mutation Database (HGMD), or Western Database of Lipid Variants (WDLV) databases, in the proband or a first-degree relative. FH diagnosis in a patient with a DNA mutation but normal LDL-C levels is unclear. Yearly follow-up of the proband is suggested and cascade screening of family members should be initiated. Note: In any case, cascade screening should be implemented; treatment decision should be at the discretion of the treating physician.
Recommendations:

- Use DLC, Simon Broome or FH Canada Recommendation for diagnosis.
- Cascade Screening protocols be implemented at local, provincial and national level in Canada and offered to first degree relatives of patients with FH.
- Genetic testing be offered, when available, to complement a diagnosis of FH and enable cascade screening.
- Current risk calculators should not be used to determine risk in patients with FH.
- Conventional risk factors such as age, sex, HDL-C, hypertension, smoking, lipoprotein(a), and diabetes by assessed.
- Patients should adopt a healthy lifestyle.
- For patients with FH requiring medications, a personalized plan should include statins as the primary therapy and secondary agents as required including ezetimibe and PCSK9 inhibitors.
- CCS guideline targets should be recommended.
- Statins should not be used during pregnancy (stop statins at least 1 month before stopping contraception or before attempting conception, or immediately upon confirming pregnancy).
- Suggest that statin therapy be considered usually between 8 and 10 years of age if LDL-C remains > 4.9 mmol/L or >4.1 mmol/L with a family history of ASCVD.
FOURIER Study

- Population: 27,564 patients with atherosclerotic CVD and LDL levels of at least 1.8 mmol/L or higher who were receiving statin therapy

- Compared evolocumab to placebo
  - 140mg every 2 weeks
  - 420mg every month

- Patient choose the dosing frequency of evolocumab and can elect to switch every 12 weeks
  - Dose titrations were not permitted

- Background Lipid Lowering Therapy
  - on optimized regimen
    - Moderate-High intensity statin ± Ezetimibe
  - Patients are not to change open-label background lipid-lowering therapy after randomization

Fourier: LDL-C Levels Over Time

- LDL-C was significantly reduced in evolocumab group
  - Median = 0.78 mmol/L
  - 42% achieved levels ≤ 0.65 mmol/L vs < 0.1% in placebo

Data shown are median values with 95% confidence intervals in the two arms; ITT.
Fourier: Primary Endpoint

- Composite of CV Death, MI, Stroke, Hospitalization for UA or Coronary Revascularization
- HR = 0.85; Median duration of 26 months
Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome: Odyssey Outcomes Trial

- Population of patients with ACS in the last 1 – 12 months with an LDL of at least 1.8 mmol/L and were receiving maximally tolerated statin
  - Run in period of placing patients on high-intensity/maximally tolerated dose of atorvastatin or rosuvastatin for 2 – 16 weeks

- Compared:
  - Alirocumab 75 mg SC every 2 weeks (n=9462)
  - Placebo SC every 2 weeks (n=9462)
  - LDL-C Targets defined as 0.6 - 1.3 mmol/L
  - Median follow up 2.8 years

- Outcome:
  - Primary: composite of death from CHD, nonfatal MI, fatal or nonfatal stroke or UA requiring hospitalization

Odyssey Outcomes: 
Median LDL Levels Over Time

Baseline mean LDL 2.38 mmol/L

Approx 60% reduction on treatment

1.0 mmol/L 1.2 mmol/L 1.7 mmol/L
Odyssey Outcomes: Results

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

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

Placebo
Alirocumab

Number at Risk
Placebo 9462
Alirocumab 9462

15
12
9
6
3
0
Years Since Randomization

MACE (%)
## Odyssey Outcomes: Safety

<table>
<thead>
<tr>
<th>Adverse events – no (%)</th>
<th>Alirocumab (n=9451)</th>
<th>Placebo (n=9443)</th>
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</thead>
<tbody>
<tr>
<td>Any</td>
<td>7165 (75.8)</td>
<td>7282 (77.1)</td>
</tr>
<tr>
<td>Serious</td>
<td>2202 (23.3)</td>
<td>2350 (24.9)</td>
</tr>
<tr>
<td>Leading to discontinuation</td>
<td>343 (3.6)</td>
<td>324 (3.4)</td>
</tr>
<tr>
<td>Injection site</td>
<td>360 (3.8)</td>
<td>203 (2.1)</td>
</tr>
</tbody>
</table>
Summary of PCSK9 Outcome Studies

- Patients with existing CVD and LDL>1.8 mmol/L while on maximally tolerated statin:
  - Evolocumab: 27,564 patients over 2.2 years
    - New CVD events: 9.8%, placebo 11.3%, statistically significant
      - NNT=67
      - CVD reduction: independent of baseline LDL
      - Death (any cause): no difference
  - Alirocumab: 18,924 patients post ACS over 2.8 years
    - New CVD events: 9.5%, placebo 11.1%, statistically significant
      - NNT=63
      - Death (any cause): 3.5%, placebo 4.1%, statistically significant
      - NNT=167

- Adverse events:
  - Primary injections site reactions: NNH approx. 100
Summary of PCSK9 Inhibitors in Practice

- Public coverage approved for the use in Heterozygous Familial Hypercholesterolemia as recommended by CADTH
  - Evolocumab/Alirocumab
- Company sponsored programs provide coverage in patients with FH
- Used sparingly at present
  - Should be added to statins, not replacing them
  - May see in high risk atherosclerotic patients if uncontrolled on statins and willing to pay/have 3rd party coverage
Hypertriglyceridemia

▪ An independent marker of increased cardiovascular disease risk

▪ Studies of statins combined with extended-release niacin and fibrates have shown no ASCVD risk reduction benefit

▪ A reduced incidence of non-fatal CVD events was reported with low-intensity statin and EPA versus low-intensity statin monotherapy in a Japanese primary and secondary prevention RCT\(^1\)

▪ Previous meta-analysis of 10 randomized trials involving 78,000 patients did not show that n-3 fatty acids had a lower risk of major adverse CV events than those receiving placebo\(^2\) not did ASCEND which tested 1 g caps containing 840 mg of marine n-3 fatty acids daily in patients with type 2 diabetes\(^3\)

**Objective:**
- To assess the effects of icosapent ethyl in patients with elevated triglycerides on ischemic events

**Population:**
- 8179 patients with CVD or with diabetes and other risk factors, on statin therapy and with elevated TG levels (1.52 – 5.63 mmol/L and a LDL level of 1.06 to 2.59 mmol/L)

**Intervention:**
- Icosapent ethyl 2 g twice daily (n=4089) vs placebo (n=4090)

**Outcome:**
- Primary: CV death, nonfatal MI or stroke, revascularization or unstable angina: 17.2% vs 22% (HR 0.75; 95% CI 0.68-0.83; p<0.001)
- Secondary: CV death, nonfatal MI or stroke: 11.2% vs 14.8% (HR 0.74; 95% CI 0.65-0.83; p<0.001)

**Conclusion:** Among patients with elevated TG levels despite the use of statins, the risk of ischemic events was significantly lower with the use of icosapent ethyl compared to placebo.

Bhatt DL, et al. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia: Multicenter, randomized, double blind, placebo controlled trial
Key effects:

- Median change in TG level from baseline to year one was a decrease of 18.3% in the icosapent ethyl group and 2.2% increase in the placebo group.

- Median change in LDL was an increase in 3.1% in icosapent group and an increase of 10.2% in placebo group.

- Rate of AF was significantly higher in the icosapent ethyl group vs placebo (5.3% vs 3.9%), as was the rate of peripheral edema (6.5% vs 5.0%).

- Rate of anemia was significantly lower in the icosapent ethyl group vs placebo (4.7% vs 5.8%) as were the rates of diarrhea (9.0% vs 11.1%) and GI adverse events (33.0% vs 35.1%).
Icosapent Ethyl:

- Possible Mechanisms of Benefit:
  - Lipid or lipoprotein reduction, but CV benefit likely greater than would have been predicted based on changes in TG
  - Anti-thrombotic effects
  - Anti-inflammatory effect
  - Membrane stabilization
  - Plaque stabilization
  - Other effects specific to it

- Current status in Canada:
  - Vascepa® (Amarin Corp) granted priority review status from Health Canada – anticipated to be filed in April 2019
So where does this leave us in 2019:
Clinical Algorithm for Managing LDL-C

RCT-Proven Non-Statin Additive Therapies for ASCVD Risk Reduction in High-Risk Patients

Maximally Tolerated Statin

- Ezetimibe: ACS within 10 days
- PCSK9 Inhibitor: Stable ASCVD + Additional risk factors; or ACS within 1-12 months
- Eicosapentanoic Acid: Stable ASCVD; or Diabetes + > Additional risk factor; TG 1.5 – 5.6 mmol/L
Summary:

- PCSK9s – will change the landscape
  - They work, they are well tolerated but they are expensive!
  - Much more focus will be made on FH patients

- Watch for continued interest in EPA....

- CCS guidelines largely hold true....

- How low should we go?