The New 2016 Canadian Dyslipidemia Guidelines

Coming this summer…

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Disclosure Statement

- Honoraria: Pfizer, Astra Zeneca, Merck, Boehringer Ingelheim, BMS, Novartis, Sanofi
- Advisory Boards: Pfizer, Boehringer Ingelheim, Sanofi, BMS, Bayer, Amgen
- Research grants: AstraZeneca, BMS, Pfizer, Bayer
- I have no stocks or financial interests in any pharmaceutical company

Learning Objectives:

- Discuss information that will potentially affect the Canadian guidelines:
  - No FAST(ing) for assessment
  - Taking steps to IMPROVE-IT (the care)
  - HOPE to redefine Intermediate risk
  - OSLERs Odyssey
  - Is it a floor, a ceiling or does it even exist?
  - Where does the patient sit in decision making….

Lipid Guidelines (where have we been)….

	2012 CCS	2013 ACC/AHA
Lipoprotein measurement for assessment	Fasting lipid panel for LDL-C with calculation of non-HDL	Fasting lipid panel for LDL-C
Lipoprotein target	LDL-C and non-HDL-C and apo B	No target LDL-C
Assessment tool	Total CVD FRS modified for family Hx, age 40-75 y	Pooled cohort risk equation, age 40-75 y
Patient to treat with statin	Established athero, most diabetes, LDL >5, most CKD patients, FRS ≥ 20%, FRS 10-19% if LDL≥3.5	Established athero, most diabetes, LDL >4.9, Pooled cohort equation risk ≥7.5%, LDL ≥ 1.8
Treating to targets	FRS <10%: 50% reduction in LDL, FRS≥10%, LDL-C≤2.0	No target, but statin intensity dictated by risk

2012 Canadian Lipid Guidelines: Current Treatment Thresholds and Targets

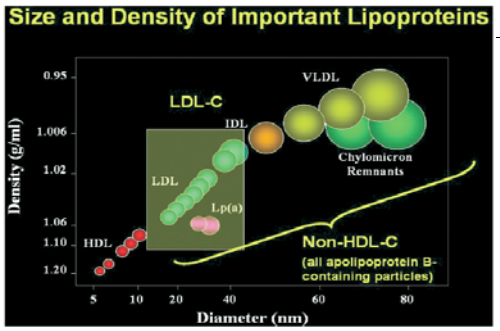
Risk level	Initiate therapy if:	Primary target (LDL-C)	Alternate target
High FRS ≥20%	• Consider treatment in all *(Strong, High)*	**≤2 mmol/L or ≥50% decrease in LDL-C** ***(Strong, Moderate)***	• **Apo B ≤0.8 g/L or** • **Non-HDL-C ≤2.6 mmol/L** ***[Strong, High]***
Intermediate FRS 10-19%	• LDL-C ≥3.5 mmol/L *(Strong, Moderate)* • For LDL-C <3.5 mmol/L consider if: ◦ Apo B ≥1.2 g/L ◦ OR Non-HDL-C ≥4.3 mmol/L *(Strong, Moderate)*	• ≤2 mmol/L or ≥50% decrease in LDL-C *(Strong, Moderate)*	• Apo B ≤0.8 g/L or • Non-HDL-C ≤2.6 mmol/L *(Strong, Moderate)*
Low FRS <10%	• LDL-C ≥5.0 mmol/L • Familial hypercholesterolemia *(Strong, Moderate)*	• ≥50% decrease in LDL-C *(Strong, Moderate)*	N/A

Non Fasting for Routine Lipid Testing

- Non fasting lipid profiles have been the standard in Denmark since 2009 and are now supported in the 2016 Eurpoean Guidelines
- Why?
  - Fasting has minimal effect on LDL and HDL with modest effect on TG
  - Non fasting and fasting HDL-C and non-HDL-C predict CVD risk in a similar fashion
- Why would this be considered?
  - Enhance adherence to testing
  - Deal with laboratory demand and wait times
  - Minimize hypoglycemia

Eur Heart J 2011;32:1769-1818
Eur Heart J (in press)
JAMA Internal Med: online April 27, 2016

Non-HDL-C as an alternate target to LDL-C



Primary and 3 Prespecified Secondary Endpoints — ITT

IMPROVE-IT

	Simva*	EZ/Simva*	p-value
Primary CVD/MI/UA/Cor Revasc/CVA	34.7	32.7	0.016
Secondary #1 All D/MI/UA/Cor Revasc/CVA	40.3	38.7	0.034
Secondary #2 CHD/MI/Urgent Cor Revasc	18.9	17.5	0.016
Secondary #3 CVD/MI/UA/All Revasc/CVA	36.2	34.5	0.035

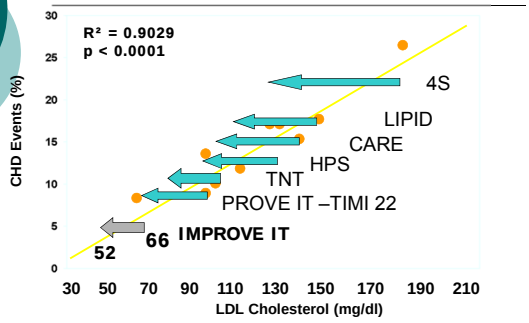
UA, documented unstable angina requiring rehospitalization; Cor Revasc, coronary revascularization (≥30 days after randomization); All D, all-cause death; CHD, coronary heart disease death; All Revasc, coronary and non-coronary revascularization (≥30 days)

IMPROVE - IT

- Design: Multicenter, DB, R controlled trial
  - N=18,144 (Simva=9077, Simva/E=9067)
  - ITT, Median follow up 6 years
  - Primary Outcome: CV mortality, major CV events, nonfatal stroke
- Population: post ACS ≤ 10 days, LDL- C:
  - 1.3 to 2.6 mmol/L on lipid lowering therapy
  - 1.3 to 3.2 mmol/L not on lipid lowering therapy
- Intervention:
  - Simva 40 mg vs Ezetimibe 10/Simva 40

Cannon C et al. N Engl J Med 2015;372:2387-2397.

The Lipid Hypothesis: LDL: "Lower is Better"

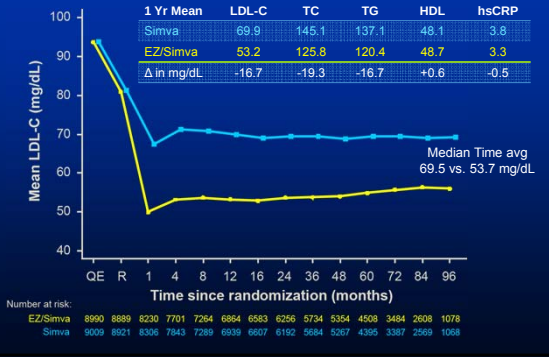


Adapted and Updated from O'Keefe, J. et al., *J Am Coll Cardiol* 2004;43:2142-6.

LDL-C and Lipid Changes

IMPROVE-IT

1 Yr Mean	LDL-C	TC	TG	HDL	hsCRP
Simva	69.9	145.1	137.1	48.1	3.8
EZ/Simva	53.2	125.8	120.4	48.7	3.3
Δ in mg/dL	-16.7	-19.3	-16.7	+0.6	-0.5

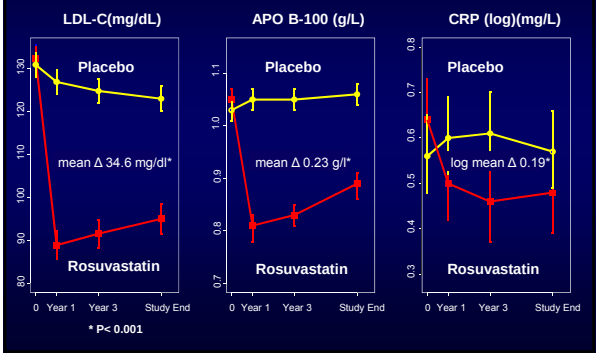


HOPE-3

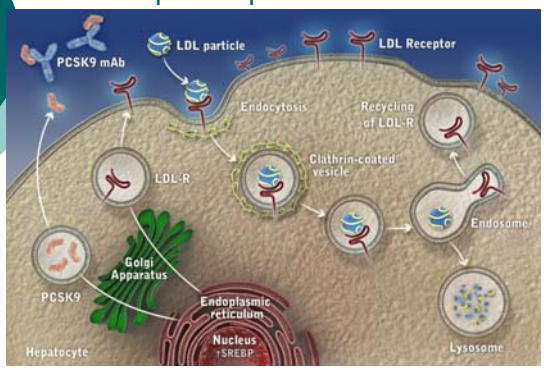
- Design: Multicenter, DB, 2x2 factorial, PC
  - N=12,705 with intermediate CV disease risk
  - Statin study: Rosuv (n=6361) vs Placebo (n=6344)
  - ITT, Median follow up 5.6 years
  - Co-primary outcomes: Composite of CV death, MI, Stroke, Above + resuscitated cardiac arrest, HF, revascularization
- Population: Women ≥ 65y, Men ≥ 55y
  - 1 or more CV risk factors (Inc WHR, smoking, dysglycemia, Low HDL, mild renal dysfunction, family history of CHD)
- Intervention:
  - Rosuvastatin 10mg daily vs placebo

Yusuf S et al. N Engl J Med DOI:10.1056/NEJMoa1600176

Cholesterol Lowering Arm: Change in LDL, Apo-B, and CRP



Impact of PCSK9 Inhibition on LDL Receptor Expression



Cholesterol Lowering: Outcomes

Outcome	Rosuvastatin N (%)	Placebo N (%)	HR (95% CI)	p
Co-Primary 1	235 (3.69)	304 (4.79)	0.76 (0.64-0.91)	0.002
Co-Primary 2	277 (4.35)	363 (5.72)	0.75 (0.64-0.88)	0.0004
Secondary 1	306(4.81)	393 (6.19)	0.77 (0.66-0.89)	0.0006
CV Death	154 (2.4)	171 (2.7)	0.89 (0.72-1.11)	0.31
MI	45 (0.7%)	69 (1.1)	0.65 (0.44-0.94)	0.02
Stroke	70 (1.1%)	99 (1.6%)	0.70 (0.52-0.95)	0.02
CV Hosp.	281 (4.4)	369 (5.8)	0.75 (0.64-0.88)	0.0003

ORIGINAL ARTICLE

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*

ORIGINAL ARTICLE

Efficacy and Safety of Evolocumab in Reducing Lipids and Cardiovascular Events

Marc S. Sabatine, M.D., M.P.H., Robert P. Giugliano, M.D., Stephen D. Wiviott, M.D., Frederick J. Raal, M.B., B.Ch., M.Med., Ph.D., Dirk J. Blom, M.B., Ch.B., M.Med., Ph.D., Jennifer Robinson, M.D., M.P.H., Christie M. Ballantyne, M.D., Ransi Somaratne, M.D., Jason Legg, Ph.D., Scott M. Wasserman, M.D., Robert Scott, M.D., Michael J. Koren, M.D., and Evan A. Stein, M.D., Ph.D., for the Open-Label Study of Long-Term Evaluation against LDL Cholesterol (OSLER) Investigators

N Engl J Med, March 15, 2015

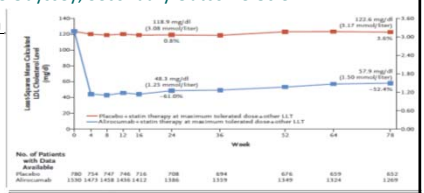
PCSK9: The new kids on the block

- PCSK9 Inhibitors – proprotein convertase subtilisin/kexin type 9 inhibitors – ability to dramatically lower LDL- C
- Evolocumab (Repatha®, Amgen – NOC Sept 12, 2015)
- Alirocumab (Praluent®, Sanofi – April 11, 2016)
- Monoclonal antibodies that inhibit PCSK9 enzyme, preventing it from binding to the LDL cholesterol receptors, with resultant increase in the number of LDL receptors available to bind and clear LDL cholesterol

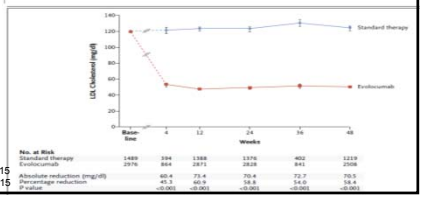
Effect on LDL:

Primary Outcome Odyssey; Secondary Outcome Osler

ODYSSEY Long Term



OSLER 1 and 2



Robinson J et al. NEJM, March 15, 2015
Sabatine M et al. NEJM, March 15, 2015

CV Events (Secondary or Post Hoc)

ODYSSEY
- Positively adjudicated CV events occurred in 4.6% of patients in alirocumab arm vs 5.1 % in placebo arm
- Post hoc analysis:
  - 1.7% A vs 3.3 % P, HR 0.52

OSLER 1 and 2
- CV event rate: 0.95% Evolocumab arm vs 2.18% in standard therapy arm at 1 year (HR 0.47)

Robinson J et al. NEJM, March 15, 2015
Sabatine M et al. NEJM, March 15, 2015

LDL-C Targets – should we have any?

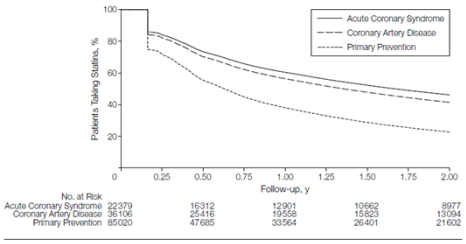
- Canadian – currently yes
- American* – currently no
- IMPROVE-IT – 1.4 mmol/L
- PCSK9 –will be under 1 mmol/L
- Community practitioners: see a target as a floor "lets get down to…"
- Lipidologists: see a target as a ceiling " we have to be under…"
- Whatever ever it is – we need to be more aggressive in the future….

What do we do with this data?

- At this point (and into the future), these agents will not replace statins
- More safety data in larger populations required – generally rare effects become apparent around the 3 – 5 million total prescription mark
- Cost – approximately $7500 annually
  - These are extremely costly agents and the impact on public and private payers will be significant
- Place in therapy???
  - Uncontrolled FH patients
  - High risk, statin intolerant patients
  - Insurance or self pay will be necessary in early going and both companies have extensive programs in place
  - Limit to Lipid Clinics at this point

Adherence to Statins is Sub-Optimal Among Canadians

Figure. Survival Curves for Adherence With Statins in 3 Cohorts



Jackevicius CA, Mamdani M, Tu JV. Adherence with statin therapy in elderly patients with and without acute coronary syndromes. *JAMA*. 2002;288(4):462-467

PCSK9 Ongoing CV Outcome Trials

	Evolocumab FOURIER	Alirocumab Odyssey Outcomes	Bococizumab Spire I/II
Time	Jan 2013- Feb 2018	Oct 2012- March 2018	Oct 2013 - Aug 2017
Population	High risk with clinical evident CV dx	ACS within last 4-52 weeks	High risk CV with background lipid therapy
Baseline	LDL ≥ 1.8	LDL ≥ 1.8	LDL ≥ 1.8
Background	Atorva 20-80 or equivalent	Not specified	Atorva 40-80 or Rosuva 20-40
N	22500	18000	12000/6300
Outcome	CV death, MI, hospitalization for UA, stroke or Cor Revasc	CHD death, MI, stroke or UA	CV death, non fatal MI, non fatal stroke or hosp for UA needing intervention

Summary

- New Canadian guidelines are forthcoming
- Data from IMPROVE-IT and HOPE 3 should and will impact these guidelines
- The role of the PCSK9 Inhibitors will be interesting and will continue to evolve from what will likely be a conservative position within the next guidelines to a potentially more prominent position in the future
- Non fasting lipid levels may be included
- Patient choice may be an option