# Statins for the Primary Prevention of Cardiovascular Disease in the Elderly

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**OBJECTIVE:** The objective is to review the evidence evaluating the efficacy of statin therapy for primary prevention of cardiovascular (CV) disease in the elderly.

**DATA SOURCES:** A literature search of MEDLINE and PubMed (1966-January 2013) using the terms HMG-CoA reductase inhibitor, statin, primary prevention, elderly, and geriatrics was performed. The search was limited to clinical trials, meta-analyses, and subanalyses, including primary prevention patients. Bibliographies of selected articles were examined to identify additional clinical trials.

**STUDY SELECTION:** Fourteen clinical trials, subanalyses, and meta-analyses were reviewed. A total of seven clinical trials and subanalyses evaluating statin therapy versus placebo in the elderly primary prevention patients with a primary endpoint of hard coronary heart disease were included.

**DATA EXTRACTION:** Data collected from the clinical trials and subanalyses included number of elderly patients randomized, therapy, duration of follow-up, and the incidence of coronary events.

**DATA SYNTHESIS:** The average annual rates of first CV event increases as patients age. There is strong evidence that supports the use of statins for secondary prevention; although primary prevention, specifically in the elderly, is less defined. This paper reviews the literature specifically for primary prevention, for which the results have shown a trend toward decreased first occurrence of coronary heart disease with statin therapy in elderly patients.

**CONCLUSION:** Statin therapy should be considered as a primary prevention therapy against coronary disease for elderly patients. Evidence-based clinical benefits are seen in this patient population. However, clinical judgment and consideration of comorbidities that may impact life expectancy should be assessed to determine appropriateness for individual patients.

**KEY WORDS:** Cardiovascular prevention, Elderly, Geriatric, Hydroxyl-3-methyl-glutaryl coenzyme A reductase, Primary prevention, Statin.

**ABBREVIATIONS:** AFCAPS/TEXCAPS = Primary Prevention of Acute Coronary Events with Lovastatin in Men and Women with Average Cholesterol Levels, ASCOT-LLA = Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm, ATP = Adult Treatment Panel, CARDS = Primary Prevention of Cardiovascular Disease with Atorvastatin in Type 2 Diabetes in the Collaborative Atorvastatin Diabetes Study, CHD = Coronary heart disease, CKD = Chronic kidney disease, Clcr = Creatinine clearance, CV = Cardiovascular, CVD = CV disease, FDA = Food and Drug Administration, HDL-C = High-density lipoprotein cholesterol, HPS = Heart Protection Study, JUPITER = Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin Trial, KDOQI = Kidney Disease Outcomes Quality Initiative, LDL-C = Low-density lipoprotein cholesterol, MEGA = Primary Prevention of Cardiovascular Disease with Pravastatin in Japan, MI = Myocardial infarction, PROSPER = Pravastatin in Elderly Individuals at Risk of Vascular Disease, TC = Total cholesterol.

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## Introduction

Primary prevention of cardiovascular disease (CVD) is important in older adults. Age itself is a positive, non-modifiable risk factor for the development of CVD. The Framingham risk score and the 2013 American College of Cardiology/American Health Association (ACC/AHA) risk-score calculator can help determine the risk of developing CVD in patients without known CVD.[1,2] Both scores use age as a variable to predict the development of CVD, and age alone can incur more risk than any other individual variable used by the tool. Using risk-scoring tools is important in the primary prevention patient population to ascertain risk versus benefit of cardiovascular (CV) risk-reduction therapy.

Older adults carry a high burden of first major CV events. Roughly two-thirds of first major coronary events occur in those 65 years of age or older.[3] For those who have not experienced CVD by age 50, the lifetime risk of developing the condition is higher than 50% for men and approximately 40% for women.[4] For those who are free of CVD at age 70, the lifetime risk of developing coronary

heart disease (CHD) is one in three for men and one in four for women.[4] In addition, the average annual rates of first CV events for men 85 to 94 years of age is 74/1,000, which is an increase from the estimated 3/1,000 for men 35 to 44 years of age, 35/1,000 for men 65 to 74 years of age, and 59/1,000 for men 75 to 84 years of age.[4] There are comparable rates of CV events in women, though they occur 10 years later in life.[4]

Despite the fact that age is directly associated with an increased risk of first major CV events, clinicians are sometimes reluctant to prescribe statin therapy for primary CV prevention in older adults. The use of statin therapy appears to decline with increased age, from 29% for patients 70 to 74 years of age to only 12% for patients 90 years of age or older.[5] Another study, which looked at Italian patients, found an increase in the percentages of patients taking lipid-lowering agents in those 70 to 79 years of age, with approximately 25% of women and 20% of men taking lipid-lowering agents for that age group.[6] For those 80 years of age or older, the use of lipid-lowering agents decreased to 15% for both men and women.[6]

There are several possible reasons for lower statin usage in the older patient population, especially those older than 80 years of age. There may be a perception that the evidence supporting statin therapy in primary prevention elderly patients is either lacking or does not demonstrate benefit. Elderly patients have unique characteristics that require special consideration from the clinician prior to starting a new medication, including evaluation of polypharmacy, cost, comorbidities, or concern for higher risk of adverse drug reactions or drug-drug interactions. There may also be concern that reduced life expectancy in the oldest patients reduces the potential for achieving benefit from a primary-prevention statin.

Given the known high risk of developing CVD in the elderly patients, an evidence-based review of statin therapy in the elderly is important. The purpose of this review article is to analyze the evidence that has evaluated the efficacy and clinical considerations of statin therapy for primary prevention in the elderly and to discuss some of the clinically relevant considerations of using statins in this population.

## Methods

The efficacy of statin therapy for primary prevention of CVD in the elderly has been evaluated in the subanalyses of randomized controlled trials as well as different meta-analyses. Relevant clinical trials were identified through a search of MEDLINE (1966-January 2013) using the terms HMG-CoA reductase inhibitor, statin therapy, primary prevention, elderly, and geriatrics. Literature searches were limited to clinical trials and meta-analyses published in the English language and clinical trials in humans. Bibliographies of selected articles were examined to identify additional clinical trials. Only trials and their subanalyses evaluating the use of statin therapy versus placebo in primary prevention patients that used primary endpoints of hard CHD (i.e., CV death, myocardial infarction, stroke) were included in this review.

## Results

### Clinical Trials Evaluating Primary-Prevention Statin Therapy

Trials that only evaluated primary prevention of CV events with statin therapy are shown in Table 1. These trials studied different statins and included patients with various ages. However, all included subgroup analyses of elderly patients categorized as 60, 65, or 70 years of age and older.

The Primary Prevention of Acute Coronary Events with Lovastatin in Men and Women with Average Cholesterol Levels (AFCAPS/TexCAPS) was a randomized, double-blind, placebo-controlled trial comparing lovastatin 20 mg or 40 mg to placebo for the prevention of the first acute major coronary event.[7] Patients enrolled were between 45 and 73 years of age for men and between 55 and 73 years of age for postmenopausal women; patients had no prior history of atherosclerotic CV disease. Baseline characteristics were similar between the placebo and lovastatin groups. Twelve percent of the patients in the placebo group were current smokers, compared with 13% in the lovastatin group; 16% and 15%, respectively, had a family history of premature CHD; and 22% in both groups had a history of hypertension.[7] Lipid panels had to meet the following criteria: total cholesterol (TC) 180 mg/dL to

**Table 1. Subgroup Analyses in Elderly Patients from Clinical Trials Evaluating Statins for Primary Prevention**

| Study | Statin Dose | A Statin Intensity as Categorized by the 2103 ACC/AHA Blood Cholesterol Guidelines | Total Number of Subjects | Primary Outcome and Benefit (benefit in the elderly subset for each study) | Study Duration |
|---|---|---|---|---|---|
| AFCAPS/ TexCAPS[7] | Lovastatin 20 mg-40 mg | Low-moderate | 6,605 (21% > 65 years) | • First acute major coronary event; 37% lower with lovastatin (116 vs183 first events; $P < 0.001$) | Mean 5.2 years |
| ASCOT-LLA[8] | Atorvastatin 10 mg | Moderate | 10,305 (63.7% > 60 years) | • Fatal CHD and nonfatal MI; 36% lower with atorvastatin (1.9% vs. 3%; $P = 0.0005$)<br>• (In pts > 60 years, 36% lower with atorvastatin [$P = 0.0027$]) | Median 3.3 years |
| MEGA[9,10] | Pravastatin 10 mg-20 mg | Low | 7,832 (% not listed)* | • First occurrence of CHD; 33% lower with pravastatin (3.3% vs. 5%; $P = 0.01$)<br>• (Benefit seen in pts > 60 years and < 60 years) | Mean 5.3 years |
| CARDS[11,12] and the sub-analysis | Atorvastatin 10 mg | Moderate | 2,838 (61.7% > 60 years; 12% > 70 years) | • First acute coronary heart disease event, coronary revascularization procedure, or stroke; 37% lower with atorvastatin (5.8% vs. 9%; $P < 0.001$)<br>• (38% reduction in pts > 65 years [$P = 0.017$]) | Median 3.9 years |
| JUPITER and secondary analysis of JUPITER[13,14] | Rosuvastatin 20 mg | High | 17,802 (32% > 70 years) | • First occurrence of major cardiovascular death; 44% lower with rosuvastatin<br>• (39% lower ($P < 0.001$) in pts 70-97 years) | Median 1.9 years (maximum 5 years) |

* The percentage of patients > 60 years of age was not included in the published MEGA trial. The baseline characteristics published prior to the study publication indicated a total of 8,009 patients enrolled, of which 23% were ≥ 65 years of age. Some patients were not included in the results of the study, although it is not clear the specifics regarding these patients or their age.[9]

**Abbreviations:** > = Older than, ≥ = Older than or equal to, < = Younger than, AFCAPS/TexCAPS = Primary Prevention of Acute Coronary Events with Lovastatin in Men and Women with Average Cholesterol Levels, ASCOT-LLA = Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm, CARDS = Primary Prevention of Cardiovascular Disease with Atorvastatin in Type 2 Diabetes in the Collaborative Atorvastatin Diabetes Study, CHD = Coronary heart disease, JUPITER = Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin Trial, MEGA = Primary Prevention of Cardiovascular Disease with Pravastatin in Japan, MI = Myocardial infarction, pts = Patients.

**Source:** References 7-14.

264 mg/dL, low-density lipoprotein cholesterol (LDL-C) 130-190 mg/dL, high-density lipoprotein cholesterol (HDL-C) ≤ 45 mg/dL for men and ≤ 47 mg/dL for women, and triglycerides ≤ 400 mg/dL. A total of 6,605 patients were included. The study was stopped early for efficacy, with a mean follow-up period of 5.2 years. Although the baseline mean age was 58.2 years, 21% of the patients were older than 65 years of age.[7] A 37% relative risk (RR) reduction for the first major coronary event (fatal or nonfatal myocardial infarction [MI], unstable angina, or sudden cardiac death) was seen in the lovastatin group compared with the placebo group (RR = 0.63, 95% confidence interval [CI] 0.50-0.79; $P < 0.001$).[7] Differences between the lovastatin group and the placebo group were apparent after one year. There was no significant treatment benefit between the subgroups, which included patients older and younger than the median age.[7] The benefit with lovastatin compared with placebo was seen in the patients who were older than the median age, older than 57 years of age for men, and older than 62 years of age for women (78 in the lovastatin group vs. 112 in the placebo group).[7] This study was limited to 21% of the patients being older than age 65.

In the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA), 10,305 patients were randomly assigned to atorvastatin 10 mg versus placebo.[8] The primary objective of this study was to assess and compare the long-term effects on the combined endpoint of non-fatal MI and fatal CHD. Patients were between 40 and 79 years of age, with a mean age of 63, and were required to have at least three other CV risk factors and a TC level 251 mg/dL or lower. In the atorvastatin group, 63.6% of the patients were older than 60 years of age, and in the placebo group, 63.9% were.[8] A total of 10,305 patients were included, and like AFCAPS/TexCAPS, this study was also stopped early with a median follow-up of 3.3 years. The early termination was because of a significant reduction in the primary endpoint of CHD event in the treatment group. The primary endpoint was lower in the atorvastatin group compared with the placebo group by 36% (hazard ratio [HR] = 0.64, 95% CI 0.50-0.83; $P = 0.0005$).[8] The benefit of atorvastatin on the primary endpoint was not significantly different in any prespecified subgroup, which included patients older than 60 years of age. A subgroup analysis of patients older than 60 years of age (total 6,570 patients) showed a significant benefit in reducing the primary endpoint in the atorvastatin group compared with placebo (HR = 0.64, 95% CI 0.47-0.86; $P = 0.0027$).[8] A limitation is this study divided the subgroup population at age 60, which is younger than some of the other trials in this review.

The primary prevention of CV disease with pravastatin in Japan (MEGA Study) assessed the effect of statin therapy and CHD in the Japanese population.[9,10] Men and postmenopausal women 40 to 70 years of age with a body weight ≥ 40 kg and TC between 220 and 270 mg/dL were included in this study. A total of 7,832 Japanese patients without CHD were analyzed for a mean follow-up of 5.3 years.[9] The primary composite endpoint was first occurrence of CHD, and patients were randomized to diet or diet plus pravastatin.[9] Pravastatin was initiated at 10 mg and was adjusted to 20 mg at follow-up visit. If TC remained elevated, the patients in either group could then be switched to other aggressive treatments, including statin therapy. Diet plus pravastatin group resulted in a 33% lower occurrence of CHD (HR = 0.67, 95% CI 0.49-0.91; $P = 0.01$), compared with the diet group.[9] In the subgroup analysis age was further analyzed and divided, younger than 60 and 60 years of age or older.[9] No difference in the benefit of pravastatin was seen between the two age groups for the first occurrence of CHD.[9] This study used a very low dose of pravastatin in a very specific population, which limits the ability to extrapolate the specific results to other populations. In addition, only about 23% of the patients initially included in the study were older than 65 years of age.

The primary prevention of CV disease with atorvastatin in type 2 diabetes mellitus (T2DM) in the Collaborative Atorvastatin Diabetes Study (CARDS) evaluated men and women 40 to 75 years of age with T2DM, but no history of CHD (MI, angina, coronary vascular surgery, cerebrovascular accident, or severe peripheral vascular disease).[11] These patients also had to have at least one or more risk factors including hypertension, retinopathy, microalbuminuria, macroalbuminuria,

or currently smoking. Patients were included if LDL-C was ≤ 160 mg/dL and triglycerides ≤ 600 mg/dL. The primary endpoint assessed was the first acute CHD event, coronary revascularization procedures, or stroke. Patients were randomized to either atorvastatin 10 mg daily or placebo.[11] If lipid-lowering therapy was indicated during the study, the investigator could prescribe additional therapy while the study drug was continued. A total of 2,838 patients were randomized in this study, with a median follow-up of 3.9 years.[11] At baseline, 23% in the placebo group and 22% in the atorvastatin group were current smokers, and 84% in both groups had hypertension. The mean age for both groups was 62 years, and more than one third of the patients were 65 years of age or older. In the atorvastatin and placebo group, 62% and 61%, respectively, were 60 years of age or older, and in both groups 12% of the patients were older than 70 years of age. The atorvastatin group resulted in a 37% reduction in the primary endpoint (HR = 0.63, 95% CI 0.48-0.83; $P = 0.001$) when compared with placebo group.[11] A *post hoc* analysis compared patients 65 to 75 years of age with the younger patients in the CARDS.[12] CARDS patients who were 65 years of age or older had a longer duration of diabetes and a higher systolic blood pressure, although had a lower HbA1C, diastolic blood pressure, body mass index, triglyceride concentration, and prevalence of cigarette smoking, all of which were significant differences.[12] Similar to the CARDS outcomes, there was a significant reduction in first CHD occurrence in the atorvastatin group with the two age groups; 38% in the group 65 years of age and older ($P = 0.017$) and 37% in the group younger than 65 years of age ($P = 0.019$).[12] A limitation to CARDS is that only 12% of patients were older than 70 years of age.

Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) looked at healthy men 50 years of age and older and women 60 years of age and older with LDL < 130 mg/dL and high-sensitivity C-reactive protein levels ≥ 2.0 mg/dL.[13] Patients were eligible if they did not have a history of CV disease. The primary endpoint was to evaluate whether treatment would decrease the rate of first major CV events. Patients were randomized to rosuvastatin 20 mg vs. placebo. A total of 17,802 patients were enrolled in this study with a median age of 66 in each group.[13] Patients were followed for a median of 1.9 years (max follow-up was 5 years). Rosuvastatin resulted in a 44% reduction in a first major CV event compared with placebo (HR = 0.56, 95% CI 0.46-0.69; $P < 0.00001$).[13] In the subgroup analysis, there was no difference between the patients older than 65 and 65 years of age and younger ($P = 0.32$).[13] A secondary analysis of JUPITER evaluated the safety and efficacy of rosuvastatin in patients 70 years of age and older.[14] Of the 17,802 patients enrolled in JUPITER, 5,695 were 70 years of age or older.[14] The median age in the older group was 74 years and the younger group was 63 years. Reduction of the first major CV event was seen with rosuvastatin in both age groups, 39% in the 70 years of age and older group ($P < 0.001$) and 49% in the 50-69 years of age group ($P < 0.001$). The rate difference between the treatment group and the placebo group was greater in the patients 70 years of age and older compared with the 50-69 years of age group, 0.77 vs 0.52 events per 100 person years, respectively.[14]

### Clinical Trials Evaluating Mixed Primary and Secondary Prevention Statin Therapy

The Pravastatin in Elderly Individuals at Risk of Vascular Disease (PROSPER) trial evaluated the benefits of pravastatin use in an elderly cohort of men and women who either had CV disease, or were at high risk.[15] More than 5,800 patients between 70 and 82 years of age were randomly assigned to pravastatin 40 mg daily or placebo with a mean follow-up period of 3.2 years. Of the total patients randomized, 3,239 patients were considered primary prevention. These primary prevention patients were considered high risk of vascular disease because of smoking, hypertension, or diabetes.[15] In the primary-prevention subgroup, 25% of the women and 45% of the men were current smokers, 80% of the women and 59% of the men had a history of hypertension, and 11% of the women and 15% of the men had a history of diabetes.[16] The primary outcome included the combined endpoint of definite or suspected death from CHD, nonfatal MI, and fatal or nonfatal stroke.[15] Overall, there was a 15% reduction in the

primary outcome with the pravastatin group (HR = 0.85, 95% CI 0.74-0.97; $P = 0.014$).[15] The predefined subgroup analysis for primary-prevention patients showed that pravastatin reduced the incidence of the primary endpoint by 6% (HR = 0.94, 95% CI 0.77-1.15).[15] The primary outcome was decreased in this subgroup for patients on statin therapy, although this was not significant. This suggests that pravastatin is beneficial for patients with existing vascular disease, but not beneficial for those without existing disease. However, this trial was not powered to make comparisons between the primary and secondary prevention groups. The authors further tested for heterogeneity and concluded there was no significant difference found between the primary and secondary prevention subgroup population with regards to the primary endpoint ($P = 0.19$).[15]

## Discussion

Several primary prevention trials have included patients 60 years of age and older, but none have specifically looked at very elderly patients 80 years of age and older. The PROSPER trial had the oldest cohort of patients, but this trial included both primary- and secondary-prevention patients, making it difficult to assess the benefit of primary-prevention statin therapy in the oldest patients. The JUPITER trial also had an older subgroup of patients, 70-97 years of age, although this only accounted for about 32% of the patients in the study. This paper is timely considering recommendations from the 2013 ACC/AHA Blood Cholesterol Guidelines.[17] These new guidelines provide minimal discussion for primary-prevention patients older than 75 years of age because of the absence of specific randomized controlled trials evaluating this specific population. However, clinicians need guidance regarding treatment of this challenging and increasing portion of the population. This paper evaluates available evidence for these patients, provides clinical interpretation, and discusses other clinically relevant aspects that need to be evaluated when considering statin therapy in elderly primary-prevention patients.

Statin therapy has shown a trend toward a decrease in the first occurrence of CHD in multiple landmark primary-prevention studies in the elderly population. This benefit was seen in patients regardless of their baseline LDL and how close the LDL was to the previously recommended treatment goal of < 100 mg/dL prior to starting therapy. Statin therapy resulted in a decrease in primary outcome despite patient's baseline LDL being close to goal in the JUPITER and CARDS trials (LDL median 108 and mean 117 ± 27.1 mg/dL, respectively).[11,13] As these trials show, patients benefit from statin therapy despite LDL levels, especially the higher-risk patients with risk factors for CVD. Benefits with statin therapy in the reduction of the primary outcomes were also seen in a relatively short amount of time, as these study durations were between roughly three and five years. The AFCAPS/TexCAPS study reported an apparent difference between the treatment and placebo groups after one year among the entire population.[7]

These studies are limited by the fact that the populations included had a wide age range. The age cutoff when referring to the elderly patient varied and most had a maximum age for inclusion. Many of the trials' maximum age for inclusion were 70 years, although the JUPITER trial enrolled 5,695 patients older than 70 years of age. Despite this difference, benefit was seen in these studies in the patients classified as elderly given the specific age cutoff.

Each of the clinical trials identified did not exclusively include an elderly population. They do not directly address the question of whether statin therapy reduces the risk of first major CV events in the elderly. However, meta-analyses have estimated the benefits of statin therapy in the elderly population. A 2009 meta-analysis of 10 primary prevention clinical trials, including 70,388 patients, demonstrated significant reductions in CV events (mortality, major coronary events, major cerebrovascular events) among patients younger than 65 years of age, but not among those older than 65 years of age.[18] However, there was no significant heterogeneity between these two subgroups, implying the same clinical benefits in the older and younger subgroups, but also suggesting that there was a lack of power among the older than 65 years of age group. This meta-analysis also included data from studies that did not meet our criteria because of including a

majority of patients with a history of CV events or lack of a true placebo group.[19-22]

## Clinical Considerations When Using Statins for Primary Prevention in the Elderly

According to the Food and Drug Administration (FDA) package inserts, specific dose adjustments are not necessary with the different statins based on a patient's age alone (Table 2). Most of the package inserts state that there are no overall differences in the safety or effectiveness between the older patients and younger patients.[23-29] However, some of the package inserts recommend using statin therapy with caution in the elderly since advanced age is a predisposing factor for myopathy.[23,24,26-28]

Other important factors to consider when choosing a statin are cost, drug-drug interactions, and adverse effects. Currently all but two statins are available as generic products (pitavastatin and rosuvastatin). Drug-drug interactions are also a concern since many elderly patients are on multiple medications. For patients treated with statin therapy, 2013 ACC/AHA Blood Cholesterol Guidelines recommend caution in individuals older than 75 years of age. It also recommends caution and to assess drug interactions in individuals who are taking concomitant medications that alter drug metabolism, taking multiple drugs, or taking drugs for conditions that require complex medication regimens.[17] Pravastatin is not extensively metabolized through the cytochrome P450 pathway, which is beneficial for patients on multiple medications to decrease the risk of a drug interaction with the statin therapy.[26] All the other statins are metabolized through the cytochrome P450 pathway to a greater extent than pravastatin.[23-25,27-29] In addition to cost and drug-drug interactions, the potential for developing adverse effects should be evaluated in this patient population. In the *post hoc* analysis for the CARDS trial and the secondary analysis for the JUPITER trial, researchers did not find a significant difference between statin and placebo with regard to myalgias in the older population.[12,14] The 2013 ACC/AHA Blood Cholesterol Guidelines indicate that patients aged older than 75 years may be at higher risk for developing adverse effects with statins, and clinical judgment should be used when selecting the appropriate dose of statin therapy.[17] Revisions to the 2012 FDA product label for statins includes that new onset diabetes is associated with statin use.[30] The association between statin use and developing diabetes is considered small and should not overshadow overall benefits.[31] However, the elderly population may be at a higher risk for developing diabetes so this is a relevant consideration. According to the 2013 ACC/AHA Blood Cholesterol Guidelines, individuals receiving statin therapy should be evaluated for new-onset diabetes mellitus according to the current diabetes screening guidelines.[17,32] The revised 2012 FDA product label for statins also included information regarding the potential for nonserious, reversible cognitive side effects. It concluded that "observational studies and clinical trials did not suggest that cognitive changes associated with statin use are common or lead to clinically significant cognitive decline."[30] The cholesterol guidelines recommend patients on statins who present with confusion or memory impairment should be evaluated for nonstatin causes in addition to the possibility of adverse effects associated with statin drug therapy.[17]

When deciding whether or not statin therapy should be initiated, the risk vs. benefit needs to be evaluated. The benefit is a reasonable likelihood of reduction in CV morbidity and mortality, whereas the risk is the potential for increased cost, pill burden, adverse effects, and drug interactions. One study evaluated long-term use of statin therapy and found that patients 75 years of age and older had a 19% greater odds of poor long-term adherence ($P < 0.001$), patients with the greatest number of other prescribed medications resulted in decreased adherence, and patients with CHD were less likely to have suboptimal adherence compared with patients without CHD.[33] The two statins we would recommend in the elderly patient population would be either pravastatin or atorvastatin. Both are available as generics, which will help with cost for the patient. Pravastatin would be the preferred statin for most patients on multiple medications because of less risk of cytochrome P450 drug interactions. It has also been studied in the oldest cohort and has been shown

**Table 2. Summary of FDA Product-Label Dosing Recommendations in Geriatric Patients**

| Statin | PK Changes | Recommendation |
|---|---|---|
| **Fluvastatin** | • Plasma levels are not significantly changed | • No dose adjustment for geriatric patients |
| **Lovastatin** | • Mean plasma level ~45% higher in the elderly patients (70-78 years of age) compared with patients between 18-30 years of age | • No dose adjustment based on age-related PK differences |
| **Pravastatin** | • Mean AUC 25%-50% higher in the elderly patients than in the healthy young patients<br>• Mean $C_{max}$, $T_{max}$, and $t_{½}$ were similar | • No dose adjustment |
| **Atorvastatin** | • Plasma concentrations are higher: $C_{max}$ 40% and AUC 30% in healthy elderly patients (65 years of age and older) | • No dose adjustment recommendation<br>• Greater sensitivity of some older adults cannot be ruled out |
| **Rosuvastatin** | • No difference in plasma concentrations between nonelderly and elderly patients (65 years of age and older) | • No dose adjustment recommendation<br>• Greater sensitivity of some older adults cannot be ruled out |
| **Simvastatin** | • Mean plasma level ~45% higher in elderly patients (70-78 years of age) compared with patients 18-30 years of age | • No dose adjustment recommendation<br>• Greater sensitivity of some older adults cannot be ruled out |
| **Pitavastatin** | • Plasma concentrations are higher: $C_{max}$ 10% and AUC 30% in the elderly patients (65 years of age and older) compared with healthy young patients | • No dose adjustment recommendation<br>• Greater sensitivity of some older adults cannot be ruled out |

**Abbreviations:** AUC = Area under the curve, $C_{max}$ = Maximum concentration, FDA = Food and Drug Administration, PK = Pharmacokinetics, $t_{1/2}$ = Half-life, $T_{max}$ = Time at maximum concentration.

**Source:** References 23-29.

to be well-tolerated in this study. Atorvastatin would be preferred in patients with renal impairment since no adjustments are needed in CKD stages 1-5, although pravastatin would still be an appropriate option with a dose adjustment for patients with CKD stages 4-5 (Table 3).[34]

A patient's life expectancy is important when considering whether or not to start statin therapy in an elderly patient. For elderly patients without a diagnosis of a terminal illness (cancer, Alzheimer's disease, failure to thrive, etc.) and life expectancy is at least five years, the benefit of statin therapy should outweigh the risk for patients with CV risk equivalents or patients with multiple CV risk factors. The primary prevention clinical trials evaluating statin therapy typically extended to five years or less, thus making a five-year benchmark defendable. A meta-analysis that evaluated 27 randomized trials showed that reduction in LDL-C with standard statin therapy reduced the five-year incidence of major coronary events, coronary revascularizations, and ischemic strokes by about one fifth per 39 mg/dL (1.0 mmol/L) reduction in LDL-C.[35] Importantly, the proportional reductions in major vascular events per 1.0 mmol/L LDL-C reduction were similar across patients with different levels of risk, even after further stratification by age, further supporting that elderly primary-prevention patients receive benefit from statin therapy. Some clinicians may choose shorter life expectancies based on clinical judgment. If pill burden is a concern for the patient or patient's family, discussions with the patient or family member

**Table 3. Summary of FDA Product-Label Dosing Recommendations for Renal Impairment**

| Statin | Moderate renal impairment not on HD | Severe renal impairment not on HD |
|---|---|---|
| **Fluvastatin** | • No specific adjustment recommendation | • Caution for doses > 40 mg daily (not studied) |
| **Lovastatin** | • No specific adjustment recommendation | • Clcr < 30 mL/min, caution for doses > 20 mg daily |
| **Pravastatin** | • No specific adjustment recommendation | • Starting dose of 10 mg daily |
| **Atorvastatin** | • No specific adjustment recommendation | • No dose adjustment needed |
| **Rosuvastatin** | • No adjustment needed for Clcr ≥ 30 mL/min/1.73 $m^2$ | • Clcr < 30 mL/min/1.73 $m^2$ start 5 mg daily and do not exceed 10 mg daily |
| **Simvastatin** | • No specific adjustment recommendation | • Start at 5 mg daily and monitor closely |
| **Pitavastatin** | • Starting dose 1 mg daily and maximum dose 2 mg daily for Clcr 30-59 mL/min/1.73 $m^2$ | • Starting dose 1 mg daily and maximum dose 2 mg daily for Clcr 15-29 mL/min/1.73 $m^2$ |

**Abbreviations:** Clcr = Creatinine clearance, FDA = Food and Drug Administration, HD = Hemodialysis.
**Source:** References 23-29.

regarding benefit should take place to determine ultimate goals for the patient. This discussion is also important to help improve adherence as one study found that the understanding of the necessity of treatment affected adherence in a positive manner.[36] The 2013 ACC/AHA Blood Cholesterol Guidelines state that evidence supports the continuation of statin therapy past 75 years of age in patients who are already prescribed these medications and tolerating them.[17] For primary prevention patients who are older than 75 years of age, the decision to start statin therapy is less clear. They similarly recommend evaluating comorbidities, adverse effects, drug-to-drug interactions, patient preference, and care priorities when considering statin therapy.

## Conclusion

Age alone is a positive, nonmodifiable risk factor that places elderly patients at high risk for CVD. Based on evidence from clinical trials extending up to five years, elderly patients with a life expectancy of five years or longer should benefit from statin therapy as primary prevention to decrease the risk of a CV event. Statin therapy should be considered, in the absence of a contraindication, in this patient population given the evidence of use in primary prevention. Although there is benefit with statin use, clinical judgment regarding benefit versus risk should always be evaluated to determine appropriateness for the individual patient. When statin therapy is initiated, using pravastatin or atorvastatin would be a relatively uncomplicated, affordable, and safe overall treatment approach unless other patient-specific factors would preclude their use.

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