Updated guidelines for the management of dyslipidemia and prevention of cardiovascular disease by pharmacists

Ricky D. Turgeon, BScPhm, ACPR; Todd J. Anderson, MD, FRCP(C); Jean Grégoire, MD, FRCP(C); Glen J. Pearson, BSc, BScPhm, PharmD, FCSHP

Introduction

Cardiovascular (CV) disease continues to be a significant cause of morbidity and mortality—coronary disease and cerebrovascular disease are the second and third leading causes of death, respectively, in Canada.¹ In 2007, a set of dyslipidemia guidelines tailored to pharmacists based on the 2006 Canadian Cardiovascular Society (CCS) recommendations was published in the *Canadian Pharmacists Journal*.² Since then, pharmacists in many provinces have expanded their scope of practice, including in some cases the ability to independently prescribe or modify existing therapies and order laboratory tests. There is growing evidence that pharmacist intervention in the management of dyslipidemia leads to improvements in lipid management.³ Moreover, expanding evidence in the realm of dyslipidemia, including trials in previously understudied populations (chronic kidney disease), innovations in CV risk communication (Cardiovascular Age) and increased awareness of the adverse effect profile of statins led to the publication of the 2012 update of the CCS guidelines for the diagnosis and treatment of dyslipidemia for the prevention of cardiovascular disease in the adult.⁴ In this article, we provide an update based on the current CCS guidelines, with practical tips for pharmacists.

Screening

Pharmacists in all practice settings can play a key role in screening individuals for dyslipidemia and overall CV risk. The CCS screening recommendations, which can serve as a template for a focused patient history and clinical assessment, are summarized in Table 1. In addition to undergoing a routine fasting lipid panel, individuals should also be screened for hypertension, diabetes and chronic kidney disease (CKD) using appropriate laboratory tests.

Cardiovascular risk assessment

- a) Pharmacists should actively engage with patients in discussion of CV risk.
- b) The following patients are considered to be at high CV risk; therefore, the use of a CV risk calculator (intended for primary prevention) is neither necessary nor appropriate:
 - Clinical evidence of atherosclerosis, as detailed in Table 1
 - Abdominal aortic aneurysm (AAA)
 - Diabetes mellitus, with additional risk factors (age ≥ 40 , age ≥ 30 plus diabetes duration ≥ 15 years, or microvascular disease [retinopathy, nephropathy, neuropathy])
 - CKD (estimated glomerular filtration rate [eGFR] ≤ 45 or urine

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TABLE 1 CCS recommendations for who to screen and how

Who	How
<p>Demographics:</p> <ul style="list-style-type: none"> • Men ≥ 40 years of age • Women ≥ 50 years of age or postmenopausal • Consider screening at an earlier age for at-risk ethnic groups (e.g., First Nations, South Asians) 	<ul style="list-style-type: none"> • Hypertension: Blood pressure using proper manual technique or device approved by Hypertension Canada • Dyslipidemia: Standard lipid panel (total cholesterol, HDL, LDL and triglycerides) • Diabetes: Fasting plasma glucose or hemoglobin A1c • Chronic kidney disease: eGFR $\pm$ UACR
<p>Family history:</p> <ul style="list-style-type: none"> • Of premature CV disease in a first-degree relative (females <65 years or males <55 years) • Of hyperlipidemia 	
<p>Or any of the following, regardless of age:</p> <ul style="list-style-type: none"> • Clinical evidence of atherosclerosis, including: <ul style="list-style-type: none"> ◦ Cerebrovascular disease (stroke or transient ischemic attack) ◦ Coronary artery disease (stable angina or previous acute coronary syndrome) ◦ Peripheral artery disease (intermittent claudication or ankle-brachial index <0.90) • Current tobacco use • Chronic obstructive pulmonary disease • Hypertension • Obesity (body mass index >27 kg/m²) • Abdominal aneurysm • Chronic kidney disease (eGFR ≤ 60 mL/min/1.73 m² or UACR ≥ 3 mg/mmol) • Diabetes mellitus • Clinical manifestations of hyperlipidemia* • Erectile dysfunction • HIV infection • Inflammatory disease (e.g., inflammatory bowel disease, systemic lupus erythematosus, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis) 	

*Includes corneal arcus (white ring around the iris of the eye), xanthelasma (yellow papules around the eyelids), xanthoma (yellowish cholesterol deposit under skin around joints or tendons, most commonly on the hands, elbows or the Achilles tendons). Examples can be seen in Hovingh et al.¹² CCS, Canadian Cardiovascular Society; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; UACR, urinary albumin-to-creatinine ratio.

- albumin-to-creatinine ratio [UACR] ≥ 30 , or eGFR $\leq 60 + \text{UACR} \geq 3$)
- Hypertension plus ≥ 3 additional risk factors (age >55 years, smoking, total cholesterol/HDL-C ratio >6 , left ventricular hypertrophy [LVH], family history of premature CV disease, electrocardiogram [ECG] abnormalities or microalbuminuria).
- c) A risk calculator incorporating validated CV risk factors—generally age, sex, smoking status, blood pressure, lipid profile, presence of diabetes and use of

CV medications—should be used to estimate a patient's overall long-term CV risk for primary prevention patients. A calculator that estimates 10-year risk based on the Framingham Heart Study is most commonly used, such as the modified Framingham Risk Score (FRS), recommended in the CCS Lipid Guidelines (specific application available at www.ccs.ca/index.php/en/resources/mobile-apps).

d) Although not specifically recommended in the 2012 update of the CCS guidelines, additional FRS-based tools are available

TABLE 2 Additional considerations when calculating cardiovascular risk

- **Accuracy:** No tool exists that predicts who will experience a CV event with 100% certainty. With that in mind, the Framingham Risk Score (FRS) provides a reasonable estimate of risk and has stood “the test of time,” with its predictive power only modestly improving when adding newer, more expensive tests (see “Secondary testing” below).
- **Age:** In the Framingham Heart Study, increasing age was one of the strongest risk factors for a CV event and contributes heavily to a patient’s FRS. Thus, patients who maintain the same level of control of their modifiable CV risk factors will still have an increasing FRS over time. Additionally, the FRS becomes less accurate at the higher extremes of age because of the natural increasing comorbidity burden, particularly cancer, with age.
- **Family history:** The CCS guidelines recommend doubling of calculated Framingham 10-year CV percent risk for patients (age 30–59) who have a family history of premature CV disease, which is referred to as the modified FRS. The modified FRS awaits formal validation. In otherwise low-risk patients, the modified FRS may overestimate risk and lead to overtreatment.¹³
- **Patients receiving treatment:** The Framingham calculator was not intended for use in patients already receiving pharmacotherapy for CV risk management. For example, the Framingham calculator does not take into account the use of ASA, or the inferior CV reduction of β -blockers, despite similar blood pressure reduction compared with other antihypertensives.¹⁴
- **Risk categories:** The CCS acknowledges that the 3 risk categories used in the guidelines are arbitrary but useful yardsticks that should be supplemented by clinical judgment and patient values whenever possible.
- **Secondary testing:** Some of the most widely used secondary testing methods are the ankle-brachial index (ABI), high-sensitivity C-reactive protein (hs-CRP) and coronary artery calcium (CAC).
 - **ABI:** Measures the ratio of systolic blood pressure between the legs and arms. A lower ratio (especially <0.90) indicates decreased perfusion pressure to the lower extremities, which strongly suggests peripheral artery disease (PAD). Patients with PAD have similar CV risk as those with existing CAD and should be targeted with aggressive CV reduction.^{15,16}
 - **hs-CRP:** A marker of inflammation, which is involved in the pathogenesis of atherosclerosis. In patients at intermediate risk (10%–19%), it very rarely leads to meaningful improvements in risk prediction, such as moving a patient into one of the more definitive low-risk (<10%) or high-risk ($\geq$ 20%) categories.¹⁷
 - **CAC:** Involves a computed tomography (CT) scan of the chest to measure calcification of the coronary arteries, which is a measure of coronary atherosclerosis. This technique holds promise in further stratifying a subset of intermediate-risk patients, although additional validation studies are needed before widespread and routine clinical use are recommended.¹⁸

CCS, Canadian Cardiovascular Society; ASA, acetylsalicylic acid.

TABLE 3 Monitoring of statins

Adverse effect	Parameter	Comment
Cognitive impairment	Mini Mental Status Exam	Statins are rarely if ever the culprit.
Hepatotoxicity	Patient report of severe nausea, vomiting or abdominal pain with jaundice Liver enzymes (alanine aminotransferase [ALT]) at baseline only	Routine liver enzyme monitoring is no longer recommended ¹⁹ ; instead, ALT should be measured if hepatotoxicity is suspected based on signs and symptoms.
Diabetes mellitus	Fasting plasma glucose Hemoglobin A1c	
Myotoxicity	Patient report of myalgias, muscle cramps, dark urine Creatine kinase (CK)	Routine CK monitoring is no longer recommended ¹⁹ ; instead, CK should be measured if myotoxicity is suspected based on signs and symptoms.

TABLE 4 Nonstatin lipid-lowering agents

Cholestyramine	<p>Evidence of efficacy and safety:</p> <ul style="list-style-type: none"> • A single RCT from 1984 serves as the single clinical outcome study supporting cholestyramine for reduction of CV events.²³ This double-blind RCT found that cholestyramine 24 g/d vs matching placebo powder in 3806 men age 35-59 years with total cholesterol ≥ 6.9 mmol/L and LDL-C ≥ 5.0 mmol/L reduced the risk of definite coronary death or myocardial infarction by an absolute 1.7%. <p>Other uses:</p> <ul style="list-style-type: none"> • Familial hypercholesterolemia • Hypercholesterolemia during pregnancy • Cholestatic pruritus
Ezetimibe	<p>Evidence of efficacy and safety:</p> <ul style="list-style-type: none"> • Available on the Canadian market since 2003, there is no published evidence to date that confirms that ezetimibe's effect on LDL-C reduction decreases CV events. The SHARP study did demonstrate that the combination of simvastatin and ezetimibe decreased CVD events in subjects with chronic kidney disease compared with placebo; however, no statin-only arm was tested, and the relative contribution of ezetimibe to the CVD reduction cannot be determined.²⁴ Overall, ezetimibe is well tolerated, and an ongoing large RCT is slated to shed some light on the long-term effect of ezetimibe on CV and non-CV clinical outcomes. <p>Other uses:</p> <ul style="list-style-type: none"> • Familial hypercholesterolemia
Fibrates	<p>Evidence of efficacy and safety:</p> <ul style="list-style-type: none"> • In patients not receiving a statin, fibrates have shown a small reduction in nonfatal CV events.²⁵ Conversely, in the ACCORD trial of type 2 diabetic patients already receiving a statin, fenofibrate did not produce a statistically significant reduction in CV events.²⁶ Therefore, there appears to be a small role for fibrates in patients unable to take a statin but not as adjunctive therapy to statins. As with statins, fibrates can cause muscle-related symptoms and rhabdomyolysis. <p>Other uses:</p> <ul style="list-style-type: none"> • Treatment of hypertriglyceridemia to prevent pancreatitis
Niacin	<p>Evidence of efficacy and safety:</p> <ul style="list-style-type: none"> • The Coronary Drug Project, a randomized, placebo-controlled secondary prevention trial conducted between 1966 and 1975, demonstrated a significant reduction in CVD events in patients treated with niacin compared with placebo.^{27,28} More recently, 2 large RCTs failed to identify any CV benefit of niacin when added to statin therapy.^{29,30} Additionally, intolerance to niacin is common, primarily due to flushing, itching and gastrointestinal upset. Additional adverse effects related to niacin include diabetes, liver enzyme elevations and myopathy. Thus, niacin's potential place in therapy is in a small subset of patients who have contraindications to statins but can tolerate niacin.
Omega-3 fatty acids	<p>Evidence of efficacy and safety:</p> <ul style="list-style-type: none"> • Although observational studies and early RCTs suggested a beneficial effect of omega-3 fatty acid intake on CV events, modern, higher quality meta-analyses and RCTs have not demonstrated any beneficial CV effects of omega-3 fatty acid supplementation.^{31,32} It is still reasonable to recommend omega-3-rich foods such as fish, but nondietary omega-3 fatty acid supplementation is no longer recommended. <p>Other uses:</p> <ul style="list-style-type: none"> • Treatment of hypertriglyceridemia to prevent pancreatitis

RCT, randomized controlled trials; CV, cardiovascular; LDL-C, low-density lipoprotein cholesterol; CVD, cardiovascular disease.

to calculate CV risk and benefits of CV risk therapies, which may be useful in specific clinical or patient care discussions. These include the Mayo Clinic Statin/Aspirin Choice Decision Aid (<http://statindecisionaid.mayoclinic.org>) and the Absolute CVD Risk/Benefit Calculator (www.bestsclencemedicine.com/chd/calc2.html). The Mayo Clinic tool calculates CV risk and provides the CV benefits and adverse effects expected from starting either a statin or acetylsalicylic acid (ASA) for primary prevention. The Absolute CV Risk/Benefit Calculator is similar to the Mayo Clinic tool but also allows for the discussion of the effect of lifestyle and additional pharmacotherapies (e.g., diabetes and hypertension management) on CV risk.

- e) In addition, patients with a calculated 10-year risk of CV events $\geq 20\%$ are considered to be at high CV risk.
- f) “Cardiovascular Age,” which is automatically calculated with the FRS in the CCS Dyslipidemia Guideline app, can be used to motivate behavioural change. Cardiovascular Age provides patients with an estimate of the effect of risk factors on aging of their CV system compared with their chronological age. For example, a 45-year-old nondiabetic male smoker with total cholesterol 5.0 mmol/L, HDL-C 1.0 mmol/L and untreated blood pressure 130/80 has a Cardiovascular Age of 49.4 years. Thus, his risk factors are “causing” accelerated aging of his CV system by 4.4 years. Cardiovascular Age may be particularly useful in eliciting emotional response and behavioural change in younger individuals with high risk factor burden, such as smoking, with low short-term—but high lifetime—CV risk.
- g) Secondary testing (addition of biomarkers, such as high-sensitivity C-reactive protein [hs-CRP], or diagnostic tests, such as coronary artery calcium scoring, to the basic Framingham calculator to further stratify CV risk) may be considered for intermediate-risk patients (10-year CV risk 10%-19%) for whom treatment decisions are uncertain. However, in most jurisdictions these secondary tests are only available to primary care or specialist physicians.

- h) For patients not currently receiving pharmacotherapy for CV risk reduction, CV risk assessment should be repeated:

- Yearly if latest 10-year CV risk $\geq 5\%$
- Every 3 to 5 years if $< 5\%$

Who should be treated?

Ultimately, patients are the ones to decide whether to initiate and continue lifelong therapy to reduce their CV risk. Nonetheless, treatment is generally recommended based on randomized controlled trial (RCT) evidence of benefit outweighing harms in the following patient populations:

- a) All high-risk individuals (Framingham CV risk $\geq 20\%$ or any factors as presented in the CV risk section).
- b) Intermediate-risk individuals (Framingham CV risk 10%-19%) with
 - LDL-C ≥ 3.5 mmol/L or
 - Non-HDL-C ≥ 4.3 mmol/L (easily calculated from standard lipid panel by subtracting HDL-C from the total cholesterol) or
 - Apolipoprotein B (apoB) ≥ 1.2 g/L.
- c) Low-risk individuals (Framingham CV risk $< 10\%$) with
 - LDL-C ≥ 5.0 mmol/L or
 - Evidence of familial hypercholesterolemia

Lipid targets

The CCS guidelines recommend the following lipid targets:

- a) For high- and intermediate-risk individuals:
 - LDL-C level ≤ 2.0 mmol/L or a $\geq 50\%$ reduction from baseline
 - Alternate treatment targets include apoB ≤ 0.8 g/L or non-HDL-C ≤ 2.6 mmol/L.
- b) For low-risk individuals, a reduction in LDL-C $\geq 50\%$ from baseline is recommended.

Lifestyle changes

- a) Healthy eating habits should be encouraged in all individuals, particularly those at higher risk of CV disease, including the following recommendations:
 - Consume sufficient calories to maintain a healthy body weight
 - Eat a diet rich in vegetables, fruit, whole-grain cereals and polyunsaturated and monounsaturated oils
 - Avoid trans fats and limit saturated and total fats to $< 7\%$ and $< 30\%$ of daily total caloric intake, respectively

- Maintain fiber intake to >30 g/d
 - Limit cholesterol intake to 200 mg/d
- b) Pharmacists can recommend a diet that has been shown to reduce CV events or improve risk factors, such as the Mediterranean, Portfolio or Dietary Approach to Stop Hypertension (DASH) diets. Among these, the Mediterranean diet has the best evidence, as it has demonstrated consistent reduction in mortality and nonfatal CV events in both primary and secondary prevention.^{5,6}
 - c) All patients should aim for ≥150 minutes per week of moderate-to-vigorous intensity aerobic exercise, in bouts of ≥10 minutes, to reduce CV risk.
 - d) All users of tobacco products should be encouraged to quit.
 - e) Alcohol intake should be limited to 1 to 2 drinks per day.

Statin monitoring and toxicities

- a) For patients treated with statins, current recommendations for safety monitoring are summarized in Box 1.
- b) Pharmacists should be cognizant of drug-drug interactions with statins, particularly the following:
 - Pharmacokinetic: Inhibitors of cytochrome P450 (CYP) 3A4 (for atorvastatin, lovastatin, simvastatin), such as calcium channel blockers, calcineurin inhibitors, azole antifungals, grapefruit juice, macrolide antibiotics and protease inhibitors, and inhibitors of CYP 2C9 (fluvastatin and rosuvastatin) increase levels of the respective statins and increase the risk of adverse effects.
 - Pharmacodynamic: Combined use of a statin with certain agents, such as colchicine, fibrates and niacin may increase the risk of myotoxicity. Gemfibrozil should not be prescribed with a statin due to the increased risk of myositis.
 - Selection of noninteracting medications or switching to a noninteracting statin should be considered as a standard management option. However, if initiating the short-term use of a necessary interacting agent, patients may be counselled to hold off on taking the statin for the short duration of use of the interacting drug.
 - In patients initiating long-term use of an interacting agent, consideration should

be made to empirically decrease the statin dose or switch to a noninteracting statin (e.g., pravastatin), where it is clinically appropriate.

- c) In the event of statin intolerance, proper patient history and evaluation, including cessation and rechallenge of statins as necessary, should be undertaken to identify a tolerated dose of statin. For a comprehensive review of potential and established statin-related adverse effects, see a recent update by Mancini et al.⁷
- d) **Cognitive impairment:** Although there are anecdotal reports of statins causing cognitive impairment, a systematic review of 57 studies, including RCTs and real-world cohorts, showed that statins do not increase the incidence of dementia or worsen performance on cognitive function tests.⁸
- e) **Myalgias:** Because statins have the strongest and most consistent evidence for CV reduction of any lipid-lowering therapy, the goal should be to find a tolerable statin-based regimen before moving down to alternate lipid-lowering agents that either lack clinical outcome evidence or have evidence of no effect. For statin-related myalgia, evidence supports strategies of switching to a different statin, implementation of alternate-day statin dosing regimens, as well as N-of-1 trials—in accordance with the patient—to find a tolerable statin regimen.^{7,9} In contrast, evidence for the efficacy of concomitant use of coenzyme Q10, vitamin D or any other supplement, vitamin or mineral is of low quality and inconsistent; therefore, these agents should not be recommended for this indication.
- f) **Diabetes:** Statins should not be withheld because of the small increase in blood glucose.
 - In one meta-analysis, for every 255 individuals initiating a statin, 1 extra person developed diabetes over 4 years.¹⁰ Conversely, statins prevented 5.4 CV events for every additional case of diabetes. This effect seems to be dose-dependent, with an additional case of diabetes over 5 years for every 125 patients initiating a higher versus lower dose statin.¹¹ Likewise, the higher statin dose prevented 3.2 CV events for each new case of diabetes caused.
 - To quantify this in another way, a cohort study found that statin use was associated

BOX 1 The Canadian-American controversy: “Treat-to-target” vs “Fire-and-forget”?

Over the years, 2 predominant strategies have been developed to manage use of lipid-lowering therapies: Treat-to-target and fire-and-forget.

The treat-to-target approach, endorsed by the 2012 CCS guidelines, involves intensifying lifestyle and pharmacologic treatment in order to achieve specific lipid levels. Advocates for treating to target lipid levels point to the pathophysiologic role of LDL-C in atherosclerosis formation and observational association between lower achieved lipid levels and reduced risk of CV events as evidence for this strategy.

The fire-and-forget approach, endorsed by the 2013 ACC/AHA dyslipidemia guidelines,¹⁹ fundamentally involves measuring lipid levels only for the sake of initial CV risk prediction. Once therapy is initiated, routine lipid panels are not repeated and no particular absolute or relative lipid targets are sought. Drug therapy involves the initiation of a “lipid-lowering drug” (usually a statin) at a fixed dose that has demonstrated benefit in RCTs. A higher dose (such as atorvastatin 80 mg once daily) may be attempted, as RCTs have shown a marginal further reduction in CV events up to this higher dose range, with concomitant increase in typical statin adverse effects (see “Statin monitoring and toxicity” section).²⁰ Fire-and-forget advocates generally avoid using nonstatin lipid-lowering agents, as most have generally failed to reduce CV events in RCTs (see Table 4).

For a detailed review of the similarities and differences between international guidelines, the interested reader is referred to additional references.^{21,22} However, for the purposes of clinical management of patients, practitioners should adhere to the recommendations of the Canadian Cardiovascular Society. This article provides the details of those guidelines, which will continue to be updated as new information becomes available.

CCS, Canadian Cardiovascular Society; LDL-C, low-density lipoprotein cholesterol; ACC/AHA, American College of Cardiology/American Heart Association; RCT, randomized controlled trial.

with a fasting blood glucose that was approximately 0.1 mmol/L higher than nonuse at 2 years. A small 2-month RCT found an increase in hemoglobin A1c of approximately 0.3% with atorvastatin 10–80 mg versus placebo. In patients already at risk of diabetes (e.g., metabolic syndrome, body mass index ≥ 30 or prediabetes), this small increase

in blood glucose measures may be sufficient to push an individual patient above the diagnostic threshold for diabetes. Ultimately, these patients are also at higher CV risk and thus more likely to benefit from statin therapy. Fortunately, such a small increase in blood glucose is unlikely to lead to increased risk of diabetes-related complications. ■

From the Faculty of Pharmaceutical Sciences (Turgeon), University of British Columbia, Vancouver, BC; the Libin Cardiovascular Institute of Alberta (Anderson), University of Calgary, Calgary, Alberta; L'Institut de cardiologie de Montréal (Grégoire), Université de Montréal, Montreal, Quebec; and the Mazankowski Alberta Heart Institute (Pearson), University of Alberta, Edmonton, Alberta. Contact Glen.Pearson@ualberta.ca.

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References

1. Statistics Canada. Leading causes of death, by sex (both sexes). Available: www.statcan.gc.ca/tables-tableaux/sum-som/l01/cst01/hlth36a-eng.htm (accessed July 20, 2014).
2. Pearson GJ, Thompson AE, Semchuk WS. 2007 guidelines for the management of dyslipidemia and prevention of cardiovascular disease by pharmacists. *Can Pharm J (Ott)* 2007;140:383-8.
3. Charrois TL, Zolezzi M, Koshman SL, et al. A systematic review of the evidence for pharmacist care of patients with dyslipidemia. *Pharmacotherapy* 2012;32:222-3.
4. Anderson TJ, Gregoire 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. *Can J Cardiol* 2013;29:151-67.
5. de Lorgeril M, Renaud S, Mamelle N, et al. Mediterranean alpha-linolenic acid-rich diet in secondary prevention of coronary heart disease. *Lancet* 1994;343:1454-9.
6. Estruch R, Ros E, Salas-Salvado J, et al. Primary prevention of cardiovascular disease with a Mediterranean diet. *N Engl J Med* 2013;368:1279-90.
7. Mancini GB, Tashakkor AY, Baker S, et al. Diagnosis, prevention and management of statin adverse effects and intolerance: Canadian Working Group Consensus update. *Can J Cardiol* 2013;29:1553-68.
8. Richardson K, Schoen M, French B, et al. Statins and cognitive function: a systematic review. *Ann Intern Med* 2013;159:688-97.
9. Joy TR, Monjed A, Zou GY, et al. N-of-1 (single-patient) trials for statin-related myalgia. *Ann Intern Med* 2014;160:301-10.
10. Sattar N, Preiss D, Murray HM, et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. *Lancet* 2010;375:735-42.
11. Preiss D, Seshasai SR, Welsh P, et al. Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis. *JAMA* 2011;305:2556-64.
12. Hovingh GK, Davidson MH, Kastelein JJ, O'Connor AM. Diagnosis and treatment of familial hypercholesterolaemia. *Eur Heart J* 2013;34:962-71.
13. Brindle P, Beswick A, Fahey T, Ebrahim S. Accuracy and impact of risk assessment in the primary prevention of cardiovascular disease: a systematic review. *Heart* 2006;92:1752-9.
14. Lindholm LH, Carlberg B, Samuelsson O. Should beta blockers remain first choice in the treatment of primary hypertension? A meta-analysis. *Lancet* 2005;366:1545-53.
15. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20 536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;360:7-22.
16. Steg PG, Bhatt DL, Wilson PW, et al. One-year cardiovascular event rates in outpatients with atherothrombosis. *JAMA* 2007;297:1197-206.
17. Emerging Risk Factors Collaboration. C-reactive protein, fibrinogen and cardiovascular disease prediction. *N Engl J Med* 2012;367:1310-20.
18. Yeboah J, McClelland RL, Polonsky TS, et al. Comparison of novel risk markers for improvement in cardiovascular risk assessment in intermediate-risk individuals. *JAMA* 2012;308:788-95.
19. Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA guideline for 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):2889-934.
20. Mills EJ, O'Reagan C, Eyawo O, et al. Intensive statin therapy compared to moderate dosing for prevention of cardiovascular events: a meta-analysis of >40 000 patients. *Eur Heart J* 2011;32:1409-15.
21. Anderson TJ, Gregoire J, Hegele RA, et al. Are the ACC/AHA guidelines on the treatment of blood cholesterol a game change? A perspective from the Canadian Cardiovascular Society Dyslipidemia Panel. *Can J Cardiol* 2014;30:377-80.
22. Morris PB, Ballantyne CM, Birtcher KK, et al. Review of clinical practice guidelines for the management of LDL-related risk. *J Am Coll Cardiol* 2014;64:196-206.
23. The Lipid Research Clinics Coronary Primary Prevention Trial results. I. Reduction in incidence of coronary heart disease. *JAMA* 1984;251:351-64.
24. Baigent C, Landray MJ, Reith C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (study of heart and renal protection): a randomised placebo controlled trial. *Lancet* 2011;377:2181-92.
25. Jun M, Foote C, Lv J, Neal B, Patel A, Nicholls SJ, et al. Effects of fibrates on cardiovascular outcomes: systematic review and meta-analysis. *Lancet* 2010;375:1875-84.
26. Ginsberg HN, Elam MB, Lovato LC, et al, for the ACCORD Study Group. Effects of combination lipid therapy in type 2 diabetes mellitus. *N Engl J Med* 2010;362:1563-74.
27. Coronary Drug Project Research Group. Clofibrate and niacin in coronary heart disease. *JAMA* 1975;231:360-381.
28. Canner PL, Berge KG, Wenger NK, et al. Fifteen year mortality in coronary drug project patients: long-term benefit with niacin. *J Am Coll Cardiol* 1986;8:1245-55.
29. The AIM-HIGH Investigators. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. *N Engl J Med* 2012;365:2255-67.
30. The HPS2-THRIVE Collaborative Group. Effects of extended-release niacin with laropiprant in high-risk patients. *N Engl J Med* 2014;371:203-12.
31. Rizos EC, Ntzani EE, Bika E, et al. Association between omega-3 fatty acid supplementation and risk of major cardiovascular disease events: a systematic review and meta-analysis. *JAMA* 2012;308:1024-33.
32. The Risk and Prevention Study Collaborative Group. N-3 fatty acids in patients with multiple cardiovascular risk factors. *N Engl J Med* 2013;368:1800-8.