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THE CHALLENGE OF PRESCRIBING STATINS FOR PRIMARY PREVENTION IN THE ELDERLY

Tara Farquharson
HBSc, BScPhm, ACPR
Leslie Dan Faculty of Pharmacy, University of Toronto; Department of Pharmacy Services, Mount Sinai Hospital

Chris Fan-Lun
BScPhm, ACPR, CGP
Leslie Dan Faculty of Pharmacy, University of Toronto; Department of Pharmacy Services, Mount Sinai Hospital

Corresponding Author:
Chris Fan-Lun
Cfan-lun@mtsinai.on.ca

Abstract

The evidence describing statin therapy for primary prevention in the elderly (aged ≥75) is limited. The evidence to date includes a meta-analysis by Savarese et al., which is comprised mostly of subanalyses of studies using mild to moderate potency statins in elderly populations. This study suggests limited reduction in cardiac and cerebrovascular events, with no prolongation of survival. Side effects such as myopathy and rhabdomyolysis may be more common in the elderly, especially if frail, with compromised renal function and with high dose statin use. Thus, the decision of whether to use a statin in this population should be guided by careful consideration of cardiac risk, polypharmacy, frailty and comorbidities.

Les preuves soutenant l'utilisation des statines en prévention primaire chez les personnes âgées (≥ 75 ans) sont limitées. Pour le moment, les preuves d'efficacité se limitent à une méta-analyse effectuée par Savarese et al., qui comprend surtout des sous-analyses d'études utilisant des statines de puissance faible à modérée dans des populations âgées. Cette méta-analyse suggère une réduction limitée des événements cardiaques et vasculaires cérébraux, sans prolongation de la survie. Les effets indésirables, tels la myopathie et la rhabdomyolyse, pourraient être plus fréquents chez les personnes âgées, particulièrement si elles sont frêles, si elles ont une insuffisance rénale ou si elles utilisent de hautes doses de statines. Ainsi, la décision d'utiliser ou non les statines chez les patients âgés de 75 ans et plus devrait être prise en tenant compte des risques cardiaques, de la polypharmacie, de la fragilité et des comorbidités.

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The challenge of prescribing statins for primary prevention in the elderly

Cardiovascular diseases (CVD) and cerebrovascular disease, comprised of nonfatal myocardial infarction, death due to coronary heart disease, fatal and nonfatal stroke, are leading causes of death and disability in Canada. Among seniors, 14.8% of those aged 65-74 years report having heart disease, with the proportion climbing to 22.9% at age 75 or higher. In this same age group, 7.1% of Canadians report living with the effects of a stroke.[1]

There is solid evidence supporting the use of 3-hydroxy-3-methyl-glutaryl coenzyme A reductase inhibitors (statins) for secondary prevention of cardiovascular events and death in nonfrail elders.[2,3] Initiation or continuation of statins in older patients for primary prevention becomes a more challenging question. A recent meta-analysis by Savarese et al. (www.ncbi.nlm.nih.gov/pubmed/23954343) included patients aged 65 or older that showed statins compared to placebo significantly reduced the risk of myocardial infarction by 39.4% (p=0.003) and reduced the risk of stroke by 23.8% p=0.006).[4] However, the risk of all cause death (p=0.21) and of cardiovascular death (p=0.493) were not significantly reduced suggesting benefits may be in quality rather than quantity of life.[4] In this context, the benefits of statin therapy must be balanced against the risks for adverse effects, polypharmacy, nonadherence and patient preferences.

Background

The most recently published American College of Cardiology/American Heart Association (ACC/AHA) guidelines on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular disease (ASCVD) risk recognizes the uncertainty of statins for primary prevention in older patients (see http://circ.ahajournals.org/content/early/2013/11/11/01.cir.0000437738.63853.7a).[5] Specifically, the authors state the risks and benefits of primary prevention of ASCVD in patients >75 years of age should be evaluated and require consideration of other factors including comorbidities, goals of care, risk of adverse effects, drug-drug interactions and patient preference. This suggestion is based on expert opinion, due to a lack of evidence in this population.[5]

Assessment of cardiovascular risk

There are several limitations to assessing cardiovascular risk in the very old (>85 years). Older patients are more likely to experience life altering complications from CV events, including reduced mobility, increased care requirements, hospitalizations and decline in quality of life.[6] Although hypercholesterolemia is a major risk factor for development of CVD, measuring lipid levels without an absolute risk assessment may have limited benefit and give an inaccurate representation of a patient's CVD risk.[7] The relative risk per unit change in cholesterol decreases with age because of the higher absolute risk of CVD in older people.[8] There are several studies suggesting that in the very old, higher cholesterol levels are associated with better survival and may be a marker for successful aging or robustness.[9,10,11]

It is important to recognize that the strongest predictor of cardiovascular risk in any risk equation is age. However, both the Framingham 10-year Risk CVD calculation and the Pooled Cohort Equations to estimate the 10-year primary risk of ASCVD risk[12,13] are not designed for nor recommended in people ≥80 years of age.[14] Theoretically, the elderly should experience greater absolute benefit from lipid lowering therapy because of their age. However, the power of the classic risk factors (age, sex, systolic blood pressure, etc.) to predict risk of CVD seems to diminish with advancing age.[15]

Evidence for statin risk reduction in primary prevention

There are limited randomized controlled trials comparing statins to placebo in the elderly population without CVD. Clinical trials often exclude polymorbid older adults and rarely include adults >75 years of age with significant frailty. Thus, the approach to preventing ASCVD in older adults comes from

extrapolating from a more robust and generally younger adult population. Although the majority of studies showed a positive trend towards statins for stroke prevention, PROSPER showed no difference (Table 1).

The PROSPER trial was one of the largest studies specifically designed to analyze cardiovascular outcomes in the elderly for primary and secondary prevention.[16] In the primary prevention arm, inclusion risk factors included one of current smoker, hypertension or diabetes. In the overall population pravastatin showed benefit in the primary (combined) outcome of coronary heart disease death or nonfatal myocardial infarction or fatal or nonfatal stroke for primary and secondary prevention. However, a post hoc subgroup analysis showed there was no statistically significant benefit for primary prevention (Table 1)**.** This raises the strong possibility of a lack of benefit from statins in primary prevention.

The meta-analysis by Savarese et al. (www.ncbi.nlm.nih.gov/pubmed/23954343) demonstrated the use of low to moderate intensity statins for primary prevention in the elderly with baseline LDL greater than 2.8 mmol/L and at least one risk factor appears to modestly reduce the absolute risk for MI and stroke (Table 2).[4] However, there is no statistically significant impact on longevity in the elderly. Another important outcome is nonfatal stroke leading to disability in statin clinical trials. However, the outcome of nonfatal stroke may include mild strokes and TIAs; the number of strokes leading to disability, such as impaired cognition due to stroke, is not reported separately. Thus, the nonfatal stroke metric reported in trials might not be relevant to the frail elderly.

The joint ACC/AHA Task Force that led the development of the blood cholesterol guideline (http://circ.ahajournals.org/content/early/2013/11/11/01.cir.0000437738.63853.7a) concluded that there was insufficient evidence to support an ASCVD event reduction benefit from statin initiation in individuals >75 years of age without ASCVD or diabetes.[5] Although the guidelines support the continuation of statins in older adults who are already taking and tolerating these medications, coexisting diseases in the elderly with significant polymorbidity may limit any benefit of statin preventative therapy due to other competing risks of mortality.[17]

Table 1. Comparison of evidence for statins

Study	1° endpoint	Comparison	Outcomes	Comments
PROSPER[16] Follow up: 3.2 years Average age: 75 Age range: 70-82	CHD, nonfatal MI, fatal and nonfatal stroke	Pravastatin 40 mg n=2891 vs Placebo n=2913	**2° prevention:** Pravastatin: 17.4% Placebo: 21.7% **ARR**: 4.3% **RRR**: 19.8% **HR**: 0.78 (0.66-0.93) **NNT:** 23 **1° prevention:** Pravastatin: 11.4% Placebo: 12.1% **ARR**: 0.7% **RRR**: 9% **HR**: 0.94 (0.77-1.15) **NNT:** 142	• Designed to study elderly • **Controversy over length of study:** May have been too short to show a difference between groups • Outcomes in other studies of younger people for similar timeframes (ASCOT-LAA and CARDS) have shown significant differences. The high risk elderly population should result in a higher likelihood for finding differences • Life expectancy is reduced in the elderly population, and if significant benefit requires >3.2 years of therapy, then the benefit of therapy may be questioned

Study	1° endpoint	Comparison	Outcomes	Comments
ASCOT-LLA[31] (>65 years group) Follow up: 3.3 years Average age: 71	Nonfatal MI (including silent MI) and fatal CHD	Atorvastatin 10 mg n=2189 vs Placebo n=2256	In >65 year old group: **MI + fatal CHD:** **HR**: 0.64 (0.5-0.83)	• Analysis of an antihypertensive trial arm (atenolol + thiazide, or amlodipine + perindopril) • Looked at results for patients >65 and <65
MEGA[32] Follow up: 5 years Average age: N/A n=7832	First occurrence of CHD	Diet alone n=N/A vs Diet + pravastatin 10-20 mg n=N/A	**CHD:** 3.3 vs 4.8%, **HR:** 0.69 (0.49 – 0.97) **Stroke:** 2.2 vs 3.4%, **RRR:** 56% **HR:**0.65 (0.43-0.97)	• Japanese population >45 years • No baseline comparison of groups • Did not isolate results of elderly patients from other patients
CARDS[33] (for >65 group) Follow up: 3.9 years Average age: 69	Time to first acute CHD event, coronary revascularization or stroke	Atorvastatin 10 mg n=572 vs Placebo n=557	**Major CV event:** 7.2 vs 11.1% **ARR**: 3.9% **RRR:** 38% **p**<0.05 **NNT:** 26	• Analyzed two groups of patients: <65 and >65 years • All patients had history of diabetes
JUPITER[34] Follow up: 1.9 years Median age: 74	First CV event	Rosuvastatin 20 mg n=2878 vs Placebo N=2817	**CV event:** **HR**: 0.61 (0.46-0.82) NNT: 62 (39-148) **MI:** **HR**: 0.55 (0.31-1) **NNT:** 211(106-32,924) **Stroke:** **HR**: 0.55 (0.33-0.93) **NNT:** 161 (86-1192)	• Included patients with elevated C-reactive protein ≥2 mg/mL • Exploratory secondary analysis of patients ≥70 years old • Industry involved in randomization and funding
AFCAPS [35] Follow up: 5.2 years Average age: 58	First acute, major CV event	Lovastatin 20-40 mg n=3301 vs Placebo n=3304	**First acute major CV event:** **RRR:** 63% (50-79%)	• Included patients 45-73 years • Excluded patients with uncontrolled hypertension, hyperlipidemia and diabetes

ARR = absolute risk reduction RRR = relative risk reduction, NNT = number needed to treat (based on study duration), CHD=coronary heart disease, MI = myocardial infarction, CI = confidence interval, N/A = not available

Table 2. Summary of meta-analysis of statin trials in the elderly by Savarese et al.

Title	Study type	Results	Comments
Savarese et al.[4] Follow up: 3.5 years Average age: 73 n=24,674	Meta-analysis of low-moderate potency statins (see Table 3)	**MI:** 2.7% vs 3.9% **ARR:**1.2% **NNT:** 83 p=0.003 **Stroke:** 2.1% vs 2.8% **ARR:** 0.7% **NNT:** 142 p=0.006	• MI statistic was heterogeneous (could not accurately be compared) – this was corrected by excluding PROSPER and results were similar • Each statistic included different studies: **MI:**AFCAPS, ASCOT-LLA, CARDS, JUPITER, PROSPER **Stroke:** ASCOT-LLA, CARDS, JUPITER, MEGA, PROSPER • No mortality difference
Inclusion Risk Factors			
At least one of: Hypertension (systolic blood pressure >150 mmHg or treatment with antihypertensive Diabetes Smoking C-reactive protein >2 mg/L Hypercholesterolemia (total cholesterol 4-9 mmol/L)			
Minor Risk Factors			
Subclinical atherosclerosis Coronary artery calcium scoring Peripheral vascular disease Renal dysfunction			
Source: Savarese G, Gotto AM, Paolillo S et al. Benefits of statins in elderly subjects without established cardiovascular disease: a meta-analysis. J Am CollCardiol 2013;62(22):2090-9.[4]			

Appropriate statin dosing for primary prevention in the elderly

Few studies have evaluated the use of high intensity statin therapy (which is more likely to cause side effects) for primary prevention in the elderly.[5,18,19,20,21] The evidence available supports low to moderate potency statin therapy (Table 3), with the exception of the JUPITER trial, which included high potency rosuvastatin 20 mg. JUPITER reported increased adverse events in the elderly, suggesting high intensity statin therapy may not be appropriate in this population.[21] Among the studies in the meta-analysis by Savarese et al., there were no obvious differences in results between studies using low versus moderate statin intensity. In addition, the new ACC/AHA guidelines suggest fixed statin dosing with less focus on achieving target LDL or non-HDL levels, since there is a lack of evidence to support this practice.[5]

Table 3. Studied daily dosages of statins for primary prevention in elderly subjects

Atorvastatin 10 mg	Lovastatin 20-40 mg	Pravastatin 10-40 mg	Rosuvastatin 20 mg
Source: Savarese G, Gotto AM, Paolillo S et al. Benefits of statins in elderly subjects without established cardiovascular disease: a meta-analysis. J Am Coll Cardiol 2013;62(22):2090-9.[4]			

Statin safety concerns in the elderly

In the Heart Protection study (HPS),[18] which compared simvastatin 40 mg to placebo in patients 40-80 years old, myopathy or rhabdomyolysis occurred in nine out of 10,269 patients, six of whom were subjects greater than 65 years of age.

Both the HPS[18] and SEARCH[22] studies identified that the rates of ALT and/or AST level elevations occur more frequently with the use of high potency statins than low potency statins. However, this rarely results in hepatotoxicity (one per million person years of statin use)[23,24], and hepatologists do not recommend discontinuation unless signs indicate hepatotoxicity (Table 4). It is not clear if hepatotoxicity is more common in the elderly due to its rare occurrence.

Statin safety is a concern in older adults, as they may have several characteristics that predispose them to statin-related muscular adverse effects (Table 5). The effectiveness of statins is established in people who are generally healthier and robust. Thus, when these medications are used in older or frail individuals, unexpected or rarer side effects from clinical trials tend to emerge and become more common. The PRIMO study[25] identified some of the strongest predictors for muscular symptoms with high potency statin use (Table 6), in a predominantly middle aged population. Overall, muscular symptoms were reported in 10.5% of patients, with median onset of one month. Muscle pain prevented moderate exertion during daily activities in 38% of patients, while 4% were confined to bed or unable to work. There is no evidence to suggest that any one statin is more or less likely to cause myopathies, with the exception of fluvastatin, which has not been well studied for efficacy in the elderly.[25,26]

Frailty is a complex state of increased vulnerability and decreased ability to maintain homeostasis, which places those individuals at risk for multiple adverse health outcomes, including death, disability and institutionalization.[27] The clinical phenotype of frailty is based upon interrelated declines in strength, muscle mass, energy, physical activity and weight loss. With loss of muscle mass and decreased muscle function, there is a decline in muscle strength and exercise tolerance, which predict both slower walking speed and further decreases in physical activity.[28] These interconnections support the concept of a "cycle" of frailty. Statin-related muscular adverse effects may exacerbate this cycle. A measure of frailty such as the Clinical Frailty Scale (http://geriatricresearch.medicine.dal.ca/pdf/Clinical%20Faily%20Scale.pdf) can be used to predict adverse outcomes and provide help to plan interventions or to predict a patient's risk of death or need for institutional care.[29]

Table 4. Criteria for identifying adverse effects of statins, and suggested solutions[23,24,36]

Adverse effect	Criteria	Action
Myalgia	• Muscle pain • Normal creatine kinase	Continue monitoring (risk for further pain)
Myositis	• Muscle pain • Elevated creatine kinase <10 times upper limit of normal	Continue monitoring (risk for further pain) Check TSH[a] Consider switching statin or reducing dose
Rhabdomyolysis	• Muscle pain • Creatine kinase >10 times upper limit of normal	Stop statin Check TSH[a] Check serum creatinine, urine myoglobin

Adverse effect	Criteria	Action
Hepatotoxicity	• ALT and AST >3 times upper limit of normal	Monitor for: • Jaundice, malaise fatigue, hepatomegaly • Elevated bilirubin, prothrombin increases Consider discontinuation of statin based on risk–benefit Refer to gastroenterologist or hepatologist if necessary
[a] Hypothyroidism may induce hypercholesterolemia and elevate creatine kinase.		

Table 5. Risk factors associated with statin-related adverse events based upon evidence and drug interactions[23,24,25,26,36]

Risk factors	Drug interactions with statins:
Advanced age (>80 years age) Female gender High dose statin Muscle spasm or unexplained cramps History of increased creatine kinase Low body mass Frailty Asian ancestry Renal or hepatic dysfunction Hypothyroidism (untreated) Multiple comorbidities Polypharmacy Alcoholism Surgery or trauma Infection	Macrolide antibiotics (erythromycin, clarithromycin) Antiviral agents (HIV protease inhibitors) Verapamil (specifically interacts with simvastatin) Diltiazem (specifically interacts with lovastatin, atorvastatin) Amiodarone Antifungals (itraconazole, ketoconazole) Cyclosporine Grapefruit juice (>1 quart/day)

Table 6. Relative potency of statins

High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	Low-Intensity Statin Therapy
Daily dose lowers LDL-C, on average, by approximately ≥50%	Daily dose lowers LDL-C, on average, by approximately 30% to <50%	Daily dose lowers LDL-C, on average, by <30%
Atorvastatin (40†)–80 mg **Rosuvastatin 20 (*40*) mg**	**Atorvastatin 10 (*20*) mg** **Rosuvastatin (*5*) 10 mg** **Simvastatin 20–40 mg‡** **Pravastatin 40 (*80*) mg** **Lovastatin 40 mg** *Fluvastatin XL 80 mg* **Fluvastatin 40 mg BID** *Pitavastatin 2–4 mg*	*Simvastatin 10 mg* **Pravastatin 10–20 mg** **Lovastatin 20 mg** *Fluvastatin 20–40 mg* *Pitavastatin 1 mg*

Taken from Stone et al.[5] with permissions.

Conclusion

Statins provide a modest benefit in reduction of myocardial infarction and stroke over a 3.5 year period in elderly patients (primary prevention), though there is a lack of evidence for efficacy in individuals greater than 80 years of age. In this setting, clinical judgment should play an important role in therapeutic decisions with respect to initiation and continuation of statins.

Elderly patients should not receive high-intensity statin therapy for primary prevention due to concerns regarding side effects and a lack of evidence that high intensity doses are more efficacious. Low- and moderate-intensity dose statins have shown benefits in studies, and there appears to be no difference between these two with evidence currently available. Appropriate recommendations are listed in Table 6. Choice of one agent over another should be decided based on co-administration of other medications to prevent drug interactions (Table 5) or history of intolerance to different agents. Doses should be based upon presumed risk, weighed against comorbidities, polypharmacy, frailty and risk of side effects (e.g., rhabdomyolysis, hepatotoxicity etc.).

When treating elderly individuals with statins for primary prevention, thoughtful consideration should be given to their life expectancy and determining if the benefit of statins will be realized. *Most primary prevention studies took 3-4 years to achieve a 1% absolute risk reduction in their primary outcomes and it has been suggested that statins should be considered for primary prevention for elderly patients with a life expectancy of five years.*[30] One cannot assume that a mortality benefit shown in nonfrail populations applies to frail populations. In addition, the goals of therapy may not be to prolong life in the frail. With severe frailty and multimorbidity, there are uncertainties regarding whether statin trial outcomes are clinically meaningful and the magnitude of any benefit conferred, partly because of the decreased life expectancy in the severely frail. In these frailer patients, it is vital to understand if a treatment has improved or slowed a decline in functioning. The issue of treatment futility should be considered, particularly with competing causes of mortality in which preventative therapy would not be expected to be of benefit. These include severe cognitive dysfunction or dementia, nursing home residence and advanced metastatic disease.

Key points:

- Evidence to guide statin therapy for primary prevention in the elderly, especially those >75 years old, is limited;
- Use of statins for primary prevention in the elderly modestly reduces the risk of myocardial infarction and stroke but does not significantly prolong survival;
- High dose statins for primary prevention are not appropriate in the elderly; and
- The decision to treat older patients should take into consideration risk factors for CVD, comorbidities, polypharmacy, frailty, life expectancy, risk of side effects (e.g., rhabdomyolysis, hepatotoxicity).

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