REVIEW ARTICLE

# Statin therapy for primary cardiovascular prevention in adults older than 75 years

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**ABSTRACT**
Cardiovascular disease (CVD) is a major contributor to morbidity and mortality worldwide. An abundance of research demonstrated that low-density lipoprotein cholesterol (LDL-C) is an important risk factor for CVD that can be modified with the drug class hydroxymethylglutaryl-CoA reductase inhibitors, or statins. Statins have an unequivocal benefit in reducing CVD risk across age groups for secondary prevention. However, the benefit of these drugs for primary prevention in adults older than 75 years of age remains equivocal and controversial. The global population is aging rapidly and primary CVD prevention recommendations to guide statin therapy above the age of 75 years are necessary. However, current trends in statin therapy illustrate that it is underutilized for primary prevention in that age group. Concerns exist regarding the higher incidence of common adverse events from statin use in the older population; however, there are no confirmatory data regarding these associations. In the light of available evidence, it is reasonable to offer statin therapy for primary prevention to all older individuals following a shared decision-making process that takes life expectancy, polypharmacy, frailty, and potential adverse effects into consideration. Combination therapies with other agents for the management of dyslipidemia should be considered to facilitate the use of tolerable doses of statins. Future investigations of dyslipidemia therapies must appropriately include this at-risk population to identify optimal drugs and drug combinations that have a high benefit-to-risk ratio for the prevention of CVD in the very old.

**Introduction** Cardiovascular disease (CVD), including ischemic heart disease, heart failure, and strokes, was responsible for 17.8 million deaths globally in 2017.[1] Moreover, according to the United States Centers for Disease Control and Prevention (CDC), heart disease and stroke accounted for 655 381 and 147 810 deaths, respectively, in the United States in 2018.[2] Data from multiple trials and studies over the years have illustrated that low-density lipoprotein cholesterol (LDL-C) is a risk factor for CVD and can be modified with the drug class hydroxymethylglutaryl-CoA (HMG-CoA) reductase inhibitors, or statins. Statin use has successfully reduced the incidence of CVD and CVD-related mortality.[3,4]

The benefits of statin use for primary and secondary prevention of CVD is well understood for patients younger than 75 years. However, the role of statin therapy for primary prevention in adults older than 75 years is not well established.[5] In 2017, Mortensen et al[6] noted that many guidelines do not include recommendations for statin use as primary prevention in patients older than 75 years. They attribute this age limit to lack of evidence for this age demographic. As a result, the 2019 American College of Cardiology / American Heart Association guidelines, 2016 United States Preventive Services Task Force guidelines, 2019 European Society of Cardiology and the European Atherosclerosis Society guidelines, and 2018 National Lipid Association guidelines all recommended that the decision to initiate statin therapy for primary prevention in this population should be based on shared-decision making and clinical judgement.[7-10] In 2016, the population of individuals older than 75 years was 20.6 million. Moreover, the average life expectancy in 2016

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was 78.6 years, and rising.[11] As the population ages and the average life expectancy increases, it is important to include these factors in recommendations to help guide clinicians.

Odden et al[12] utilized a forecasting model to predict the cardiovascular and financial benefits of statin use in patients older than 75 years. This model predicted that if all adults aged between 75 and 94 years were treated with statins for primary prevention, there would be 8 million new statin prescriptions as well as 105 000 fewer myocardial infarctions (MIs) and 68 000 fewer coronary heart disease deaths per year. The model also predicted that if all adults aged 75 to 94 years with a history of cardiovascular disease were to use statins for primary prevention, the United States would save 14 billion USD in disease expenses over the next 10 years.

This review article will discuss the current evidence regarding statin use for primary prevention in adults above the age of 75 years. The aim of this review was to summarize the available data on the side effects and health outcomes for patients older than 75 years taking statins for primary prevention of CVD.

**Trends in statin prescribing** Despite absence of concrete evidence or guidelines in this population, multiple studies have analyzed statin prescribing trends to obtain a better understanding of the current approach for the elderly.

Ofori-Asenso et al[13] studied trends in statin use between 2007 and 2016 in Australian patients older than 65 years. They concluded that women were 18% less likely to initiate statin therapy than men across all age groups (age-adjusted rate ratio [RR], 0.82; 95% CI, 0.79–0.83). Statin therapy was used in approximately 15% of individuals aged 65 to 74 years (sex-adjusted RR, 1.15; 95% CI, 1.13–1.16) and it was 45% (sex-adjusted RR, 1.45; 95% CI, 1.44–1.47) more likely to be initiated compared with those aged 75 to 84 years and those aged 85 years or older, respectively. Lastly, the proportion of patients who were prescribed high-intensity therapy on initiation of statin treatment increased from 23.6% in 2007 to 30.5% in 2016 (RR, 1.26; 95% CI, 1.21–1.31). Atorvastatin was the most commonly prescribed statin during in this 10-year period. Likewise, Rodriguez et al[14] studied 63 576 Veterans Affairs patients, of which 8553 (13.5%) were women and 26 879 (29.0%) were of non-White ethnicity, and illustrated that veteran patients older than 75 years were less likely to be on a statin and less likely to be taking a high-intensity statin if they were already on statin therapy. Women were less likely to be treated than men as well (odds ratio [OR], 0.88; 95% CI, 0.83–0.92). In summary, these studies demonstrated that those older than 75 years were less likely to initiate statin therapy for primary prevention compared with those younger than 75 years. Women of all ages were less likely to be prescribed statin therapy as well.

Similarly, Panozzo et al[15] studied the National Institute of Health data of 109 306 patients from 2008 to 2018 with regard to the incidence of statin use in patients older than 75 years. This study echoed Ofori-Asenso et al[13] in that women were less likely to be prescribed a statin than men and that statin prescribing frequency decreased with age. However, this study also added that patients above the age of 75 with diabetes mellitus were 2-fold more likely to be prescribed a statin than a patient without diabetes (76.1 versus 34.5 initiators per 1000 member-years, respectively).

Of note, a study collected data on 4 424 818 Danish individuals and found that statin prescribing became highest for ages 75 to 84 years in 2010 and was higher in men than women (37% and 33%, respectively).[16] They also noted that statin prescribing for primary prevention decreased with age.

Lastly, adherence to statin therapy for primary prevention has been cited as an issue in the elderly population. A systematic review and meta-analysis on articles reporting statin use in older individuals was conducted to better understand the factors that play a role in nonadherence for statin users older than 65 years.[17] The authors noted that the data for nonadherence frequency in adults older than 75 years is equivocal. Furthermore, the study found that patients older than 65 years who were started on a statin for primary prevention were 49% more likely to be noncompliant with their statin compared with patients initiated on a statin for other indications nonadherence (OR, 1.49; 95% CI, 1.40–1.59).

These studies demonstrated that statin use for primary prevention is not common above the age of 75 and that women of all ages are typically less likely to be taking a statin for primary prevention.

**Myalgia** Myalgia, or muscle pain, is one of the most common side effect of statin therapy, but data on the effect of age on myalgia intensity is scarce. This symptom seems to intensify with more lipophilic statins, such as simvastatin.[18] Ito et al[19] analyzed 4451 patients who reported worsening or new muscle pain while taking a statin and a cytochrome P450 isozyme, organic anion transporting polypeptide 1B1, or P-glycoprotein inhibitor simultaneously. Patients taking a statin and cytochrome P450 inhibitor had a higher risk for new or worsening myalgias. Use of a statin and a medication that inhibits both organic anion transporting polypeptide 1B1 and P-glycoprotein was associated with a higher incidence of patients stopping their statin due to myalgias. This study was conducted on a population with a mean age of 61 years.

Iwere et al[20] conducted a meta-analysis and systematic review of 8 trials that included data on statin use and myopathy which encompassed adults older than 65 years. This study found no difference in myalgias between statin and nonstatin groups (OR, 1.03; 95% CI, 0.9–1.17; $P$ = 0.66). No additional risk of rhabdomyolysis was found between the groups as well (OR, 2.93; 95% CI, 0.3–28.18; $P$ = 0.35).

Nanna et al[21] analyzed data from the Patient and Provider Assessment of Lipid Management (PALM) registry in 2015 and found that the frequency of statin use for primary prevention was similar between patients younger and older than 75 years (62.6% in those >75 years old vs 63.1% in those ≤75 years old; $P$ = 0.83). Of the study patients, 1704 (25%) were older than 75 years. Interestingly, they also found that patients older than 75 years were less likely to report myalgias compared with those younger than 75 years (27.3% vs 33.3%; $P$ <0.001). Similarly, Robinson et al[22] reported that patients older than 75 years who were prescribed statins with ezetimibe reported similar rates of adverse-drug effects as their counterparts younger than 75 years.

In summary, these studies suggest that statin therapy does not increase the frequency of myalgias in those older than 75 years unless they are concurrently taking an inhibitor of cytochrome P450 isozyme, organic anion transporting polypeptide 1B1, or P-glycoprotein simultaneously. However, some of the aforementioned studies did not stratify their results by age. Further trials investigating the presence of myalgias with statins, specifically in those older than 75 years, are warranted.

## Cardiovascular and cerebrovascular disease

Guo et al[23] analyzed data from a clinical trial studying the effects of 10 mg of rosuvastatin daily vs placebo on cerebrovascular small vessel disease. Cerebrovascular small vessel disease was assessed in 227 patients older than 75 years and on a statin for primary prevention of cerebrovascular disease with a baseline magnetic resonance imaging. A follow-up magnetic resonance imaging study was completed every 2 to 3 years thereafter. Participants were evaluated for white matter hyperintensities volume, lacunes, enlarged perivascular spaces, and microbleeds. Patients on rosuvastatin, compared with the nonstatin group, had a reduced progression of white matter hyperintensities (hazard ratio [HR], 0.408; 95% CI, 0.233–0.716, $P$ <0.001), lacunes (HR, 0.417; 95% CI, 0.257–0.676; $P$ <0.001), and enlarged perivascular spaces (HR, 0.466; 95% CI, 0.249–0.873; $P$ = 0.005). Statin therapy did not increase the risk of microbleeds as well (HR, 0.703; 95% CI, 0.374–1.692; $P$ = 0.416).

Statin therapy reduced the risk of stroke, cerebrovascular disease, and CVD-related events in the elderly. Eilat-Tsanani et al[24] conducted a historical population-based cohort study and found that both men and women older than 75 years who received a statin experience fewer atherosclerotic CVD events compared with those not on a statin. Furthermore, a population-based cohort study conducted in France in 2019 analyzed 120 173 patients older than 75 years who were taking statins.[25] A total of 5396 (4.5%) patients were hospitalized due to a coronary or cerebrovascular event. The HR for a coronary event was 1.46 (95% CI, 1.21–1.75) and for a cerebrovascular event, 1.26 (95% CI,1.05–1.51) when comparing nonstatin and statin users. The study concluded that patients who were older than 75 years and discontinued their statin had a 33% increase in hospitalization risk for a cardiovascular event.

The JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) and HOPE-3 (Heart Outcomes Prevention Evaluation-3) trials are 2 of few trials that addressed the issue of statin use for primary prevention in the elderly. Glynn et al[26] studied the patient population from the JUPITER trial and found that patients older than 70 years with an elevated C-reactive protein level and without hyperlipidemia receiving rosuvastatin, compared with placebo, had lower rates of a first cardiovascular event. Moreover, the HOPE-3 trial included men older than 55 years and women older than 65 years who did not have cardiovascular disease and were at intermediate risk, as defined by having at least one of the following: elevated waist-to-hip ratio, history of a low level of high-density lipoprotein cholesterol, current or recent tobacco use, dysglycemia, family history of premature coronary disease, and mild renal dysfunction.[27] Women older than 60 years with 2 of the aforementioned risk factors were also included. A total of 12 705 subjects across 21 countries were enrolled and randomly assigned to receive a placebo or 10 mg of rosuvastatin daily. Of the patients taking statins, 3.7% either died from cardiovascular causes or had nonfatal MI or nonfatal stroke compared with 4.8% of those receiving placebo (HR, 0.76; 95% CI, 0.64–0.91; $P$ = 0.002). Muscle symptoms were reported in 5.8% of patients taking statins compared with 4.7% in the placebo group ($P$ = 0.005).

Savarese et al[28] analyzed 24 674 patients enrolled across 8 trials in regard to outcomes in patients receiving statins as compared with placebo for primary prevention. The study population did not have a documented history of cardiovascular disease. The mean age was 73 years and 42.7% of patients were women. The mean patient follow-up was 3.5 years from the start of the trial. When compared with placebo, statins reduced the risk of MI by 39.4% (relative risk, 0.606; 95% CI, 0.434–0.847; $P$ = 0.003) and the risk of stroke by 23.8% (relative risk, 0.762;

95% CI, 0.626–0.926; $P$ = 0.006). Conversely, statins did not reduce all-cause mortality and cardiovascular mortality.

A retrospective study by Taylor et al[29] assessed patients older than 75 years from the Veterans Affairs system to assess statin effectiveness for primary prevention. The primary outcome was the first cardiovascular event such as cardiovascular death, MI, or nonfatal stroke. A total of 559 patients received either a moderate- or high-intensity statin and 1294 patients did not. Patients who were on a statin were more likely to experience any cardiovascular event compared with the control cohort (19.7% vs 13.2%; $P$ = 0.0004). Likewise, patients on statins were more likely to experience a nonfatal MI or stroke when compared with controls (3.2% vs 0.5%; $P$ <0.001 and 14.1% vs 10.4%; $P$ = 0.019, respectively). Diabetic patients had a lower all-cause mortality if they were on a statin compared with those not taking a statin (19.18% vs 43.58%; $P$ <0.001).

**Mortality** The beneficial effect of statins on mortality are well established for those younger than 75 years; however, data are limited regarding such an effect in the population older than 75 years. Jun et al[30] conducted a retrospective case-control study in which 11 017 statin users older than 75 years were compared with 55 085 nonusers. They analyzed the effectiveness of statins for primary prevention of stroke, MI, and all-cause mortality. In this study, patients on a statin had a reduced risk of stroke (OR, 0.74; 95% CI, 0.61–0.89) and all-cause mortality (OR, 0.73; 95% CI, 0.66–0.81) compared with nonusers. No difference in the risk of MI was found. They also found that all-cause mortality and stroke rate decreased as the duration of therapy increased.

Likewise, the SCOPE-75 (Statin and Clinical Outcomes of Primary Prevention in Individuals Aged >75 Years) study analyzed 639 statin users and 639 nonusers between 2005 and 2016 and compared cardiovascular and cerebrovascular events as well as all-cause mortality between the 2 cohorts.[31] The median follow-up was 5.2 years. Statin users, compared with nonusers, had lower rates of cardio- and cerebrovascular events (2.15 vs 1.25 events/100 person-years; HR, 0.59; $P$ = 0.005) as well as lower all-cause mortality (1.19 vs 0.65 events/100 person-years; HR, 0.56; $P$ = 0.02). Kostis et al[32] found similar results in their analysis of 35 randomized control trials. This study found that all-cause mortality was reduced in patients older than 75 years who were on a statin for primary prevention compared with their counterparts who were not.

On the other hand, the ALLHAT-LLT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial)[33] demonstrated that statin therapy above the age of 75 years may be ineffective for primary prevention in those with moderate hyperlipidemia and hypertension. This study compared mortality and coronary heart disease event rates between patients receiving 40 mg of pravastatin and those receiving their usual care, as directed by their primary care physician over a 6-year period. The HR for all-cause mortality in the pravastatin group vs the usual care group was 1.34 (95% CI, 0.98–1.84; $P$ = 0.07) for adults 75 years and older. The study also found that coronary heart disease rates were not significantly different among these groups before and after adjusting for age, race, smoking status, and type 2 diabetes.

Similarly, Kim et al[34] assessed 5629 patients aged from 75 to 100 years and compared the differences in outcomes based on statin intensity. Low-intensity statin users had an increased risk of cardiac or cerebrovascular events (HR, 1.41; 95% CI, 1.02–1.95; $P$ = 0.04) compared with the high-intensity group (HR, 0.36; 95% CI, 0.17–0.76; $P$ = 0.007). Low- and high-intensity statin users had an increased risk of all-cause mortality compared with moderate-intensity users (HR, 1.43; 95% CI, 1.02–2; $P$ = 0.038 and HR, 1.54; 95% CI, 1.18–2.01; $P$ = 0.001, respectively).

A Korean study compared 685 statin users and 685 nonusers older than 75 years. Statins were prescribed for primary prevention. The authors identified temporal differences in mortality outcomes between the groups.[35] When compared with nonusers, the HRs for statin users were 0.83 ($P$ = 0.04) for all-cause mortality, 1.24 ($P$ =0.003) for cardiovascular events, and 1.18 ($P$ = 0.06) for new-onset diabetes mellitus. Furthermore, use of statin for more than 5 years, compared with less than 5 years, yielded a lower all-cause mortality (HR, 0.76; $P$ = 0.01) but had no impact on cardiovascular events (HR, 0.88; $P$ = 0.36) or new-onset diabetes mellitus (HR, 0.95; $P$ = 0.78) despite adjusting for age, sex, body mass index, diabetes mellitus, hypertension, aspirin use, and antiplatelet use.

Among United States veterans older than 75 years, one study found that initiation of statin therapy for primary prevention significantly reduced all-cause and cardiovascular mortality.[36] This study retrospectively analyzed 326 981 veterans (mean age, 81.1, of which 97% were men and 91% were White) between 2002 and 2012. A total of 57 178 veterans (17.5%) were on statins (mean follow-up, 6.8 years), and 206 902 total deaths occurred during the study period, of which 78.7 vs 98.2 per 1000 person-years were for statin and nonstatin users, respectively (weighted incidence rate difference, –19.5; 95% CI, –20.4 to –18.5). Morevoer, 53 296 cardiovascular deaths occurred, of which 22.6 and 25.7 per 1000 person-years were for statin and nonstatin users, respectively (weighted incidence rate difference, –3.1; 95% CI, –3.6 to –2.6). The HR were 0.75 (95% CI, 0.74–0.76) for

all-cause mortality, 0.8 (95% CI, 0.78–0.81) for cardiovascular mortality, and 0.92 (95% CI, 0.91–0.94) for a composite of coronary events when comparing statin users with nonusers.

Ramos et al[37] analyzed a cohort of 46 864 individuals with and without diabetes older than 75 years who were either receiving statin therapy for primary prevention or not. Women were 63% of individuals and median follow-up was 5.6 years. For patients without diabetes, there was no reduction in all-cause mortality (HR, 0.98; 95% CI, 0.91–1.05) or atherosclerotic CVD (HR,0.94; 95% CI, 0.86–1.04) among statin users aged between 75 and 84 years when compared with nonusers. For diabetics, however, all-cause mortality and the incidence of atherosclerotic cardiovascular disease were both reduced (HR, 0.76; 95% CI, 0.65–0.89 and HR, 0.84; 95% CI, 0.75–0.94, respectively) when on statin therapy.

The PROSPER (Pravastatin in Elderly Individuals at Risk of Vascular Disease) trial[38] assessed the benefits of statins in the elderly population. This randomized control trial included men and women aged 70 to 82 years with either vascular disease or conditions that increased risk for vascular disease such as hypertension, diabetes, and smoking. A total of 2913 individuals were assigned to receive placebo and 2891 were given 40 mg of pravastatin daily. The mean follow-up was 3 years. The primary endpoint was coronary death, nonfatal MI, and fatal or nonfatal stroke. Researchers found that death due to coronary heart disease and nonfatal MI risk were reduced in the pravastatin group (HR, 0.81; 95% CI, 0.69–0.94; $P = 0.006$) and risk of stroke was unaffected.

## Impact on mental health and cognition

Declines in cognition, impaired memory, and worsening mental health conditions have also gained attention as possible side effects of statin therapy. In 2012, the United States Food and Drug Administration issued a warning about the impact statins may have on cognition. On the other hand, the 2018 American College of Cardiology/American Heart Association Cholesterol Guideline recommends considering other causes of cognitive decline, in addition to possible statin effects.[10] A study in 2015 reviewed 23 randomized control trials that reported cognitive outcomes as part of their analysis on the side effects of statins. In a meta-analysis of 14 studies that included cognitive data, 27 643 patients did not show a correlation between statin use and cognitive function in cognitively intact individuals (standardized mean difference, 0.01; 95% CI, −0.01 to 0.03; $P = 0.42$) or those with Alzheimer disease (standardized mean difference, −0.05; 95% CI, −0.19 to 0.1; $P = 0.38$).[39] Pravastatin did not have a significant impact on cognitive function, as determined by a mini-mental status exam and other psychometric tests in the PROSPER trial as well.[38]

Similarly, Zhou et al[40] analyzed the impact of statins on dementia using patients from the ASPREE trial who were 70 or older. They did not find an increased risk for dementia due to statins in this age group. Likewise, a 2019 prospective observational study conducted in Australia examined cognition, memory, and brain volume in patients aged 70 to 90 years who were taking statins.[41] Compared to nonstatin users, patients on statin therapy did not have any greater decline in cognition and memory than their nonstatin counterparts. There was no difference in brain volume changes between the 2 groups as well.

Agustini et al[42] analyzed the impact of statins on depressive symptoms in the elderly. To quantify depressive symptoms, the study used the Center for Epidemiological Studies Depression Scale-10 and compared the scores between the statin and nonstatin cohorts. This cross-sectional study published in 2019 found that depressive symptoms were more prevalent among patients aged 75 to 84 years who were on a statin, compared with those who were not (OR, 1.13; 95% CI, 1.02–1.25; $P = 0.02$). Moreover, when the results were adjusted for age, sex, smoking status, and education level, there was a 21% increase in depressive symptoms among 7219 patients in this age group.

Furthermore, severe mental illness has been associated with increased cardiovascular disease morbidity. As a result, initiation of statin therapy for primary prevention is crucial in this vulnerable population. Blackburn et al[43] found that patients with and without severe mental illness in the United Kingdom had similar rates of statin therapy for primary prevention in the 60-to-74-years age group. However, despite the implementation of policies for lipid monitoring in adults with severe mental illness, adults older than 75 with schizophrenia had lower rates of statin initiation for primary prevention compared with those without schizophrenia.

Based on the available literature, there appears to be no connection between impaired cognition and statin use. However, this conclusion was based on data from trials not specifically looking for an association of statin use and cognition. To better understand the effects of statins on cognition, a clinical trial known as the PREVENTABLE (Pragmatic Evaluation of Events And Benefits of Lipid-lowering in Older Adults) trial is currently underway. This trial will enroll 20 000 adults without cardiovascular disease or dementia who are older than 75 years. Participants will either receive placebo or 40 mg of atorvastatin daily. The follow-up period will be 5 years. The primary outcome will be the number of patients without the diagnosis of new dementia at the end of the trial (ClinicalTrials.gov identifier, NCT04262206).

**Conclusions** Statins have an unequivocal benefit in reducing CVD risk across age groups for secondary CVD prevention.[44-63] However, the benefit of these drugs for primary prevention in adults older than 75 years of age remains equivocal and controversial.[64] The global population is aging rapidly and primary CVD prevention recommendations to guide statin therapy above the age of 75 years are necessary. The current trends in statin therapy illustrate that statins are underutilized for primary prevention in the 75-and-older age group as well as in women. Concerns exist regarding the higher incidence of common adverse events from statin use in the older population; however, existing literature on statin use and cognition demonstrated that there is no known association between statin use and cognitive decline. However, a majority of these studies included patients below the age of 75 years. Further investigation via trials such as the PREVENTABLE trial are needed to clarify the potential association in those older than 75 years. On the other hand, it appears that myalgias in this age group have been well studied, and that there is no difference in risk of myalgias between those younger and older than 75 years.

In light of available evidence, it is reasonable to offer statin therapy for primary prevention to all older individuals following a shared decision-making process that takes life expectancy, polypharmacy, frailty, and potential adverse effects into consideration. Combination therapies with other agents used for the management for dyslipidemia should be considered to facilitate the use of tolerable doses of statins. Future investigations of dyslipidemia therapies must appropriately include this at-risk population to identify optimal drugs and drug combinations that have a high benefit-to-risk ratio for the prevention of CVD in the very old.

## ARTICLE INFORMATION

**CONFLICT OF INTEREST** None declared.



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