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Managing Hypercholesterolemia in the High-risk CV Patient – A New Strategy for Further Reducing Risk

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Cardiovascular disease (CVD), including coronary artery and cerebrovascular disease, is the second most common cause of death in Canada, responsible for 25% of mortality in 2013. An additional 2.4 million Canadian adults live with the sequelae of CVD. Among known CVD risk factors established by a wealth of clinical trial and real-world data, and multiple meta-analyses, is hypercholesterolemia, most notably, elevated levels of low-density lipoprotein cholesterol (LDL-C). This body of evidence has also been definitive in demonstrating that reducing levels of LDL-C with the use of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, otherwise known as statins, can result in a reduction of CV events and mortality. However, the use of statins is associated with substantial residual CV risk, even at maximally tolerated doses, and a small but important percentage of patients exhibit statin intolerance. Among the non-statin therapeutic options, the recent approval by Health Canada for use in certain patients of two proprotein convertase subtilisin / kexin type 9 (PCSK9) inhibitors provides a potent and safe new therapy to further lower LDL-C significantly. In this issue of *Cardiology Rounds,* we will examine the emerging role of PCSK9 inhibitors, recently presented outcomes evidence from the FOURIER trial, as well as the high-risk CV patient who might benefit from this new therapeutic option.

Despite decades of advances in pharmacotherapy and surgical management, cardiovascular disease (CVD) remains a leading cause of morbidity and mortality in Canada. In 2013, CVD was the cause of more than one-quarter of all deaths in Canada.[1] Approximately 2.4 million Canadians aged ≥20 years live with heart disease, including 490 300 who have experienced at least 1 myocardial infarction (MI) and 426 000 who have had a stroke.[2,3] An analysis of the Canadian Health Measures Survey estimated an overall mean 10-year risk of a CVD event of 8.9% among Canadians aged 20-79 years, and 19.7% were classified as being at high CVD risk according to Canadian Cardiovascular Society guidelines (ie, having a high-risk condition or a Framingham Risk Score ≥20%).[4,5] Heart disease is the number one cause of death in women over the age of 55, killing more women than men. Women are more likely to die from heart disease than any other disease.[2]

CVD also represents a significant pharmacoeconomic burden on the Canadian healthcare system, costing an estimated $20.9 billion annually in 2005 and projected to rise to $28.3 billion in 2020 (estimates in constant 2008 dollars).[6]

Management of Dyslipidemia with Statins

It is well established that CVD develops as a result of a combination of genetic and environmental factors (Table 1).[7,8] The primary causative process of CVD is atherosclerosis, characterized by the accumulation of lipids, inflammatory molecules, and other cellular debris in the arterial walls. A high level of serum cholesterol was described by Glass et al as being a unique CV risk factor because it is sufficient to initiate the development of atherosclerosis in the absence of other risk factors.[7] Intracellular cholesterol levels are controlled by sterol regulatory element-binding protein (SREBP) transcription factors, which stimulate several genes that initiate cholesterol biosynthesis, including increased expression of 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-R), the rate-limiting enzyme that induces endogenous cholesterol biosynthesis and is the target of statin drugs.[7,9]

Statins inhibit the activity of HMG-R, which activates SREBP, increases low-density lipoprotein (LDL) receptors, and produces greater hepatic clearance of LDL.[7] There are currently 6 approved statins in Canada: lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, and rosuvastatin. These agents have been studied in multiple landmark trials, involving patients with established CVD and those

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Table 1: Genetic and environmental risk factors for cardiovascular disease[7,8]

- Age
- Sex
- Family history
- Genetic factors
- Diabetes mellitus / insulin resistance
- Smoking
- Sedentary lifestyle
- Obesity / dietary habits
- Hypertension
- Dyslipidemia
  - High levels of low- and very low-density lipoprotein (LDL and VLDL)
  - Low levels of high-density lipoprotein (HDL)
  - Small LDL particles
  - Elevated serum lipoprotein (a)
- Elevated serum homocysteine
- Prothrombotic factors
- Inflammatory markers

at risk. The 2010 meta-analysis of the Cholesterol Treatment Trialists' (CTT) Collaboration concluded that for each 1-mmol/L reduction in LDL cholesterol (LDL-C) with statin treatment there was a 22% reduction in the risk of major CV events.[10] Similar benefit was observed across all baseline LDL-C levels, even for those with LDL-C <2 mmol/L, and the relationship between LDL-C and CV event risk remained constant irrespective of patient clinical characteristics or baseline prognostic factors. Subsequent analyses show this benefit was observed no matter what method of LDL-C lowering was employed (Robinson meta regression analysis).

The Canadian Cardiovascular Society (CCS) recommends statins as standard first-line therapy for most patients at moderate to high CV event risk.[11] The American Heart Association / American College of Cardiology (AHA/ACC) guidelines recommend treatment based upon the findings of clinical trials which do not consider cholesterol targets.[12] For high-risk patients the guidelines recommend intensive statin therapy without a focus on achieving LDL targets. In contrast the CCS and European Guidelines[13] consider treating to target to be the standard of care.

The Canadian Health Measures Survey found that 39% of Canadians aged 6–79 years have high total cholesterol levels, including 57% of individuals aged 40–59 years; LDL-C was ≥3.5 mmol/L in 40% of the 40–59 year age group.[14] Statins were prescribed for 2.8 million Canadians aged 20–79 years, representing 11.6% of this population, and another 3.7 million met the 2012 CCS guideline recommendations for statin therapy.[4]

Limitations to statin effectiveness

Despite the substantial benefits of statin therapy, limitations remain. Residual CV event risk persists even with maximum LDL-C reduction using statins. The CTT determined an annual rate of major CV events of 3.2% despite statin therapy.[10] As noted by Sampson et al,[15] 3 studies that evaluated the additional benefit of high-intensity statin in the reduction of CV events - the PROVE IT-TIMI 22, IDEAL, and TNT studies - had major CV event rates of 22.4%, 12.0%, and 8.7%, respectively, in the patient groups receiving atorvastatin 80 mg.[16-18]

Statin intolerance is another important consideration in the management of patients at high CV risk. A number of adverse effects have been reported with statin use (Table 2).[19] Despite a relatively low incidence of serious adverse effects in clinical trials, a Canadian Working Group Consensus Conference emphasized the large number of statin-intolerant patients, given the high prevalence of statin prescriptions.[20] In their study of the clinical and economic consequences of statin intolerance, Graham et al determined a 5% rate among all statin users.[21] A health system database analysis determined that 14.3% of patients with a high-risk indication for statins had discontinued their treatment due to intolerance, including 3.0% with a statin allergy.[22]

The Canadian Working Group recognised muscular complaints as the principal limitation to statin usage.[20] Approximately 7%–29% of patients reported statin-associated muscle symptoms, according to the findings of a European Atherosclerosis Society Consensus Panel from clinical trials, patient registries, and clinical experience.[23] However, many of these patients do not have true intolerance and suffer from a nocebo effect stimulated by ill-informed press and inadequate information provided by healthcare professionals.

Non-statin Lipid-modifying Therapies (LMTs)

The need for other cholesterol lowering strategies in addition to or replacing statins includes treatment to further lower LDL levels in an attempt to reduce the residual risk, the reduction of LDL in patients who do not achieve LDL targets despite the use of a maximally tolerated dose of a statin, and in patients who are intolerant to statins. Options for non-statin reductions in LDL-C include ezetimibe, bile acid sequestrants and PCSK9 inhibitors. Fibrates do not have much of an impact on LDL reduction and are largely used in patients with high triglycerides and low HDL-C. Niacin is no longer recommended for lipid control based on the negative results of clinical trials.[11,24,25]

Bile acid sequestrants were shown to significantly reduce CV events, though the key study was performed before the advent of statins.[26] The CCS guidelines state that it may be reasonable, despite the absence of trial data, to consider a bile acid sequestrant in high-risk patients who cannot achieve LDL-C goals on a maximally tolerated statin.[11]

Ezetimibe was approved by Health Canada in 2003 for the management, alone or as combination therapy, of primary hypercholesterolemia, homozygous familial hypercholes-

Table 2: Reported adverse effects of statins[19]

- Muscle-related symptoms
- Elevated hepatocellular enzymes
- Cancer
- New diabetes
- Hemorrhagic stroke
- Fatigue
- Neuro-psychiatric effects and insomnia
- Proteinuria / hematuria
- Erectile dysfunction
- Alopecia

terolemia, and homozygous sitosterolemia.[27] On the basis of the results of IMPROVE-IT,[28] the CCS guidelines recommend ezetimibe in combination with maximally tolerated statin as an option in the treat-to-target management of dyslipidemia (LDL-C <2.0 mmol/L or >50% reduction) as well as for the reduction of CVD events in adults ≥50 years with chronic kidney disease not treated with dialysis or kidney transplant.[11]

Proprotein convertase subtilisin / kexin type 9 (PCSK9) inhibitors

More recently, 2 members of a new class of LMT have been approved by Health Canada. Evolocumab and alirocumab are fully human monoclonal antibodies that target PCSK9, a serine protease that regulates cell surface receptors, including the LDL receptor, and is principally expressed by the liver.[29,30] PCSK9 promotes lysosomal degradation of LDL receptors, which inhibits the recycling of the LDL receptor and thus impairs clearance of LDL-C. The inhibition of PCSK9 represents a novel mechanism of LDL-C reduction that is additive to that of statins, as well as providing a potent LMT option for patients who are intolerant or unresponsive to statins. Development of a third PCSK9 inhibitor, bococizumab, was discontinued further to the gradual loss of LDL-C lowering, high levels of immunogenicity, and injection-site reactions.[31]

Evolocumab and alirocumab are indicated as combination therapy with maximally tolerated statins for the reduction of LDL-C in patients with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic (AS) CVD.[32,33] Evolocumab is also indicated as part of LDL-C-lowering combination therapy in adults or adolescents (≥12 years) with homozygous familial hypercholesterolemia (HoFH). The CCS guidelines suggest that PCSK9 inhibitors be considered to lower LDL-C level for patients with atherosclerotic CVD in those not at LDL-C goal despite maximally tolerated statin doses with or without ezetimibe therapy.[11] However, for patients whose LDL-C is >20% away from target, no add-on drug other than a PCSK9 inhibitor is likely to get the LDL-C to target.

Evolocumab and alirocumab are administered with prefilled autoinjectors. The dose for evolocumab in patients with HeFH or ASCVD is either 140 mg every 2 weeks (q2w) or 420 mg once monthly.[32] For patients with HoFH, the initial dose of evolocumab is 420 mg monthly; the dose can be increased after 12 weeks to 420 mg q2w if the patient has an inadequate response. The starting dose of alirocumab is 75 mg q2w; it may be increased to a maximum dose of 150 mg q2w.[33]

Clinical studies demonstrated that PCSK9 inhibitors, in combination with statins ± other lipid-lowering agents, produce a 40%-60% reduction in LDL-C beyond what is achieved with statin therapy.[34-38] The very low LDL-C levels that result are not associated with significant increases in adverse effects.

PCSK9 inhibitors in statin-intolerant patients

Both evolocumab and alirocumab have been tested against ezetimibe in cohorts of patients with intolerance to statins.

The GAUSS-3 trial identified patients with uncontrolled LDL-C (mean baseline LDL 5.7mmol/L) and intolerance to statins confirmed by blinded, placebo-controlled statin challenge; and randomized 218 of these patients to evolocumab or ezetimibe.[39] The mean percent reduction in LDL-C in the ezetimibe group was 16.7% from baseline to Week 24; evolocumab reduced LDL-C from baseline by 52.8% at 24 weeks (P<0.001). In terms of safety, the ezetimibe group reported more muscle symptoms than those taking evolocumab (28.8% versus 20.7%) and more ezetimibe patients than evolocumab patients discontinued their treatment further to muscle symptoms (6.8% versus 0.7%).

In the ODYSSEY ALTERNATIVE trial, 361 patients at moderate to high CV risk who discontinued statins due to muscle symptoms were randomized to alirocumab 75 mg q2w, ezetimibe 10 mg daily, or atorvastatin 20 mg daily (rechallenge) for 24 weeks.[40] Alirocumab could be uptitrated to 150 mg q2w at Week 12. The primary endpoint – mean percent change in LDL-C from baseline to week 24 – was 14.6% for ezetimibe and 45.0% for alirocumab (P<0.0001). There were fewer musculoskeletal complaints (32.5% versus 41.1%) and musculoskeletal complaints leading to discontinuation (15.9% versus 20.2%) associated with alirocumab versus ezetimibe.

Heterozygous familial hypercholesterolemia

In the 12-week RUTHERFORD-2 study, 329 HeFH patients were randomized to evolocumab 140 mg q2w or 420 mg monthly or to placebo.[34] Patients were taking statins with or without other LMTs, with 87% on high-intensity statin therapy. The baseline average LDL-C was 4.0 mmol/L. Compared with controls, the mean LDL-C reductions with evolocumab 140 mg q2w and 420 mg monthly were 61% and 60%, respectively (P<0.0001 for each).

The ODYSSEY FH I and FH II trials randomized a total of 735 HeFH patients taking maximally tolerated statin with or without other LMTs to alirocumab 75 mg q2w or placebo.[35] This initial dose was uptitrated to 150 mg q2w in patients with LDL-C ≥1.8 mmol/L at Week 12, which occurred in 43.4% and 38.6% of FH I and FH II patients, respectively. Baseline mean LDL-C levels were 3.74 mmol/L in FH I and 3.48 mmol/L in FH II. Mean LDL-C reductions relative to placebo at Week 24 were 56.3% (FH I) and 50.2% (FH II) among patients who had been uptitrated and 48.4% and 47.6%, respectively, for patients who remained on the initial alirocumab dose (P<0.0001 for all differences).

Homozygous familial hypercholesterolemia

In TESLA Part B,[41] 49 HoFH patients were randomized to evolocumab 420 mg monthly or placebo, in combination with other LMTs (all on statins and 92% on ezetimibe). Ten patients were aged 13-17 years, 7 of whom received evolocumab. The mean LDL-C at baseline was 9.0 mmol/L. At Week 12, the mean reduction in LDL-C with evolocumab was 30.9% versus placebo (P<0.0001).

Clinical ASCVD

Evolocumab was investigated in clinical ASCVD patients in the LAPLACE-2 combination therapy study and the DESCARTES long-term efficacy study.[36,37] In LAPLACE-2, 296 with clinical ASCVD were randomized to different statin regimens in an open-label format and then randomized to evolocumab 140 mg q2 or 420 mg monthly or to placebo for 12 weeks.[36] The mean baseline LDL-C after 4 weeks of statin therapy was 2.8 mmol/L. At Week 12, LDL-C was reduced versus placebo by 74% for the 140 mg q2w dose and by 63%

for the 420 mg monthly dose ($P<0.0001$ for each). In DESCARTES, patients were initiated on 1 of 4 background LMTs for a run-in period of 4-12 weeks: diet alone, diet + atorvastatin 10 mg daily, atorvastatin 80 mg daily, or atorvastatin 80 mg daily + ezetimibe 10 mg daily.[37] Those with an LDL-C of ≥1.9 mmol/L after this run-in treatment were randomized to evolocumab 420 mg monthly or placebo. The mean baseline LDL-C on background therapy was 2.7 mmol/L. The overall mean reduction in LDL-C versus placebo was 57.0% ($P<0.001$), and was significant ($P<0.001$) for all baseline treatment groups.

COMBO I and COMBO II studied alirocumab in patients with hypercholesterolemia at very high CV risk.[38] All COMBO I patients were taking maximally tolerated statins with or without other LMTs, while COMBO II employed ezetimibe 10 mg daily on top of existing statin therapy as the control. Patients were randomized to alirocumab 75 mg q2w or control, with the option of dose uptitration (150 mg q2w) in line with other studies. The mean baseline LDL-C was 2.6 mmol/L for COMBO I, and was 2.8 for the alirocumab group and 2.7 for the control (ezetimibe) group for COMBO II; 16.8% of alirocumab patients were uptitrated in COMBO I and 18.4% in COMBO II. At 24 weeks, the reduction in LDL-C compared with placebo was 42.7% in those who were uptitrated and 46.0% in those who remained on the initial dose ($P<0.0001$ for each) in COMBO I. In COMBO II, the mean difference in LDL-C reduction for alirocumab versus ezetimibe was 27.7% (47.8% versus 20.1%; $P<0.0001$).

Effect on CV mortality and morbidity: FOURIER trial

More recently, the 'Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk' (FOURIER) trial evaluated the impact of evolocumab on composites of major CV events (primary outcome: CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization; secondary outcome: CV death, MI, or stroke) in 27 564 ASCVD patients with LDL-C ≥1.8 mmol/L.[42] All patients were on an effective dose of statin, 69.3% at high intensity. Patients were randomized to the previously studied evolocumab doses (140 mg q2w or 420 mg monthly) or to placebo. The median baseline LDL-C was 2.4 mmol/L and 69.3% of patients were taking high-intensity statins. The majority of patients had a high CV risk condition:

- 81.1% with a previous MI
- 19.4% with a history of nonhemorrhagic stroke
- 13.2% with peripheral artery disease
- 36.6% with diabetes mellitus (DM)

The median duration of follow-up was 2.2 years.

The mean LDL-C reduction at 48 weeks for evolocumab versus placebo was 59% ($P<0.001$). Significant reductions were observed in the primary and secondary endpoints with evolocumab versus placebo. The primary endpoint occurred in 9.8% of evolocumab patients and in 11.3% of controls, representing a 15% reduction in risk (hazard ratio 0.85; 95% CI 0.79-0.92; $P<0.001$) (Figure 1). Occurrence of the key secondary endpoint was reduced by 20% with evolocumab (5.9% versus 7.4%; HR 0.80; 95% CI 0.73-0.88; $P<0.001$). The incidence of fatal and nonfatal cardiac events was reduced, with relative reductions of 26.1% for MI (3.4% with evolocumab versus 4.6% for placebo; $P<0.001$), 21.1% for stroke (1.5% versus 1.9%; $P=0.01$), and 21.4% for coronary revascularization (5.5% versus 7.0%; $P<0.001$); there were no significant reductions in CV or all-cause mortality or hospitalization for unstable angina. These effects of evolocumab were consistent across different patient groups (eg, age, sex, type of atherosclerotic vascular disease), baseline LDL-C levels, and statin intensities.

The investigators noted that these reductions in CV risk tended to increase over time. For the primary endpoint, the benefit was 12% in the first year and 19% thereafter; the first-year and beyond benefits for the secondary endpoint were 16% and 25%, respectively. A similar phenomenon has been observed with statin treatment.[43]

No significant differences were observed between the evolocumab and control groups in terms of adverse effects, including new-onset DM and neurocognitive events; the sole exception was injection-site reactions, which were more frequent in the evolocumab group (2.1% versus 1.6%; $P<0.001$).

Potential adverse effects

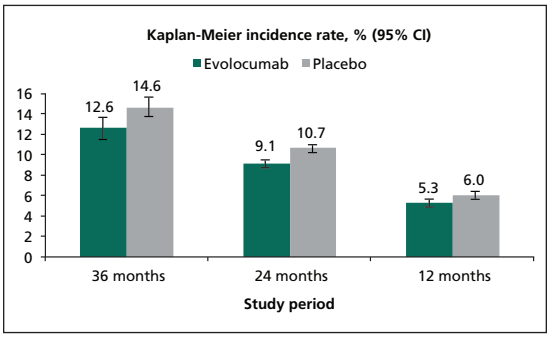
Despite the overall safety profile of evolocumab and alirocumab in clinical studies, some concerns have been raised about potential adverse effects. The United States Food and Drug Administration requested in early 2014 that patients receiving PCSK9 inhibitors be monitored for neurocognitive adverse effects.[43] Because of the high concentration of total cholesterol in the brain, significant reductions were believed to have the potential to adversely affect neurological function. However, no study to date has established a causal relationship between cholesterol reduction in the central nervous system and functional impairment.[44]

Effect on cognitive function: EBBINGHAUS study

The 'Evaluating PCSK9 Binding Antibody Influence On Cognitive Health in High Cardiovascular Risk Subjects' (EBBINGHAUS) study investigated the effect of evolocumab on cognitive function using the Cambridge Neuropsychological Test Automated Battery (CANTAB) Assessments.[45] In this study, 1974 patients were recruited from the FOURIER trial, with a primary endpoint of spatial working memory strategy index of executive function. As presented at the 2017 ACC meeting, mean change in the primary outcome was -0.21 for evolocumab and -0.29 for placebo (P for noninferiority <0.0001).[46] Furthermore, no differences between evolocumab and placebo were seen for any of the secondary endpoints nor in patient questionnaire and detailed analysis of adverse events, and no evidence of differences in cognitive tests by achieved nadir LDL-C, even <0.65 mmol/L.

Concern has been expressed regarding the potential increase in new-onset DM among patients treated with PCSK9 inhibitors. The study evidence to date does not

Figure 1: FOURIER study: incidence of the primary outcome[42]



support this hypothesis; a pooled analysis of 10 ODYSSEY Phase III studies demonstrated no evidence of an increased incidence of DM in 3448 patients who did not have DM at baseline.[47]

Conclusion

As CV-related morbidity and mortality remain at a high level in the Canadian population, research continues to expand the clinician's therapeutic options. Elevation of LDL-C is an established causative factor and treatment target in the development and prevention of major CV events. While statins are the current first-line agents, residual risk and statin intolerance are important considerations in the management of the patient at high CV risk. PCSK9 inhibitors represent an important new therapeutic option for significantly reducing LDL-C. Of particular importance to clinicians, the 2-year FOURIER trial now provides evidence of significant benefit with the use of evolocumab in the reduction of CV event risk without a marked increase in adverse effects.

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References:

1. Statistics Canada. Deaths and mortality rate (age standardization using 1991 population), by selected grouped causes and sex, Canada, provinces and territories: annual. Available at: http://www5.statcan.gc.ca/cansim/a05?lang=eng&id=01020552. Accessed on April 24, 2017.
2. Public Health Agency of Canada. Heart disease in Canada. Available at: https://www.canada.ca/en/public-health/services/publications/diseases-conditions/heart-disease-canada.html. Accessed on April 20, 2017.
3. Ontario Stroke Network. Stroke statis & facts. Available at: http://ontariostrokenetwork.ca/information-about-stroke/stroke-stats-and-facts. Accessed on April 24, 2017.
4. Hennessy DA, Tanuseputro P, Tuna M, et al. Population health impact of statin treatment in Canada. Statistics Canada Health Reports. Catalogue no. 82-003-X. Release data: January 20, 2016.
5. Anderson TJ, Grégoire J, Hegele RA, et al. 2012 update of the Canadian Cardiovascular Society guidelines for the diagnosis and treatment of dyslipidemia for the prevention of cardiovascular disease in the adult population. *Can J Cardiol.* 2013;29(2):151-167.
6. Conference Board of Canada. Report: Achieving heart health targets would lead to big savings for Canada. New release 10-73; 2008. Available at: http://www.conferenceboard.ca/press/newsrelease/10-02-08/report_achieving_heart_health_targets_would_lead_to_big_savings_for_canada.aspx. Accessed on April 24, 2017.
7. Glass CK, Witztum JL. Atherosclerosis: the road ahead. *Cell.* 2001;104(4):503-516.
8. Sayols-Baixeras S, Luis-Ganella C, Lucas G, Elosua R. Pathogenesis of coronary artery disease: focus on genetic risk factors and identification of genetic variants. *Appl Clin Genet.* 2014;7:15-32.
9. Brown MS, Goldstein JL. The SREBP pathway: regulation of cholesterol metabolism by proteolysis of a membrane bound transcription factor. *Cell.* 1997;89:331-340.
10. Cholesterol Treatment Trialists' (CTT) Collaborators; Baigent C, Blackwell L, Emberson J, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: A meta-analysis of data from 170 000 participants in 26 randomised trials. *Lancet.* 2010;376(9753):1670-1681.
11. Anderson TJ, Grégoire J, Pearson GJ, et al. 2016 Canadian Cardiovascular Society guidelines for the management of dyslipidemia for the prevention of cardiovascular disease in the adult. *Can J Cardiol.* 2016;32(11):1263-1282.
12. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, Goldberg AC, Gordon D, Levy D, Lloyd-Jones DM, McBride P, Schwartz JS, Shero ST, Smith SC, Jr., Watson K, Wilson PW. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2014;63(25 Pt B):2889-2934.
13. Task Force for the Management of Dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS); Reiner Z, Catapano AL, De Backer G, et al. ESC/EAS Guidelines for the management of dyslipidaemias. *Eur Heart J.* 2011;32(14):1769-818.
14. Statistics Canada. Cholesterol levels of Canadians, 2009 to 2011. Health Fact Sheet 82-625-X. February 13, 2013. Available at: http://www.statcan.gc.ca/pub/82-625-x/2012001/article/11732-eng.htm. Accessed on April 27, 2017.
15. Sampson UK, Fazio S, Linton MF. Residual cardiovascular risk despite optimal LDL-cholesterol reduction with statins: the evidence, etiology, and therapeutic challenges. *Curr Atheroscler Rep.* 2012;14(1):1-10.
16. Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med.* 2004;350(15):1495-1504.
17. LaRosa JC, Grundy SM, Waters DD, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med.* 2005;352(14):1425-1435.
18. Pedersen TR, Faergeman O, Kastelein JJ, et al; Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) Study Group. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial. *JAMA.* 2005;294(19):2437-2445.
19. Fitchett D, Mancini GBJ, Hegele R. Statin intolerance and adverse effects: Canadian Working Group consensus. Available at: https://www.ccs.ca/images/Guidelines/Slide%20Decks/Lipids_Gui_2012_Statins_SD_EN.ppt. Accessed on April 26, 2017.
20. Mancini GBJ, Baker S, Bergeron J, et al. Diagnosis, prevention, and management of statin adverse effects and intolerance: proceedings of a Canadian Working Group Consensus Conference. *Can J Cardiol.* 2011;27(5):635-662.
21. Graham JH, Sanchez RJ, Saseen JJ, Mallya UG, Panaccio MP, Evans MA. Clinical and economic consequences of statin intolerance in the United States: Results from an integrated health system. *J Clin Lipidol.* 2017;11(1):70-79.

22. Saeed B, Wright E, Evans M, Lewis M, Steinhubl S. Prevalence of statin intolerance in a high risk cohort and management strategies in contemporary cardiology. *Clin Med Res*. 2013;11(3):136. Abstract PS1-45.
23. Stroes ES, Thompson PD, Corsini A, et al; European Atherosclerosis Society Consensus Panel. Statin-associated muscle symptoms: impact on statin therapy—European Atherosclerosis Society Consensus Panel Statement on Assessment, Aetiology and Management. *Eur Heart J*. 2015; 36(17):1012-1022.
24. HPS2-THRIVE Collaborative Group; Landray MJ, Haynes R, Hopewell JC, et al. Effects of extended-release niacin with laropiprant in high-risk patients. *N Engl J Med*. 2014;371(3):203-212.
25. AIM-HIGH Investigators; Boden WE, Probstfield JL, Anderson T, et al. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. *N Engl J Med*. 2011;365(24):2255-2267.
26. The Lipid Research Clinics Coronary Primary Prevention Trial results. I. Reduction in incidence of coronary heart disease. *JAMA*. 1984; 251(3):351-364.
27. Merck Canada Inc. Ezetrol® (ezetimibe tablets) Product Monograph. Date of preparation: March 6, 2012.
28. Cannon CP, Blazing MA, Giugliano RP, et al; IMPROVE-IT Investigators. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med*. 2015;372(25):2387-2397.
29. Chan JC, Piper DE, Cao Q, et al. A proprotein convertase subtilisin/kexin type 9 neutralizing antibody reduces serum cholesterol in mice and nonhuman primates. *Proc Natl Acad Sci U S A*. 2009;106(24): 9820-9825.
30. Marais DA, Blom DJ, Petrides F, Gouëffic Y, Lambert G. Proprotein convertase subtilisin/kexin type 9 inhibition. *Curr Opin Lipidol*. 2012;23(6):511-7.
31. Pfizer Inc. Press release: Pfizer discontinues global development of bococizumab, its investigational PCSK9 inhibitor. November 1, 2016. Available at: http://www.pfizer.com/news/press-release/press-release-detail/pfizer_discontinues_global_development_of_bococizumab_its_investigational_pcsk9_inhibitor. Accessed on April 28, 2017.
32. Amgen Canada. Repatha™ (evolocumab) Product Monograph. Date of approval: December 15, 2016.
33. Sanofi-aventis Canada Inc. Praluent™ (alirocumab) Product Monograph. Date of approval: April 11, 2016.
34. Raal F, Scott R, Somaratne R, et al. Low-density lipoprotein cholesterol-lowering effects of AMG 145, a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 serine protease in patients with heterozygous familial hypercholesterolemia: the Reduction of LDL-C with PCSK9 Inhibition in Heterozygous Familial Hypercholesterolemia Disorder (RUTHERFORD) randomized trial. *Circulation*. 2012;126(20): 2408-2417.
35. Kastelein JJP, Ginsberg HN, Langslet G, et al. ODYSSEY FH I and FH II: 78-week results with alirocumab treatment in 735 patients with heterozygous familial hypercholesterolemia. *Eur Heart J*. 2015;36(43): 2996-3003.
36. Robinson JG, Nedergaard, BS, Rogers WJ, et al. Effect of evolocumab or ezetimibe added to moderate or high-intensity statin therapy on LDL-C lowering in patients with hypercholesterolemia: the LAPLACE-2 Randomized Clinical Trial. *JAMA*. 2014;311(18):1870-1882.
37. Blom DJ, Hala T, Bolognese M, et al; DESCARTES Investigators. A 52-week placebo-controlled trial of evolocumab in hyperlipidemia. *N Engl J Med*. 2014;370(19):1809-1819.
38. Colhoun HM, Robinson JG, Farnier M, et al. Efficacy and safety of alirocumab, a fully human PCSK9 monoclonal antibody, in high cardiovascular risk patients with poorly controlled hypercholesterolemia on maximally tolerated doses of statins: rationale and design of the ODYSSEY COMBO I and II trials. *BMC Cardiovasc Disord*. 2014;14:121.
39. Nissen SE, Stroes E, Dent-Acosta RE, et al; GAUSS-3 Investigators. Efficacy and tolerability of evolocumab vs ezetimibe in patients with muscle-related statin intolerance: the GAUSS-3 randomized clinical trial. *JAMA*. 2016;315(15):1580-1590.
40. Moriarty PM, Thompson PD, Cannon CP, et al; ODYSSEY ALTERNATIVE Investigators. Efficacy and safety of alirocumab vs ezetimibe in statin-intolerant patients, with a statin rechallenge arm: the ODYSSEY ALTERNATIVE randomized trial. *J Clin Lipidol*. 2015;9(6):758-769.
41. Raal FJ, Honarpour N, Blom DJ, et al. Inhibition of PCSK9 with evolocumab in homozygous familial hypercholesterolaemia (TESLA Part B): a randomised, double-blind, placebo-controlled trial. *Lancet*. 2015;385(9965):341-350.
42. Sabatine MS, Giugliano RP, Keech AC, et al; FOURIER Steering Committee and Investigators. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med*. 2017;376(18):1713-1722.
43. Collins R, Reith C, Emberson J, et al. Interpretation of the evidence for the efficacy and safety of statin therapy. *Lancet*. 2016;388(10059):2532-2561.
44. Swiger KJ, Martin SS. PCSK9 inhibitors and neurocognitive adverse events: exploring the FDA directive and a proposal for *N*-of-1 trials. *Drug Saf*. 2015;38(6):519-526.
45. Giugliano RP, Mach F, Zavitz K, et al; EBBINGHAUS Investigators. Design and rationale of the EBBINGHAUS trial: A phase 3, double-blind, placebo-controlled, multicenter study to assess the effect of evolocumab on cognitive function in patients with clinically evident cardiovascular disease and receiving statin background lipid-lowering therapy-A cognitive study of patients enrolled in the FOURIER trial. *Clin Cardiol*. 2017;40(2):59-65.
46. EBBINGHAUS: no effect on neurocognition with evolocumab. Available at: http://www.acc.org/latest-in-cardiology/articles/2017/03/13/17/44/sat-8am-ebbinghaus-cognitive-study-of-patients-enrolled-in-fourier-acc-2017. Accessed on April 28, 2017.
47. Colhoun HM, Ginsberg HN, Robinson JG, et al. No effect of PCSK9 inhibitor alirocumab on the incidence of diabetes in a pooled analysis from 10 ODYSSEY Phase 3 studies. *Eur Heart J*. 2016;37(39):2981-2989.

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