Dyslipidemia – What's next...

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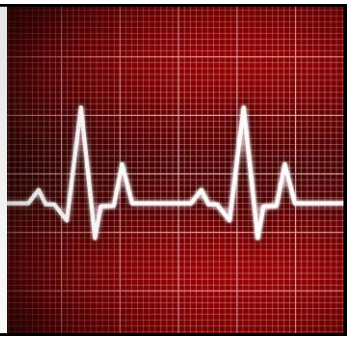


Disclosures

- 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

Before we go further...

- Please download the CCS Lipid Guideline App
- Please download the ACC Statin Intolerance Tool
- CardioRisk Calculator

BP....

- BP is a 63 year old woman, referred to your clinic for management of her dyslipidemia by her family physician and patient seen in clinic Sept 10.
- The referral indicates that she has a long standing history of dyslipidemia and that statins cause her leg pain
- Her current weight is 125lbs, height 5 feet 0 inches and BMI is "good"
- Current medications as per the MD are: "celebrex short term, Valtrex prn" and that she has tried all statins and they cause leg pain...
- CHD Risk factors as per referral: Evidence of atherosclerosis, family history of hyperlipidemia, family history of CHD (<60 yo)

BP...

- Further data provided by the referral (Sept 4 labs).....
  - CRP – WNL
  - TG 2.52 mmol/L
  - TC 8.04 mmol/L
  - HDL 1.42 mmol/L
  - LDL 5.47 mmol/L
  - Non HDL C 6.6 mmol/L
- CT:
  - Coronary Calcium Score – 181
  - 30% stenosis in LAD, RCA 40% stenosis
- Physical exam features from referral:
  - No chest pain or SOB, no obvious xanthelasmas

What would you do for this patient?

- PIP:
  - Celecoxib 200 mg capsule
    - 34 capsules on Aug 16 and Jan 18
  - Rosuvastatin 5mg tablet
    - 24 tabs on Aug 16, Jul 18, Jun 8, Apr 12, Mar 14, Feb 5, Jan 3
  - Escitalopram 10 mg tab
    - 34 tabs Aug 16
  - Ezetimibe 10 mg tab
    - 34 tabs Aug 16, Jul 18, Jun 18, Apr 09, Feb 15

Process of Care:

Target Adults for Screening (unless compelling reason)

↓

Determine Cardiovascular Risk

↓

Institute Lifestyle Changes

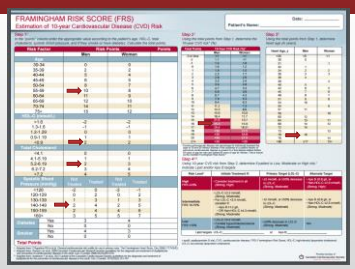
↓

Treat According to Level of Risk

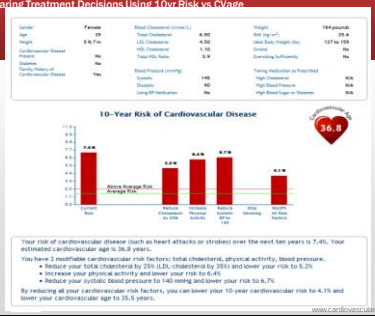
What is her level of risk?

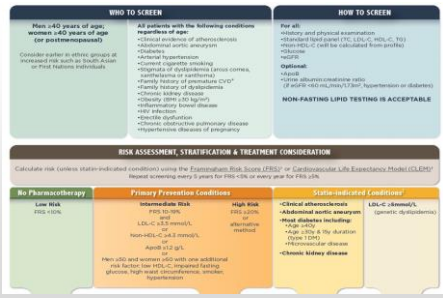
- How would you ascertain her level of risk?
  - History?
  - FRS?
  - Other?

Framingham Risk Score

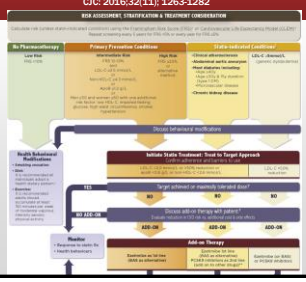


Comparing Treatment Decisions Using 10yr Risk vs CVage





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



FH Simplified Canadian Definition

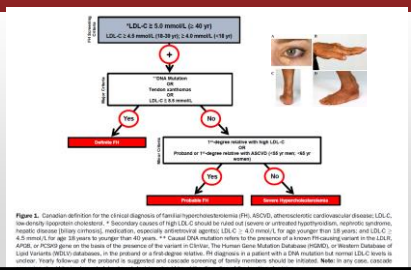


Figure 1. Canadian definition for the clinical diagnosis of familial hypercholesterolemia (FH). ASCVD, atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol. * Secondary causes of high LDL-C should be ruled out (severe or untreated hypothyroidism, nephrotic syndrome, hepatic 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

Recommended Lifestyle Changes

- Smoking cessation, including the use of pharmacological therapy, as required
- A diet low in sodium and simple sugars, with substitution of unsaturated fats for saturated and trans fats, and with increased consumption of fruits and vegetables
- Caloric restriction to achieve and maintain ideal body weight

Recommended Lifestyle Changes

- Moderate to vigorous exercise for 30-60 minutes on most, and preferably all, days of the week
- Psychological stress management
- Alcohol consumption in moderation is not contraindicated if there are no metabolic or clinical contraindications
- **All individuals are offered advice about healthy eating and activity and adopt the Mediterranean dietary pattern to lower their CVD risk**

Secondary Causes

- Type 2 DM
- Excessive alcohol consumption
- Cholestatic liver disease
- Nephrotic syndrome
- Chronic renal failure
- Hypothyroidism
- Cigarette smoker
- Obesity
- Drugs (thiazides, beta-blockers, oral estrogens, clozapine, olanzapine, protease inhibitors)

2018 CCS Position Statement on FH (CJC 2018;34:1553-1563) www.FHCanada.net

- 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

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

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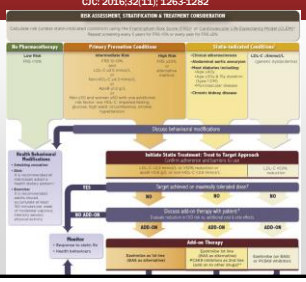


Whats next....

- Current lipid levels on Crestor 5 and Ezetimibe 10mg.....
- What about her dyslipidemia?
- What discussions might you have with her at this point?
- She has pain....
- Evaluating her muscle pain....
  - What insights do you hope to gain from her in evaluation?
  - CardioRisk Calculator
  - ACC Statin Intolerance Tool – download the app...

You have gathered her information, now what are you going to do?

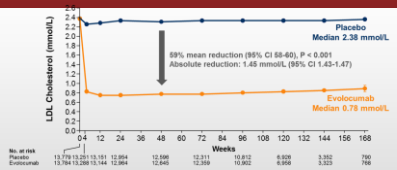
- Lifestyle?
- Drug therapy?
- Follow up?

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

Sabatine M et al. N Engl J Med 2017;376:1713-1722

Fourier: LDL-C Levels Over Time

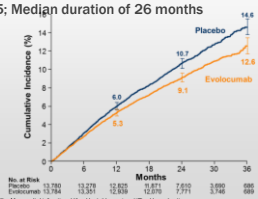


- LDL-C was significantly reduced in evolocumab group
  - Median = 0.78 mmol/L
  - 42% achieved levels ≤ 0.65 mmol/L vs < 0.1% in placebo

Data shown are median values with 95% confidence intervals in the two arms; ITT.
Sabatine MS, et al. *N Engl J Med.* [published online ahead of print March 17, 2017]. doi: 10.1056/NEJMoa1615664

Fourier: Primary Endpoint

- Composite of CV Death, MI, Stroke, Hospitalization for UA or Coronary Revascularization
- HR = 0.85; Median duration of 26 months



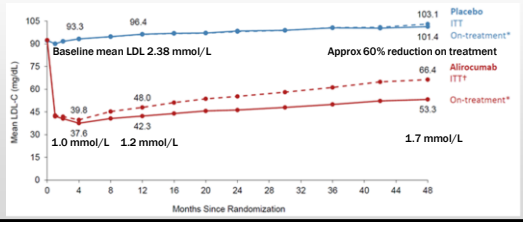
CV = Cardiovascular; MI = Myocardial infarction; UA = Unstable angina; HR = Hazard ratio
Sabatine MS, et al. *N Engl J Med.* [published online ahead of print March 17, 2017]. doi: 10.1056/NEJMoa1615664

Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome: Odyssey Outcomes Trial

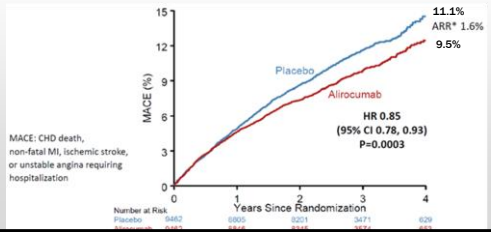
- Population of patients with ACS in the last 1 – 12 months with an LDL of at least 1.8 mmol/L and were receiving maximally tolerated statin
  - Run in period of placing patients on high-intensity/maximally tolerated dose of atorvastatin or rosuvastatin for 2 – 16 weeks
- Compared:
  - Alirocumab 75 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

Scwhartz G et al. NEJM 2018;379:2097-2107.

Odyssey Outcomes: Median LDL Levels Over Time



Odyssey Outcomes: Results



Odyssey Outcomes: Safety

Adverse events – no (%)	Alirocumab (n=9451)	Placebo (n=9443)
Any	7165 (75.8)	7282 (77.1)
Serious	2202 (23.3)	2350 (24.9)
Leading to discontinuation	343 (3.6)	324 (3.4)
Injection site	360 (3.8)	203 (2.1)

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: E 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: A 9.5%, placebo 11.1%, statistically significant
      - NNT=63
      - Death (any cause): A 3.5%, placebo 4.1%, statistically significant
      - NNT=167
- Adverse events:
  - Primary injections site reactions: NNH approx. 100

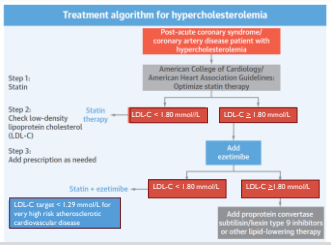
Summary of PCSK9 Inhibitors in Practice

- 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
  - Repatha Ready…
  - My Praluent Coach….
- 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

EDS Sask – PCSK9 Sask

- Initial Criteria For the treatment of patients with definite or probable diagnosis of Heterozygous Familial Hypercholesterolemia (HeFH) who are unable to reach Low Density Lipoprotein Cholesterol (LDL-C) target (i.e., LDL-C < 2.0mmol/L for secondary prevention or at least a 50% reduction in LDL-C from untreated baseline for primary prevention) despite either (A) or (B): (A) Confirmed adherence to high dose statin (e.g., atorvastatin 80mg or rosuvastatin 40mg) along with confirmed adherence to ezetimibe for at least a total of 3 months. OR
- (B) Unable to tolerate high dose statin defined as all of the following:
  - Inability to tolerate at least 2 statins with at least one started at the lowest starting daily dose.
  - For each statin (two statins in total), dose reduction is attempted for intolerable symptom (myopathy) or biomarker abnormality (creatine kinase (CK) > 5 times the upper limit of normal) resolution rather than discontinuation of statin altogether.
  - For each statin (two statins in total), intolerable symptom (myopathy) or abnormal biomarkers (creatine kinase (CK) > 5 times the upper limit of normal) changes are reversible upon statin discontinuation but reproducible by re-challenge of statins where clinically appropriate.
  - One of either: i. Other known determinants of intolerable symptoms or abnormal biomarkers have been ruled out; OR ii. Developed confirmed and documented rhabdomyolysis; OR iii. Statin use is contraindicated i.e., active liver disease, unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal. • Confirmed adherence to ezetimibe for at least a total of 3 month

So where does this leave us in 2019: Clinical Algorithm for Managing LDL-C



Rosenson, R.S. et al. J Am Coll Cardiol. 2018;72(3):314-29

Follow Up

- **Response to therapy in 6-8 weeks post initiation**
  - **What is initiated?**
  - **What discussions?**
- If drug used – ALT and CK at baseline – to identify if contraindicated (limited numbers affected). CK only in those at very high risk of myopathy (eg. Elderly with comorbidities, drug interactions or those with muscle symptoms), routine ALT not **indicated but should be performed based on clinical observations…..**