

LAURIE HERZIG MALLERY, MD, FRCPC, MSMDepartment of Medicine, Division of Geriatric Medicine,
Dalhousie University, Halifax, Nova Scotia, Canada**PAIGE MOORHOUSE, MD, MPH, FRCPC, MSM**Department of Medicine, Division of Geriatric Medicine,
Dalhousie University, Halifax, Nova Scotia, Canada**PAM McLEAN VEYSEY, BSc (Pharm)**Team Lead, Drug Evaluation Unit, Department of
Pharmacy, Nova Scotia Health Authority, Halifax,
Nova Scotia, Canada**MICHAEL ALLEN, MD, MSc**Academic Detailing Service, Continuing Professional
Development, Faculty of Medicine, Dalhousie
University, Halifax, Nova Scotia, Canada**ISOBEL FLEMING, BScPharm, ACPR**Academic Detailing Service, Continuing Professional
Development, Faculty of Medicine, Dalhousie
University, Halifax, Nova Scotia, Canada

Severely frail elderly patients do not need lipid-lowering drugs

ABSTRACT

After performing a systematic review, members of the Palliative and Therapeutic Harmonization (PATH) program and the Dalhousie Academic Detailing Service found that evidence does not support lipid-lowering therapy for severely frail elderly patients.

KEY POINTS

There is no reason to prescribe or continue statins for primary prevention in severely frail elderly patients, as these drugs are unlikely to provide benefit in terms of outcomes relevant to this population.

Statins are probably not necessary for secondary prevention in patients who are severely frail, although there may be extenuating circumstances for their use.

There is no reason to start or continue statins for heart failure, as there is insufficient evidence that they are effective for this indication in any population.

There is no reason to start or continue other lipid-lowering drugs in conjunction with statins.

As the frail elderly may be more vulnerable to the side effects of statins, lower doses may be more appropriate if these drugs are prescribed.

If there is concern regarding myopathy, a drug interaction, or other adverse effects, consider a trial of statin discontinuation.

Dr. Mallery and Dr. Moorhouse have disclosed partnership in Palliative and Therapeutic Harmonization Ltd.

doi:10.3949/ccjm.84a.15114

FRAIL ELDERLY PATIENTS are at high risk of adverse clinical outcomes, including those due to polypharmacy. Several groups tackle “deprescribing” by developing lists of medications that are potentially inappropriate for the elderly, such as the Beers or STOPP/START criteria.¹⁻⁴

See related editorial, page 143

In contrast, our group (the Palliative and Therapeutic Harmonization [PATH] program and the Dalhousie Academic Detailing Service) has developed evidence-based, frailty-specific guidelines for treating hypertension⁵ and diabetes,⁶ in which we advocate less-stringent treatment targets and tapering or discontinuing medications, as needed.

The PATH program⁷ is a clinical approach that prioritizes the consideration of frailty when making treatment decisions. The Dalhousie Academic Detailing Service collaborates with the Nova Scotia Health Authority to research and develop evidence-informed educational messages about the treatment of common medical conditions.

Here, we address lipid-lowering therapy in this population.

■ CONSIDERING FRAILTY

Frailty is defined in several ways. The Fried model^{8,9} identifies frailty when 3 of the following characteristics are present: unintentional weight loss, exhaustion, muscle weakness, slow walking speed, or low levels of activity. The Clinical Frailty Scale^{10,11} and the Frailty Assessment for Care-planning Tool (FACT)⁵ use deficits in cognition, function, and mobility to define frailty. According to these scales, people are considered

severely frail when they require assistance with basic activities of daily living (such as bathing or dressing), owing to cognitive or physical deficits from any cause.

In reviewing the evidence, we consider five questions:

- What is the quality of the evidence? (Up to 48% of clinical practice guideline recommendations may be based on low-level evidence or expert opinion.¹²)
- How did the study population compare with the frail?
- Are study outcomes and potential benefits clinically relevant to those who are frail?
- How long did it take for the clinical benefit of a treatment to become apparent, and are the frail elderly likely to live that long?
- Have the harms of treatment been sufficiently considered?

■ WHAT IS THE QUALITY OF THE EVIDENCE?

We found no studies that specifically evaluated the benefit of lipid-lowering for severely frail older adults. Therefore, we examined randomized controlled trials that enrolled non-frail older adults,^{13–28} subgroup analyses of randomized controlled trials,^{29,30} meta-analyses that analyzed subgroups of elderly populations,^{31,32} and publications describing the study designs of randomized controlled trials.^{33–37}

Most of the evidence comes from post hoc subgroup analyses of elderly populations. Although meta-analysis is commonly used to compare subgroups, the Cochrane handbook and others consider subgroup comparisons observational by nature.^{38,39} (See Table 1 for lipid-lowering studies discussed in this article.)

Studies of statins for primary prevention of cardiovascular disease

For evidence of benefit from lipid-lowering for primary prevention (ie, to reduce the risk of cardiovascular events in patients with no known cardiovascular disease at baseline but at increased risk), we reviewed the meta-analysis conducted by the Cholesterol Treatment Trialists' (CTT) Collaborators.³² Since this meta-analysis included the major trials that enrolled elderly patients, individual publications of post hoc, elderly subgroups were, for the most part, not examined individually. The exception to this approach was a decision to

report on the PROSPER¹³ and JUPITER²⁸ trials separately, because PROSPER is the most representative of the elderly population and JUPITER reached the lowest LDL-C of primary prevention trials published to date and included a large elderly subgroup (n = 5,695).

Savarese et al⁴⁰ evaluated the benefits of statins for older adults who did not have established cardiovascular disease. We did not report on this meta-analysis, as not all of the subjects that populated the meta-analysis were representative of a typical prevention population. For instance, in the Anglo-Scandinavian Cardiac Outcomes Trial lipid-lowering arm,⁴¹ 14% of the subjects had had a previous stroke or transient ischemic attack. In the Antihypertensive and Lipid-Lowering Treatment Trial,⁴² 16% of the population had a family history of premature coronary heart disease.

In addition, all the trials in the Savarese meta-analysis were also included in the CTT meta-analysis.³² The CTT reports on baseline risk using patient-level data stratified by age and risk, which may be more relevant to the question of primary prevention for older adults, as highlighted in our review.

PROSPER (Prospective Study of Pravastatin in the Elderly at Risk),¹³ a well-conducted, double-blind, randomized controlled trial with low probability of bias, compared pravastatin 40 mg and placebo. It was the only study that specifically enrolled older adults, with prespecified analysis of primary and secondary prevention subgroups. The primary prevention subgroup accounted for 56% of the 5,084 participants.

JUPITER (Justification for the Use of Statins in Prevention)²⁸ compared rosuvastatin 20 mg and placebo in 17,802 participants. All had low-density lipoprotein cholesterol (LDL-C) levels below 3.4 mmol/L (130 mg/dL) and elevated levels of the inflammatory biomarker high-sensitivity C-reactive protein (hsCRP), ie, 2 mg/L or higher. Subsequently, Glynn et al performed a post hoc, exploratory subgroup analysis of elderly participants (N = 5,695).²⁹

The JUPITER trial had several limitations.^{43,44} The planned follow-up period was 5 years, but the trial was stopped early at 1.9 years, after a statistically significant difference was detected in the primary composite

TABLE 1

Studies of lipid-lowering therapy discussed in this paper

Study	Design	Population	Mean follow-up
PROSPER ¹³	Randomized controlled trial Pravastatin 40 mg vs placebo	N = 5,804, mean age 75 Primary and secondary prevention Mini-Mental State score ≥ 24 of 30	3.2 years
JUPITER ^{28,29}	Randomized controlled trial Rosuvastatin 20 mg vs placebo	N = 5,695 (elderly subgroup) Median age 74 Primary prevention	1.9 years (stopped prematurely)
CTT ³²	Meta-analysis	Not applicable ^a	Variable
Afilalo et al ³¹	Meta-analysis	N = 19,569 Age range 65–82 Secondary prevention	4.9 years
SPARCL ^{27,30}	Randomized controlled trial Atorvastatin 80 mg vs placebo	N = 2,249 (subgroup age ≥ 65) Mean age of subgroup 72.4 Secondary prevention	4.9 years
GISSI-HF ²⁵	Randomized controlled trial Rosuvastatin 10 mg vs placebo	N = 4,574, mean age 68 Heart failure, NYHA class II to IV	3.9 years (median)
CORONA ²⁶	Randomized controlled trial Rosuvastatin 10 mg vs placebo	N = 5,011, mean age 73 Heart failure, NYHA class II to IV	2.7 years

^a The CTT meta-analysis presents the effects of statins on major vascular events per annum, per 1.0 mmol/L reduction in LDL-C according to 5-year risk at baseline. The analysis in patients > 70 years old includes a total of 2,952 events in the statin group and 3,385 events in the control group (or a total of 6,337 events).

CORONA = Controlled Rosuvastatin Multinational Trial in Heart Failure; CTT = Cholesterol Treatment Trialists; GISSI-HF = Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca Heart Failure; JUPITER = Justification for the Use of Statins in Prevention; NYHA = New York Heart Association; PROSPER = Prospective Study of Pravastatin in the Elderly at Risk; SPARCL = Stroke Prevention by Aggressive Reduction in Cholesterol Levels

outcome of reduction in all vascular events. Studies that are stopped early may exaggerate positive findings.⁴⁵

Further, JUPITER's patients were a select group, with normal LDL-C levels, elevated hsCRP values, and without diabetes. Of 90,000 patients screened, 72,000 (80%) did not meet the inclusion criteria and were not enrolled. This high rate of exclusion limits the generalizability of study findings beyond the shortcomings of post hoc subgroup analysis.

The meta-analysis performed by the CTT Collaborators³² used individual participant data from large-scale randomized trials of lipid-modifying treatment. This analysis was specific to people at low risk of vascular disease. In a supplementary appendix, the authors described the reduction in major vas-

cular events for each 1.0 mmol/L decrease in LDL-C in three age categories: under age 60, ages 61 to 70, and over age 70.

The authors also stratified the results by risk category and provided information about those with a risk of major vascular events of less than 20%, which would be more representative of a purer primary prevention population.

For the elderly subgroup at low risk, the CTT Collaborators³² only reported a composite of major vascular events (coronary death, nonfatal myocardial infarction [MI], ischemic stroke, or revascularization) and did not describe individual outcomes, such as prevention of coronary heart disease.

Study results are based on postrandomization findings and therefore may be observational, not experimental.⁴⁶

Studies of statins for secondary prevention of cardiovascular disease

The aim of secondary prevention is to reduce the risk of recurrent cardiovascular events in patients who already have cardiovascular disease.

To address the question of whether statins reduce cardiovascular risk, we reviewed:

PROSPER,¹³ which included a pre-planned analysis of the secondary prevention population.

Afilalo et al,^{31,47} who performed a meta-analysis of the elderly subgroups of nine major secondary prevention studies (19,569 patients) using published and unpublished data.

To address the question of whether statins benefit individuals with heart failure, we found two relevant studies:

GISSI-HF (Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca Heart Failure)²⁵ and **CORONA** (Controlled Rosuvastatin Multinational Trial in Heart Failure),²⁶ which were large, international, well-conducted randomized controlled trials that examined statin use in heart failure.

To answer the question of whether statins benefit individuals after a stroke or transient ischemic attack, we found one relevant study:

SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels),²⁷ which evaluated the benefit of statins in older adults with a history of stroke or transient ischemic attack. It was a prospective, double-blind, placebo-controlled, international trial conducted at 205 centers. One to 6 months after their cerebrovascular event, patients were randomized to receive either atorvastatin 80 mg or placebo. Given the young age of patients in this trial (mean age 63), we also reviewed a post hoc subgroup analysis of the elderly patients in SPARCL (age > 65).³⁰

■ HOW DID THE STUDY POPULATION COMPARE WITH THOSE WHO ARE FRAIL?

Frail older adults are almost always excluded from large-scale clinical trials,⁴⁸ leading to uncertainty about whether the conclusions can be applied to those with advanced frailty.

Although age is an imperfect proxy measure of frailty,⁴⁹ we consider the age of the study population as well as their comorbidities.

Participants in the studies we reviewed were generally younger and healthier than those who are frail, with mean ages of about 75 or less (**Table 1**).

PROSPER was the most representative study, as it specifically enrolled older adults, albeit without frailty,¹³ and excluded people with poor cognitive function as defined by a Mini Mental State Examination score less than 24.

JUPITER enrolled a select population, as described above. The median age in the elderly subgroup was 74 (interquartile range 72–78).²⁹

The **Afilalo et al**³¹ meta-analysis primarily included studies of young-elderly patients, with a mean age of less than 70. **PROSPER**¹³ was an exception.

The **GISSI-HF study**,²⁵ which examined the benefit of statins in heart failure, described their study population as frail, although the mean age was only 68. Compared with those in GISSI-HF, the **CORONA** patients²⁶ with heart failure were older (mean age 73) and had more severe heart failure. Accordingly, it is possible that many of the **CORONA** participants were frail.

■ ARE STUDY OUTCOMES CLINICALLY RELEVANT TO THOSE WHO ARE FRAIL?

Because baseline cardiovascular risk increases with age, the elderly should, in theory, experience greater absolute benefit from lipid-lowering. However, there is uncertainty about whether this is true in practice.

Some, but not all, epidemiologic studies show a weaker relationship between cholesterol levels and cardiovascular morbidity and mortality rates in older compared to younger adults.^{50,51} This may be because those with high cholesterol levels die before they get old (time-related bias), or because those with life-threatening illness may have lower cholesterol levels.⁵⁰ In addition, classic risk factors such as age, sex, systolic blood pressure, cholesterol values, diabetes, smoking, and left ventricular hypertrophy on electrocardiography may have less power to predict cardiovascular risk among older patients.⁵²

The goal of treatment in frailty is to prevent further disability or improve quality of

No studies have specifically evaluated the benefit of lipid-lowering for severely frail older adults

TABLE 2

Coronary heart disease outcomes

Trial and outcome	Event rate		P value	Absolute risk reduction	Relative risk reduction	Number needed to treat (95% CI)
	Placebo	Statin				
Primary prevention studies						
PROSPER ¹³						
Coronary heart disease death and nonfatal myocardial infarction	8.8%	7.9%	.401	0.9%	9%	NS ^a
JUPITER ^{28,29}						
Myocardial infarction	1.1%	0.6%	.046	0.5%	45%	211 (106–32,924)
Secondary prevention studies						
PROSPER ¹³						
Coronary heart disease death and nonfatal myocardial infarction (includes definite and suspect events)	16.8%	12.7%	.004	4.1%	24%	25 (15–77)
Afilalo et al meta-analysis ³¹						
Nonfatal myocardial infarction	NA	NA	NA	NA	26% ^b	38 (16–118) ^b
Combined primary and secondary prevention studies						
PROSPER ¹³						
Nonfatal myocardial infarction (excluding silent and unrecognized events)	4.3%	3.4%	.099	0.9%	20%	NS ^a

^a Not statistically significant ($P > .05$) and numbers needed to treat (NNT) not calculated on these results. NNT calculated on raw numbers if not provided in publication. See Table 1 for duration of treatment required for NNT.

^b Afilalo et al provided relative risk reductions and NNTs in their publication. Absolute risk reductions not calculated on meta-analytic outcomes.

CI = confidence interval; NA = not available; NS = not statistically significant

life. Therefore, meaningful outcomes for lipid-lowering therapy should include *symptomatic* nonfatal MI and its associated morbidity (eg, heart failure and persistent angina) or *symptomatic* nonfatal stroke leading to disability. Outcomes without sustained clinical impact, such as transient ischemic attack, nondisabling stroke, or silent MI, while potentially important in other populations, are less relevant in severe frailty. Notably, in many statin studies, outcomes include asymptomatic heart disease (eg, silent MI and “suspected events”) and nondisabling stroke (eg, mild stroke, transient ischemic attack). When symptomatic outcomes are not reported separately, the impact of the reported benefit on quality of life and function is uncertain.

The outcome of all-cause mortality is generally recognized as a gold standard for determining treatment benefit. However, since

advanced frailty is characterized by multiple competing causes for mortality, a reduction in all-cause mortality that is achieved by addressing a single issue in nonfrail populations may not extend to the frail.

To more fully understand the impact of lipid-lowering therapy on quality of life and function, we examined the following questions:

Do statins as primary prevention reduce symptomatic heart disease?

Outcomes for coronary heart disease from PROSPER and JUPITER are summarized in Table 2.

PROSPER. In the PROSPER primary prevention group,¹³ statin therapy did not reduce the combined outcome of coronary heart disease death and nonfatal MI.

The JUPITER trial demonstrated a statistically significant benefit for preventing MI

in the elderly subpopulation (ages 70–97),²⁹ but the number needed to treat was high (211 for 2 years), with a wide confidence interval (CI) (95% CI 106–32,924). The trial did not adequately differentiate between symptomatic and asymptomatic events, making it difficult to determine outcome relevance. Also, due to the methodologic limitations of JUPITER as described above, its results should be interpreted with caution.^{43,44}

The CTT Collaborators³² did not report individual outcomes (eg, coronary heart disease) for the elderly low-risk subgroup and, therefore, this meta-analysis does not answer the question of whether statins reduce symptomatic heart disease in primary prevention populations.

Taken together, these findings do not provide convincing evidence that statin therapy as primary prevention reduces the incidence of symptomatic heart disease for severely frail older adults.

Do statins as secondary prevention reduce symptomatic heart disease?

Most studies defined secondary prevention narrowly as treatment for patients with established coronary artery disease. For instance, in the Afilalo et al meta-analysis,³¹ the small number of studies that included individuals with other forms of vascular disease (such as peripheral vascular disease) enrolled few participants with noncardiac conditions (eg, 29% in PROSPER¹³ and 13% in the Heart Protection Study²⁰).

Therefore, any evidence of benefit for secondary prevention demonstrated in these studies is most applicable to patients with coronary heart disease, with less certainty for those with other forms of cardiovascular disease.

In PROSPER,¹³ the secondary prevention group experienced benefit in the combined outcome of coronary heart disease death or nonfatal MI. In the treatment group, 12.7% experienced this outcome compared with 16.8% with placebo, an absolute risk reduction of 4.1% in 3 years ($P = .004$, number needed to treat 25, 95% CI 15–77). This measure includes coronary heart disease death, an outcome that may not be generalizable to those who are frail. In addition, the outcome of nonfatal MI includes both symptomatic and suspected events. As such, there is uncertainty

whether the realized benefit is clinically relevant to frail older adults.

The Afilalo et al meta-analysis³¹ showed that the number needed to treat to prevent one nonfatal MI was 38 (95% CI 16–118) over 5 years (Table 2). However, this outcome included both symptomatic and asymptomatic (silent) events.

Based on the available data, we conclude that it is not possible to determine whether statins reduce symptomatic heart disease as secondary prevention for older adults who are frail.

Do statins reduce heart disease in combined populations?

In the combined primary and secondary population from PROSPER,¹³ pravastatin decreased the risk of nonfatal symptomatic MI from 4.3% in the placebo group to 3.4%, a relatively small reduction in absolute risk (0.9%) and not statistically significant by our chi-square calculation ($P = .099$).

Do statins prevent a first symptomatic stroke in people with or without preexisting cardiovascular disease?

Preventing strokes that cause functional decline is an important outcome for the frail elderly. Stroke outcomes from PROSPER,¹³ JUPITER,²⁹ and the Afilalo et al meta-analysis³¹ are summarized in Table 3.

For primary prevention:

In PROSPER (primary prevention),¹³ there was no statistically significant benefit in the combined outcome of fatal and nonfatal stroke or the single outcome of transient ischemic attack after 3.2 years.

JUPITER,²⁹ in contrast, found that rosuvastatin 20 mg reduced strokes in primary prevention, but the absolute benefit was small. In 2 years, 0.8% of the treatment group had strokes, compared with 1.4% with placebo, an absolute risk reduction of 0.6% ($P = .023$, number needed to treat 161, 95% CI 86–1,192).

Neither PROSPER nor JUPITER differentiated between disabling and nondisabling strokes.

For secondary prevention:

In PROSPER (secondary prevention),¹³ there was no statistically significant benefit in the combined outcome of fatal and nonfatal stroke or the single outcome of transient isch-

Studies that are stopped early may exaggerate positive findings

TABLE 3

Stroke outcomes

Trial and outcome	Event rate		P value	Absolute risk reduction	Relative risk reduction ^a	Number needed to treat (95% CI)
	Placebo	Statin				
Primary prevention studies						
PROSPER ¹³						
Fatal or nonfatal stroke	3.7%	3.8%	.882	0.1% increase	3% increase	NS ^b
Transient ischemic attack	2.3%	1.9%	.422	0.4%	18%	NS
JUPITER ^{28,29}						
Stroke (percent based on raw number of events)	1.4%	0.8%	.023	0.6%	45%	161 (86–1,192)
Secondary prevention studies						
PROSPER ¹³						
Fatal and nonfatal stroke	5.5%	5.7%	.838	0.2% increase	3% increase	NS
Transient ischemic attack	5.1%	3.6%	.065	1.5%	29%	NS
Afilalo meta-analysis ³¹						
Stroke (disabling and nondisabling)	NA	NA	NA	NA	25%	58 ^c (27–177)
SPARCL ²⁷						
Fatal or nonfatal stroke	13.1%	11.2%	.03	1.9%	15%	52 (26–1,303)
Nonfatal stroke	11.8%	10.4%	.11	1.4%	12%	NS
SPARCL subgroup ≥ 65 ³⁰						
Fatal or nonfatal stroke	16.2%	14.7%	.33	1.5%	10%	NS
SPARCL subgroup < 65 ³⁰						
Fatal or nonfatal stroke	10.5%	7.9%	.022	2.6%	24%	39 (21–354)

^a Numbers for relative risk reduction are rounded to the nearest whole number

^b Not statistically significant ($P > .05$) and numbers needed to treat not calculated on these results. Number needed to treat (NNT) calculated on raw numbers if not provided in publication. See Table 1 for duration of treatment required for NNT. CI = confidence interval

^c Afilalo et al provided relative risk reductions and NNT. Absolute risk reductions not calculated on meta-analytic outcomes.

emic attack after 3.2 years.

The Afilalo et al secondary prevention meta-analysis demonstrated a 25% relative reduction in stroke (relative risk 0.75, 95% CI 0.56–0.94, number needed to treat 58, 95% CI 27–177).³¹

Notably, the stroke outcome in Afilalo included both disabling and nondisabling strokes. For example, in the Heart Protection Study,²⁰ the largest study in the Afilalo et al meta-analysis, approximately 50% of nonfatal, classifiable strokes in the overall study population (ie, both younger and older patients) were not disabling. Including disabling and

nondisabling strokes in a composite outcome confounds the clinical meaningfulness of these findings in frailty, as the number needed to treat to prevent one disabling stroke cannot be calculated from the data provided.

Do statins prevent a second (symptomatic) stroke in people with a previous stroke?

SPARCL²⁷ (Table 3) examined the question of whether statins decrease the risk of recurrent ischemic stroke for patients with a prior history of stroke or transient ischemic attack. There was a statistically significant reduction in the primary composite outcome of fatal and

Frail older adults are almost always excluded from large-scale clinical trials

nonfatal stroke, with 11.2% of the treatment group and 13.1% of the placebo group experiencing this outcome, an absolute risk reduction of 1.9% at 5 years ($P = .03$; number needed to treat 52, 95% CI 26–1,303). However, the difference in nonfatal stroke, which is the outcome of interest for frailty (since mortality has uncertain relevance), was not statistically significant (10.4% with treatment vs 11.8% with placebo, $P = .11$).

An exploratory subgroup analysis of SPARCL patients based on age³⁰ showed a smaller, nonsignificant reduction in the primary end point of fatal and nonfatal stroke in the group over age 65 (relative risk 0.90, 95% confidence interval 0.73–1.11, $P = .33$) compared with the younger group (age < 65) (relative risk 0.74, 95% CI 0.57–0.96, $P = .02$).

The applicability of these results to the frail elderly is uncertain, since the subgroup analysis was not powered to determine outcomes based on age stratification and there were differences between groups in characteristics such as blood pressure and smoking status. In addition, the outcome of interest, nonfatal stroke, is not provided for the elderly subgroup.

In conclusion, in both primary and secondary prevention populations, the evidence that statins reduce nonfatal, symptomatic stroke rates for older adults is uncertain.

Do statins decrease all-cause mortality for primary or secondary prevention?

Due to competing risks for death, the outcome of mortality may not be relevant to those who are frail; however, studies showed the following:

For primary prevention, there was no decrease in mortality in PROSPER¹³ or in the elderly subgroup of JUPITER.²⁹

For secondary prevention, an analysis of PROSPER trial data by Afilalo et al³¹ showed a significant 18% decrease in all-cause mortality (relative risk 0.82, 95% CI 0.69–0.98) using pravastatin 40 mg.

A decrease in all-cause mortality with statins was also reported in the pooled result of the Afilalo et al meta-analysis.³¹

What are the reported composite outcomes for primary and secondary prevention?

While we were most interested in the symptomatic outcomes described above, we recognize that the small numbers of events make it

difficult to draw firm conclusions. Therefore, we also considered composite primary outcomes, even though most included multiple measures that have varying associations with disability and relevancy to frail older adults.

For primary prevention, in the PROSPER preplanned subgroup analysis,¹³ there was no statistical benefit for any outcome, including the primary composite measure. In contrast, the elderly subpopulation in the JUPITER trial²⁸ showed a treatment benefit with rosuvastatin 20 mg compared with placebo for the primary composite outcome of MI, stroke, cardiovascular death, hospitalization for unstable angina, or revascularization. The number needed to treat for 2 years was 62 (95% CI 39–148).

In the CTT meta-analysis,³² patients at all levels of baseline risk showed benefit up to age 70. However, there was no statistically significant benefit in the composite primary outcome of coronary deaths, nonfatal myocardial infarction, ischemic stroke, or revascularization in the population most representative of elderly primary prevention—those who were more than 70 years old with a 5-year baseline risk of less than 20%.

For secondary prevention, in PROSPER,¹³ the subpopulation of patients treated for secondary prevention experienced benefit in the primary composite outcome of coronary heart disease death, nonfatal MI, or fatal or nonfatal stroke, achieving a 4% absolute risk reduction with a number needed to treat of 23 (95% CI 14–81) over 3 years.

Do statins decrease disability?

PROSPER was the only study that reported on disability. Compared with placebo, pravastatin did not decrease disability in the total population as measured by basic and instrumental activities of daily living scales.

Do statins help patients with heart failure?

Neither GISSI-HF²⁵ nor CORONA²⁶ found significant benefit from rosuvastatin 10 mg, despite LDL-C lowering of 27% in GISSI-HF and 45% in CORONA.

Do ezetimibe or other nonstatin lipid-lowering agents improve outcomes?

There is no definitive evidence that ezetimibe provides clinically meaningful benefit as a single agent.

For combination therapy, the IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial)⁵³ showed that adding ezetimibe 10 mg to simvastatin 40 mg after an acute coronary syndrome reduced the risk of nonfatal myocardial infarction compared with simvastatin monotherapy (event rate 12.8% vs 14.4%; hazard ratio 0.87, 95% CI 0.80–0.95; $P = .002$) for a population with a mean age of 64. The risk of any stroke was also reduced; strokes occurred in 4.2% of those receiving combination therapy vs 4.8% with monotherapy (hazard ratio 0.86, 95% CI 0.73–1.00, $P = .05$). After a median of 6 years, 42% of patients in each group had discontinued treatment. Given the very specific clinical scenario of acute coronary syndrome and the young age of the patients in this trial, we do not think that this study justifies the use of ezetimibe for severely frail older adults.

There is no evidence that other combinations (ie, a statin plus another lipid-lowering drug) improve clinical outcomes for either primary or secondary prevention in any population.⁵⁴

■ WILL FRAIL PATIENTS LIVE LONG ENOUGH TO BENEFIT?

It is often difficult to determine the number of years that are needed to achieve benefit, as most trials do not provide a statistical analysis of varying time frames.

The PROSPER trial¹³ lasted 3.2 years. From the Kaplan-Meier curves in PROSPER, we estimate that it took about 1.5 years to achieve a 1% absolute risk reduction and 2.5 years for a 2% absolute risk reduction in coronary heart disease death and nonfatal MI in the combined primary and secondary groups.

JUPITER²⁸ was stopped early at 1.9 years. The Afilalo et al meta-analysis³¹ was based on follow-up over 4.9 years.

IMPROVE-IT⁵³ reported event rates at 7 years. The authors note that benefit in the primary composite outcome appeared to emerge at 1 year, although no statistical support is given for this statement and divergence in the Kaplan-Meier curves is not visually apparent.

The duration of other studies ranged between 2.7 and 4.9 years (Table 1).^{26–28}

It has been suggested that statins should be considered for elderly patients who have a life

expectancy of at least 5 years.³ However, many older adults have already been taking statins for many years, which makes it difficult to interpret the available timeframe evidence.

In a multicenter, unblinded, randomized trial,⁵⁵ statins were either stopped or continued in older adults who had a short life expectancy and a median survival of approximately 7 months. Causes of death were evenly divided between cancer and noncancer diagnoses, and 22% of the patients were cognitively impaired. Discontinuing statin therapy did not increase mortality or cardiovascular events within 60 days. Nevertheless, stopping statin therapy did not achieve noninferiority for the primary end point, the proportion of participants who died within 60 days. Statin discontinuation was associated with improved quality of life, although the study was not blinded, which could have influenced results.

■ HAVE THE HARMS BEEN SUFFICIENTLY CONSIDERED?

Frail older adults commonly take multiple medications and are more vulnerable to adverse events.⁵⁶

Many statins require dose reduction with severe renal impairment (creatinine clearance < 30 mL/min/1.73 m²), which would be a common consideration in severely frail older adults.

Myopathy

Myopathy, which includes myalgias and muscle weakness, is a statin-related adverse event that can impair quality of life. Myopathy typically develops within the first 6 months but can occur at any time during statin treatment.⁵⁷ When muscle-related adverse effects occur, they may affect the elderly more significantly, particularly their ability to perform activities of daily living, rise from a chair, or mobilize independently. Another concern is that older adults with dementia may not be able to accurately report muscle-related symptoms.

It is difficult to ascertain the true prevalence of myopathy, especially in advanced age and frailty. Randomized controlled trials report incidence rates of 1.5% to 5%, which is comparable to placebo.^{57,58} However, inconsistent definitions of myopathy and exclusion of subjects with previous statin intolerance or adverse effects during run-in periods limit interpretability.

Myopathy typically develops within the first 6 months of statin treatment, but can occur at any time

We conclude that medications should be used in this population only if they improve quality of life or function

ity.⁵⁷ Clinical experience suggests that muscle complaints may be relatively common.^{59–61}

Advanced age, female sex, low body mass index, and multisystem disease are all associated with frailty and have also been described as risk factors for statin-associated muscle syndromes.⁶¹ Physiologic changes associated with frailty, such as reduced muscle strength, decreased lean body mass, impaired functional mobility, decreased reserve capacity, and altered drug metabolism may increase the risk and severity of myopathy.⁶²

Adverse cognitive events

Meta-analyses of randomized clinical trials and narrative reviews find no definitive relationship between statin therapy and adverse cognitive events.^{63–67} Nevertheless, there have been case reports of memory loss associated with the use of statins, and the US Food and Drug Administration has issued a warning that statins have been associated with memory loss and confusion.⁶⁸

It may be difficult to determine whether a statin is causing or aggravating cognitive symptoms among individuals with dementia without a trial withdrawal of the drug.

■ OUR RECOMMENDATIONS

The recommendations below are intended for adults with severe or very severe frailty (ie, a score of 7 or 8 on the Clinical Frailty Scale¹¹ or FACT⁵ and therefore apply to most older adults living in long-term care facilities.

Primary prevention

There is no reason to prescribe or continue statins for primary prevention, as it is unlikely that they would provide benefit for outcomes that are relevant in this population.

Secondary prevention

Statin treatment is probably not necessary for secondary prevention in those with severe frailty, although there may be extenuating circumstances that justify statin use.

Heart failure

There is no reason to start or continue statins for heart failure, as there is insufficient evidence that they are effective for this indication in any population.

Ezetimibe

There is no evidence that ezetimibe reduces cardiovascular events in any population when used as monotherapy. For a select population with acute coronary syndromes, ezetimibe has a modest effect. Given the very specific clinical scenario of acute coronary syndrome, we do not think that the available evidence justifies the use of ezetimibe for severely frail older adults.

Agents other than ezetimibe combined with statins

There is no reason to start or continue other lipid-lowering drugs in conjunction with statins.

Statin dosing

As statin adverse effects have the potential to increase with advancing age and frailty, lower doses may be appropriate.⁶⁸

Adverse events

Consider stopping statins on a trial basis if there is concern regarding myopathy, drug interactions, or other adverse effects.

■ BOTTOM LINE: DO STATINS IMPROVE QUALITY OF LIFE OR FUNCTION?

In primary prevention for older adults, there is doubt that statins prevent cardiovascular disease and stroke-related events because the main study involving the elderly did not show a benefit in the primary prevention subgroup.¹³ Additionally, there is no conclusive evidence that statin treatment decreases mortality in primary prevention.^{13,29}

There is insufficient information to determine whether the frail elderly should receive statins for secondary prevention. Although there is evidence that treatment decreases measures of coronary heart disease and stroke, it is unclear whether it improves quality of life or function for those who are frail. To answer this question, we need more information about whether reported outcomes (such as stroke and MI) are associated with disability, which is not provided in many of the studies we reviewed. When disability was specifically considered in the PROSPER trial for the combined population of primary and secondary prevention, treatment with statins had no impact on basic and instrumental activities of daily living.

Some experts may not agree with our interpretation of the complex evidence presented in this article. Others may ask, “What is the harm in using statins, even if there is no definitive benefit?” However, the harms associated with statin therapy for the frail are poorly defined. In the face of these uncertainties and in the absence of definitive improvement in quality of life, we believe that “less is more” in the context of severe frailty.⁶⁹

The cost of medications should also be considered, especially in long-term care facilities, where there is an added expense of drug administration that diverts human resources

away from interactions that are more congruent with respecting the lifestage of frailty.

Careful review of evidence before applying clinical practice guidelines to those who are frail should become the norm. When considering treatment of frail patients, the five questions described in this review shed light on the applicability of clinical trial evidence. Therapies that are highly effective in healthier populations may be less effective when individuals are severely frail. Accordingly, we propose that medications should only be used if they improve quality of life or function. ■

REFERENCES

1. Ontario Pharmacy Research Collaboration. Deprescribing guidelines for the elderly. www.open-pharmacy-research.ca/research-projects/emerging-services/deprescribing-guidelines. Accessed December 28, 2016.
2. Scott IA, Hilmer SN, Reeve E, et al. Reducing inappropriate polypharmacy: the process of deprescribing. *JAMA Intern Med* 2015; 175:827–834.
3. O'Mahony D, O'Sullivan D, Byrne S, O'Connor MN, Ryan C, Gallagher P. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. *Age Ageing* 2015; 44:213–218.
4. American Geriatrics Society 2012 Beers Criteria Update Expert Panel. American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults. *J Am Geriatr Soc* 2012; 60:616–631.
5. Mallery LH, Allen M, Fleming I, et al. Promoting higher blood pressure targets for frail older adults: a consensus guideline from Canada. *Cleve Clin J Med* 2014; 81:427–437.
6. Mallery LH, Ransom T, Steeves B, Cook B, Dunbar P, Moorhouse P. Evidence-informed guidelines for treating frail older adults with type 2 diabetes: from the Diabetes Care Program of Nova Scotia (DCPNS) and the Palliative and Therapeutic Harmonization (PATH) program. *J Am Med Dir Assoc* 2013; 14:801–808.
7. Moorhouse P, Mallery L. Palliative and therapeutic harmonization: a model for appropriate decision-making in frail older adults. *J Am Geriatr Soc* 2012; 60:2326–2332.
8. Fried LP, Tangen CM, Walston J, et al; Cardiovascular Health Study Collaborative Research Group. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* 2001; 56:M146–M156.
9. Morley JE, Malmstrom TK, Miller DK. A simple frailty questionnaire (FRAIL) predicts outcomes in middle aged African Americans. *J Nutr Health Aging* 2012; 16:601–608.
10. Rockwood K, Song Z, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly people. *CMAJ* 2005; 173:489–495.
11. Morley JE, Vellas B, van Kan GA, et al. Frailty consensus: a call to action. *J Am Med Dir Assoc* 2013; 14:392–397.
12. Tricoci P, Allen JM, Kramer JM, Califf RM, Smith SC Jr. Scientific evidence underlying the ACC/AHA clinical practice guidelines. *JAMA* 2009; 301:831–841.
13. Shepherd J, Blauw GJ, Murphy MB, et al; PROSPER study group. PROSpective Study of Pravastatin in the Elderly at Risk. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet* 2002; 360:1623–1630.
14. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994; 344:1383–1389.
15. Miettinen TA, Pyörälä K, Olsson AG, et al. Cholesterol-lowering therapy in women and elderly patients with myocardial infarction or angina pectoris: findings from the Scandinavian Simvastatin Study Group (4S). *Circulation* 1997; 96:4211–4218.
16. Lewis SJ, Moye LA, Sacks FM, et al. Effect of pravastatin on cardiovascular events in older patients with myocardial infarction and cholesterol levels in the average range. Results of the Cholesterol and Recurrent Events (CARE) trial. *Ann Intern Med* 1998; 129:681–689.
17. Hunt D, Young P, Simes J, et al. Benefits of pravastatin on cardiovascular events and mortality in older patients with coronary heart disease are equal to or exceed those seen in younger patients: results from the LIPID trial. *Ann Intern Med* 2001; 134:931–940.
18. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. *N Engl J Med* 1998; 339:1349–1357.
19. Heart Protection Study Collaborative Group. The effects of cholesterol lowering with simvastatin on cause-specific mortality and on cancer incidence in 20,536 high-risk people: a randomized placebo-controlled trial. *BMC Med* 2005; 3:6.
20. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomized placebo-controlled trial. *Lancet* 2002; 360:7–22.
21. Pitt B, Mancini GB, Ellis SG, Rosman HS, Park JS, McGovern ME. Pravastatin limitation of atherosclerosis in the coronary arteries (PLAC 1): reduction in atherosclerosis progression and clinical events. PLAC 1 investigation. *J Am Coll Cardiol* 1995; 26:1133–1139.
22. Jukema JW, Bruschke AV, van Boven AJ, et al. Effects of lipid lowering by pravastatin on progression and regression of coronary artery disease in symptomatic men with normal to moderately elevated serum cholesterol levels. The Regression Growth Evaluation Statin Study (REGRESS). *Circulation* 1995; 91:2528–2540.
23. Serruys PW, Foley DP, Jackson G, et al. A randomized placebo-controlled trial of fluvastatin for prevention of restenosis after successful coronary balloon angioplasty; final results of the fluvastatin angiographic restenosis (FLARE) trial. *Eur Heart J* 1999; 20:58–69.
24. Serruys PW, de Feyter P, Macaya C, et al; Lescol Intervention Prevention Study (LIPS) Investigators. Fluvastatin for prevention of cardiac events following successful first percutaneous coronary intervention: a randomized controlled trial. *JAMA* 2002; 287:3215–3222.
25. Tavazzi L, Maggioni AP, Marchioli R, et al; GISSI-HF Investigators. Effect of rosuvastatin in patients with chronic heart failure (the GISSI-HF trial): a randomized, double-blind, placebo-controlled trial. *Lancet* 2008; 372:1231–1239.
26. Kjekshus J, Apatrei E, Barrios V, et al; CORONA Group. Rosuvastatin in older patients with systolic heart failure. *N Engl J Med* 2007; 357:2248–2261.
27. Amarenco P, Bogousslavsky J, Callahan A, et al; Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Investigators. High-dose atorvastatin after stroke or transient ischemic attack. *N Engl J Med* 2006; 355:549–559.
28. Ridker PM, Danielson E, Fonseca FA, et al; JUPITER Study Group. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med* 2008; 359:2195–2207.

29. Glynn RJ, Koenig W, Nordestgaard BG, Shepherd J, Ridker PM. Rosuvastatin for primary prevention in older persons with elevated C-reactive protein and low to average low-density lipoprotein cholesterol levels: exploratory analysis of a randomized trial. *Ann Intern Med* 2010; 152:488–496, W174.
30. Chaturvedi S, Zivin J, Breazna A, et al; SPARCL Investigators. Effect of atorvastatin in elderly patients with a recent stroke or transient ischemic attack. *Neurology* 2009; 72:688–694.
31. Afilalo J, Duque G, Steele R, Jukema JW, de Craen AJ, Eisenberg MJ. Statins for secondary prevention in elderly patients: a hierarchical bayesian meta-analysis. *J Am Coll Cardiol* 2008; 51:37–45.
32. Cholesterol Treatment Trialists' (CTT) Collaborators; Mihaylova B, Emberson J, Blackwell L, et al. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. *Lancet* 2012; 380:581–590.
33. Sacks FM, Pfeffer MA, Moye L, et al. Rationale and design of a secondary prevention trial of lowering normal plasma cholesterol levels after acute myocardial infarction: the Cholesterol and Recurrent Events (CARE). *Am J Cardiol* 1991; 68:1436–1446.
34. Armitage J, Collins R. Need for large scale randomised evidence about lowering LDL cholesterol in people with diabetes mellitus: MRC/BHF Heart Protection Study and other major trials. *Heart* 2000; 84:357–360.
35. Design features and baseline characteristics of the LIPID (Long-Term Intervention with Pravastatin in Ischemic Disease) study: a randomized trial in patients with previous acute myocardial infarction and/or unstable angina pectoris. *Am J Cardiol* 1995; 76:474–479.
36. Shepherd J, Blauw GJ, Murphy MB, et al. The design of a prospective study of Pravastatin in the Elderly at Risk (PROSPER). *Am J Cardiol* 1999; 84:1192–1197.
37. Amarenco P, Bogousslavsky J, Callahan AS, et al; SPARCL Investigators. Design and baseline characteristics of the stroke prevention by aggressive reduction in cholesterol levels (SPARCL) study. *Cerebrovasc Dis* 2003; 16:389–395.
38. Interpretation of subgroup analyses and meta-regressions. In: Higgins JPT, Green S, editors. *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0. The Cochrane Collaboration, 2011. http://handbook.cochrane.org/chapter_9/9_6_6_interpretation_of_subgroup_analyses_and_meta_regressions.htm. Accessed December 5, 2016.
39. Borenstein M, Higgins JP. Meta-analysis and subgroups. *Prev Sci* 2013; 14:134–143.
40. Savarese G, Gotto AM Jr, Paolillo S, et al. Benefits of statins in elderly subjects without established cardiovascular disease: a meta-analysis. *J Am Coll Cardiol* 2013; 62:2090–2099.
41. Sever PS, Dahlof B, Poulter NR, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet* 2003; 361:1149–1158.
42. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). *JAMA* 2002; 288:2998–3007.
43. de Longheri M, Salen P, Abramson J, et al. Cholesterol lowering, cardiovascular diseases, and the rosuvastatin-JUPITER controversy: a critical reappraisal. *Arch Intern Med* 2010; 170:1032–1036.
44. Yusuf S, Lonn E, Bosch J. Lipid lowering for primary prevention. *Lancet* 2009; 373:1152–1155.
45. Briel M, Bassler D, Wang AT, Guyatt GH, Montori VM. The dangers of stopping a trial too early. *J Bone Joint Surg Am* 2012; 94(suppl 1):56–60.
46. Hayward RA, Krumholz HM. Three reasons to abandon low-density lipoprotein targets: an open letter to the Adult Treatment Panel IV of the National Institutes of Health. *Circ Cardiovasc Qual Outcomes* 2012; 5:2–5.
47. Afilalo J, Duque G, Steele R, Jukema JW, de Craen AJ, Eisenberg MJ. Statins for secondary prevention in elderly patients: a hierarchical Bayesian meta-analysis. www.ncbi.nlm.nih.gov/pubmedhealth/PMH0026417. Accessed December 5, 2016.
48. Holmes HM, Hayley DC, Alexander GC, Sachs GA. Reconsidering medication appropriateness for patients late in life. *Arch Intern Med* 2006; 166:605–609.
49. Rockwood K, Mitnitski A. Frailty defined by deficit accumulation and geriatric medicine defined by frailty. *Clin Geriatr Med* 2011; 27:17–26.
50. Petersen LK, Christensen K, Kragstrup J. Lipid-lowering treatment to the end? A review of observational studies and RCTs on cholesterol and mortality in 80+-year olds. *Age Ageing* 2010; 39:674–680.
51. Psaty BM, Anderson M, Kronmal RA, et al. The association between lipid levels and the risks of incident myocardial infarction, stroke, and total mortality: the Cardiovascular Health Study. *J Am Geriatr Soc* 2004; 52:1639–1647.
52. de Ruijter W, Westendorp RG, Assendelft WJ, et al. Use of Framingham risk score and new biomarkers to predict cardiovascular mortality in older people: population based observational cohort study. *BMJ* 2009; 338:a3083.
53. Canon CP, Blazing MA, Giugliano RP, et al; IMPROVE-IT Investigators. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med* 2015; 372:2387–2397.
54. 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; 29:151–167.
55. Kutner JS, Blatchford PJ, Taylor DH, et al. Safety and benefit of discontinuing statin therapy in the setting of advanced, life-limiting illness: a randomized clinical trial. *JAMA Intern Med* 2015; 175:691–700.
56. Tinetti ME, Bogardus ST Jr, Agostini JV. Potential pitfalls of disease-specific guidelines for patients with multiple conditions. *N Engl J Med* 2004; 351:2870–2874.
57. Rosenson RS. Current overview of statin-induced myopathy. *Am J Med* 2004; 116:408–416.
58. Mancini GB, 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; 27:635–662.
59. Cohen JD, Brinton EA, Ito MK, Jacobson TA. Understanding Statin Use in America and Gaps in Patient Education (USAGE): an internet-based survey of 10,138 current and former statin users. *J Clin Lipidol* 2012; 6:208–215.
60. Joy TR, Hegele RA. Narrative review: statin-related myopathy. *Ann Intern Med* 2009; 150:858–868.
61. Talbert RL. Safety issues with statin therapy. *J Am Pharm Assoc* (2003) 2006; 46:479–490.
62. Sewright KA, Clarkson PM, Thompson PD. Statin myopathy: incidence, risk factors, and pathophysiology. *Curr Atheroscler Rep* 2007; 9:389–396.
63. Ott BR, Daiello LA, Dahabreh IJ, et al. Do statins impair cognition? A systematic review and meta-analysis of randomized controlled trials. *J Gen Intern Med* 2015; 30:348–358.
64. 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; 29:1553–1568.
65. Rojas-Fernandez CH, Cameron JC. Is statin-associated cognitive impairment clinically relevant? A narrative review and clinical recommendations. *Ann Pharmacother* 2012; 46:549–557.
66. McGuinness B, O'Hare J, Craig D, Bullock R, Malouf R, Passmore P. Cochrane review on 'Statins for the treatment of dementia'. *Int J Geriatr Psychiatry* 2013; 28:119–126.
67. Pandey RD, Gupta PP, Jha D, Kumar S. Role of statins in Alzheimer's disease: a retrospective meta-analysis for commonly investigated clinical parameters in RCTs. *Int J Neurosci* 2013; 123:521–525.
68. Food and Drug Administration (FDA). FDA drug safety communication: important safety label changes to cholesterol-lowering statin drugs. www.fda.gov/drugs/drugsafety/ucm293101.htm. Accessed December 5, 2016.
69. Garfinkel D, Mangin D. Feasibility study of a systematic approach for discontinuation of multiple medications in older adults: addressing polypharmacy. *Arch Intern Med* 2010; 170:1648–1654.

ADDRESS: Laurie H. Mallery, MD, FRCPC, Camp Hill Veterans' Memorial Building, 5955 Veterans' Memorial Lane, Suite 2650, Halifax, NS B3H 2E1 Canada; laurie.mallery@nshealth.ca