Statins for primary cardiovascular prevention in the elderly

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Abstract

The elderly population is increasing worldwide, with subjects > 65 years of age constituting the fastest-growing age group. Furthermore, the elderly face the greatest risk and burden of cardiovascular disease mortality and morbidity. Although elderly patients, particularly those older > 75, have not been well represented in randomized clinical trials evaluating lipid-lowering therapy, the available evidence supporting the use of statin therapy in primary prevention in older individuals is derived mainly from subgroup analyses and post-hoc data. On the other hand, elderly patients often have multiple co-morbidities that require a high number of concurrent medications; this may increase the risk for drug-drug interactions, thereby reducing the potential benefits of statin therapy. The aim of this review was to present the relevant literature regarding statin use in the elderly for their primary cardiovascular disease, with the associated risks and benefits of treatment.

Keywords: Cardiovascular disease; Dyslipidaemia; Elderly; Primary prevention; Statins

1 Introduction

The incidence of cardiovascular disease (CVD) in all its clinical forms, such as coronary, cerebrovascular and peripheral vascular disease, rises sharply with age, as does the prevalence of the main cardiovascular risk factors including obesity, hypertension, dyslipidemia and type 2 diabetes mellitus. It is estimated that over 80% of men and women 75 years of age or older have clinically-manifest CVD,[1] and that the elderly have the greatest risk and burden of CVD morbidity and mortality.[2,3] Since the cardiovascular consequences are much more serious in older than younger patients, for both death and long-term disability and owing to the population ageing, cardiovascular prevention in the elderly is gaining increasing importance, and influencing health policy worldwide.

On the other hand, the elderly population is physiologically heterogeneous, ranging from incapacitated nursing home residents to marathon runners. This heterogeneity must be taken into account when preventive therapies for chronic diseases are considered.[4] The main differential characteristics between elderly and younger populations are as follows: (1) older people differ more among themselves than younger people in many ways; (2) shorter life expectancy than younger people; (3) chronological age does not correspond to vascular age; (4) substantial variation in physiological age among individuals attributable to frailty, co-morbidities and cognitive decline; (5) risk factors for cardiovascular disease do not predict outcomes as well as they do for younger individuals; (6) competing causes of mortality mask the potential benefits of some therapies; (7) frailty may exacerbate adverse effects of therapy; (8) polypharmacy may result in increased risk for drug interactions; and (9) adverse effects of therapies, especially pharmacological, are more severe in older individuals since they predispose to reduced physical activity, sarcopenia, and falls. In this respect, older adults may be at increased risk for adverse outcomes associated with the diagnostic and therapeutic interventions required for disease management due at least in part to age-associated non-cardiac vulnerabilities, such as cognitive impairment and frailty. Therefore, the applicability to older adults of intervention strategies for cardiovascular prevention based on evidence derived largely from younger and healthier populations is uncertain and requires careful scrutiny.

Preventing CVD with statins in the elderly is even more important given the considerable underuse of statin treatment in this specific population although they have, on average, the highest CVD risk.[5-8] For example, in the secon-
dary prevention setting, the probability of statins being prescribed declined with increased cardiovascular risk in patients between the ages of 66 and 74; the likelihood of receiving a statin fell by 6.4% for each yearly increase in age and each 1% increase in predicted 3-year mortality risk.\[^5\] In 2013, the American Heart Association issued a scientific statement on secondary prevention of atherosclerotic CVD in older adults.\[^9\] Obviously, there remain challenges and many barriers to implementing the CVD prevention guidelines, even when dyslipidaemia treatment is concerned.\[^10\] Some of the barriers to more effective management of dyslipidaemia, particularly concerning lipid-lowering drug therapy, are also financial constraints, especially in low and middle income European countries as demonstrated by the data on differences in achieving lipid goal values in different countries.\[^11\] The question of primary CVD prevention with statins in the elderly is complex and only subgroup analyses from randomized studies are available.\[^12\] Since the elderly without CVD and their caregivers face a high-stake decision on statin treatment, we provide an overview of the role of statin therapy in this specific population.

## 2 Lipids in the elderly

Age and sex are physiological factors with a strong influence on lipid profile. Sex differences in lipoprotein levels are further affected by age. In the Framingham Heart Study,\[^13\] low-density lipoprotein (LDL) cholesterol concentrations rose progressively with age, until 60 in men and 70 in women. In the Framingham Offspring Study,\[^14\] apolipoprotein B (apo B) levels also increased with age in both men and women, and more markedly in the latter after menopause. Interestingly, LDL cholesterol levels reach a plateau in men between the ages of 50 and 60, and in women between 60 and 70.\[^15\] These plasma changes in LDL cholesterol are due at least in part to increased liver synthesis of very-low-density lipoproteins (VLDL) and their conversion to LDL together with a decline in VLDL and LDL catabolism due to the reduced expression of LDL receptors.\[^16,17\] Concerning LDL size, age per se is associated with raised concentrations of atherogenic LDL particles rather than a reduction in particle diameter.\[^18\]

In addition, high-density lipoprotein (HDL) cholesterol levels decrease in males during adolescence and early adulthood; however, in the elderly, they are unchanged or slightly increased. In contrast, HDL cholesterol concentrations remain stable in women throughout their lifetime; however, menopause often causes a small drop in their HDL cholesterol level.\[^19\] Furthermore, triglyceride concentrations increase progressively in men, reaching peak values between the ages of 40 and 50, declining slightly thereafter. In women, triglyceride levels increase throughout life and are higher in those on oestrogen therapy.\[^15\]

In general, higher total and LDL cholesterol levels are associated with increased risk of CVD in middle-aged and early old-aged patients. This association is attenuated in old age but can be reversed.\[^20-23\] Cholesterol levels may decline in old age owing to frailty or as a result of co-morbid conditions such as cancer.\[^24\] An apparent rise in the mortality rate associated with low cholesterol levels in older people may be related to several factors, such as changes in cholesterol metabolism, malnutrition, frailty and chronic diseases, which simultaneously lower cholesterol concentrations and raise the mortality risk.\[^25,26\] After adjustment for chronic disease states, the positive association between serum cholesterol levels and increased risk of death from coronary heart disease in men and women with a mean age of 79.2 years over a 5-year follow-up was restored.\[^27\] Although the relative differences in cholesterol level-related risks diminish with age, the absolute effects of cholesterol levels on cardiovascular mortality rates are much greater in the elderly.

On the other hand, there has been substantial debate regarding statin use for primary prevention in women.\[^28-31\] However, since these studies have certain limitations, their conclusions should be viewed with caution.

## 3 Statin therapy

Meta-analyses from randomized clinical trials of statin therapy over the past two decades showed consistent reductions in cardiovascular events in both primary and secondary prevention populations, regardless of age.\[^29,32\] Further, one Cochrane review found statin therapy for those in primary prevention, over a wide age range, to be safe and effective.\[^33\]

Available evidence supporting the use of statin therapy in primary prevention in older individuals derives mainly from sub-group analyses and post-hoc data (Table 1). Earlier primary prevention trials with statins did not usually focus on the elderly. In the West of Scotland Coronary Prevention Study (WOSCOPS),\[^34\] the first primary prevention of coronary heart disease with pravastatin in men with hypercholesterolemia, no patients ≥ 65 years were included. In the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS),\[^35\] 22% of subjects were over 65 years of age and a subgroup analysis based on sex-stratified median age (> 57 years in men and 62 years in women) showed no difference in CVD risk reduction with lovastatin therapy. In the Lipid-Lowering Trial component

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Table 1. Clinical intervention studies in primary prevention of cardiovascular disease in elderly patients.

| Study                      | N     | Age range (yr) | Statin (dose)          | Mean follow-up (yr) | Main results                                                                 | NNT |
|----------------------------|-------|----------------|------------------------|---------------------|------------------------------------------------------------------------------|-----|
| AFCAPS/TexCAPS[35]         | 6,605 | 45–73          | Lovastatin (20–40 mg)  | 5.2                 | 37% reduction in non-fatal myocardial infarction, unstable angina and sudden death. | 49  |
| ALLHAT-LLT[36]             | 10,335| ≥ 55           | Pravastatin (40 mg)    | 4.8                 | No significant reductions in mortality, coronary heart disease or stroke vs. usual care (4.8 years). | NS  |
| ASCOT-LLA[37]              | 10,305| 40–75          | Atorvastatin (10 mg)   | 3.3                 | 36% reduction in non-fatal myocardial infarction and coronary death.           | 164 |
| CARDS[38]                  | 2,838 | 40–75          | Atorvastatin (10 mg)   | 3.9                 | 37% reduction in fatal and non-fatal myocardial infarction, coronary death, unstable angina, and revascularization. | 42  |
| MEGA[39]                   | 7,832 | 40–70          | Pravastatin (10–20 mg) | 5.0                 | 31% reduction in coronary events.                                              | 150 |
| CHS[40]                    | 1,914 | > 65           | Statins                | 7.3                 | 44% reduction in all-cause mortality.                                          | 46  |
| PROSPER[41]                | 5,804 | 70–82          | Pravastatin (40 mg)    | 3.2                 | 15% reduction in coronary death, non-fatal myocardial infarction and stroke.   | 59  |
| JUPITER[42]                | 17,802| 60–71          | Rosuvastatin (20 mg)   | 1.9                 | 44% reduction in non-fatal myocardial infarction, cerebrovascular event, revascularization, coronary death and unstable angina. | 95  |

NNT: number needed to treat; NS: non-significance.

of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT)[36] pravastatin 40 mg did not significantly reduce either all-cause mortality or coronary heart disease compared with usual care in older participants with well-controlled hypertension and moderately elevated LDL cholesterol. No significant heterogeneity was observed when these results were assessed in pre-specified subgroups by age (≥ 65 vs. < 65 years).

In the elderly subgroup of 6,570 patients > 60 years of age in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA)[37] the relative risk reduction in coronary events was similar to those < 60 years (34% vs. 36%, respectively). The efficacy of statin therapy in elderly patients with diabetes was evaluated in a subgroup analysis from the Collaborative Atorvastatin Diabetes Study (CARDS).[38] In 1,129 diabetic patients aged 65–75, treatment with atorvastatin 10 mg daily reduced the risk of first major coronary events by 38% compared to placebo.

Subgroup analysis of the Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA) study also revealed the benefit of pravastatin 10–20 mg daily, showing a 30–40% reduction in clinical events across multiple age ranges, including in patients > 65.[39] In the Cardiovascular Health Study,[40] a non-randomized clinical trial on primary prevention conducted in individuals > 65, the all-cause mortality rate decreased with statin treatment and the results were similar in the subgroup of subjects who were over 75 years of age.

The Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) was the first trial designed specifically to investigate the effects of pravastatin, 40 mg daily in the elderly aged 70–82 years; however, it was conducted in patients with pre-existing vascular disease or at a high risk of CVD, including stroke.[41] Although this was not a primary prevention trial, no benefit in terms of reducing total mortality was observed in subjects without CVD.

A sub-study of the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) analyzed the effects of rosuvastatin or placebo in an asymptomatic population of 5,695 subjects over the age of 70.[42] The absolute risk reduction in the incidence of non-fatal myocardial infarction, non-fatal stroke, hospitalization for unstable angina, arterial revascularization or CVD death was 48% greater in the elderly treated with a statin, and the number needed to treat (NNT) for four years to prevent one cardiovascular event was 24 compared with 36 in subjects aged 50–69 years. Furthermore, this trial also demonstrated a relatively short time to achieve this benefit.

Two meta-analyses of primary prevention trials with statins have been reported.[43,44] The first included more than 70,000 subjects found some benefits, particularly for all-cause mortality and major coronary and cerebrovascular events, in subjects over 65 years; however, they did not reach statistical significance.[43] The most recent meta-analysis pooled data from eight trials enrolling 24,674 subjects and demonstrated that statins significantly reduced the incidence of myocardial infarction by almost 40% and stroke by almost one quarter, but did not significantly prolong survival in the median 3.5-year follow-up.[44] Estimated NNT were 83 to prevent one cardiovascular event and 142
to prevent one stroke in people over the age of 65. A Cochrane Collaboration combined individual level data on older people enrolled in a larger number of primary prevention studies including those with up to 10% of participants with CVD. They estimated NNT of 196 to prevent one stroke, 56 to prevent any cardiovascular event, and 96 to prevent one death over five years. This is similar to the Cholesterol Treatment Trialists Collaborators analysis of individual data from 27 trials (average ages in the early 1960’s) of NNT of 167 to prevent one vascular event for people at a lower risk of cardiovascular events within 10 years compared to NNT of 67 for those at higher risk. At this point, it should be to stressed that the long-term value of preventive treatments in the elderly has always been somewhat uncertain, since it is difficult to know whether, and to what extent, preventive interventions preserve their impact. Thus, recommendations based only on preventive measures that extend life are misplaced in the elderly, in whom the prevention of morbidity is almost as important.

In December 2014, the Statins for Reducing Events in the Elderly (STAREE) study, a large five year randomized primary prevention clinical trial (n = 12,000) comparing atorvastatin (40 mg) with placebo in healthy people > 70 years of age was launched, with total mortality or institutionalization being the primary end-points.

4 Adverse effects

The use of statins in clinical practice has been associated with higher rates of side effects and intolerance than in clinical trials. The most frequent complaints are related to muscle. Cross-sectional studies in adults reported that 20% experienced musculoskeletal pain during statin use. Estimates of the incidence of myopathy vary widely and are unlikely to be determined from randomized trials, since many had a statin tolerance run-in phase or excluded patients with previous reports of statin intolerance.

A recent systematic review of five randomized, controlled trials and 11,132 patients on the efficacy and safety of intensive statin therapy in older patients with coronary heart disease showed that myopathy, rhabdomyolysis and creatine kinase levels > 10 times the upper normal limit occurred in very few cases, and only 13 cases were reported. In the Understanding Statin Use in America and Gaps in Patient Education survey of over ten thousand current and former statin users, muscle related side effects were reported by 29% of participants; 84% of patients were taking at least one additional medication that had potential interaction with their statin.

Adverse cognitive effects have been described as the second most common complaint of patients taking statins in the community. Reversible impaired cognition, or worsening of dementia, in older patients treated with statins have also been reported, and while the potential relationship between statins and cognitive impairment has been a subject of controversy, the US Food and Drug Administration (USFDA) issued a caveat against the prescribing of statins. Two recent systematic reviews evaluating the effects of statins on cognition have been reported: one found no evidence to suggest an effect of statins on dementia, cognitive function, or incidence of Alzheimer’s disease; in the other, in patients without baseline cognitive dysfunction, short-term data were mostly consistent with no adverse effect of statins on cognition, and long term data may support a beneficial role for statins in the prevention of dementia.

In recent years, it has been observed that the use of statins increases the risk of type 2 diabetes. In fact, in 2012 the European Medicines Agency (EMA) published guidelines related to an increased risk of diabetes associated with statin therapy. This effect is applicable to all members of the statin family (except pitavastatin), is dose-dependent and therefore, more pronounced with high-power statins and has a clear relationship with age; furthermore, this risk is increased in patients with pre-diabetes, or at high risk of developing diabetes. The European Society of Atherosclerosis recently established guidelines for the use of statins in patients at high risk of developing type 2 diabetes. The clinical significance of statin-related diabetes remains an unknown quantity in older patients who may not develop microvascular complications.

Other considerations include increases in liver transaminase levels, which usually resolve after dose reduction, or discontinuation of the drug, or may also normalize spontaneously. No association between statin use and the presence and severity of non-alcoholic fatty liver disease or liver-related mortality has been found. Data showing that the elderly are more prone to an increase in liver enzyme activity, or the risk of liver injury caused by statins than middle-aged individuals are lacking, and the review by the USFDA found serious liver injury with statins to be rare and unpredictable.

Concerning renal adverse effects, an observational study of more than two million statin users based on analysis of administrative databases concluded that high-potency statins were associated with an increased diagnostic rate of acute kidney injury, especially within the first 120 days post-statin initiation compared with low-potency statins. However, more recently, data from 149,882 patients years of follow-up from clinical trials failed to show any rise in re-
nal-related serious adverse events with statins compared with controls.\(^\text{[73]}\)

The development of cataracts was considered a side effect of statins in early studies. Although the US FDA removed this observation from labeling in 1991, cataracts have again been associated with statins in large cohort studies from England and Wales and the United States military health system.\(^\text{[74,75]}\) A recent meta-analysis showed a protective effect of statins against cataracts; however, younger age and longer statin therapy duration were associated with greater benefits, while no benefit was observed among older people.\(^\text{[76]}\) Thus, to settle the issue of the statin-cataract relationship, a randomized clinical trial should be conducted, or cataracts included as an end-point in epidemiological studies.

Finally, publication and outcome reporting biases pose a substantial threat to the validity of clinical research findings and thus, to informed decision making in health care. In this respect, it has been suggested that patient-level safety data are necessary to assess statin side effects and that published data and patient-level data can differ.\(^\text{[77]}\) Moreover, Catalá-López, et al.\(^\text{[78]}\) pointed to a significant sponsorship bias in the cost effectiveness of statins for cardiovascular prevention.

A further concern when considering statins for elderly subjects is the issue of drug interactions and the altered relationships involving drug metabolism and the ageing body. Two main predictors of drug-drug interactions are age and the severity and chronicity of disease. Significant pharmacodynamic changes that occur with ageing include a decline in gastrointestinal absorption, changes in drug volume distribution based on a fall in albumin levels, changes in total body water and lean body mass, increases in body fat percentage and, finally, drug metabolism dwindling with age. Furthermore, drug clearance decreases with age, resulting from a decline in the glomerular filtration rate.\(^\text{[79]}\)

The elderly with dyslipidemia will require different pharmacological therapies according to their associated co-morbidities. In this respect, it has been reported that 47% of patients \(> 75\) are on \(\geq 5\) drugs.\(^\text{[80]}\) On the other hand, a study of \(> 950,000\) patient records from two US databases showed that 83% of patients with dyslipidemia used a CYP3A4-metabolised statin and that, of these, 25%–30% also received a CYP3A4 inhibitor.\(^\text{[81]}\) This suggests that patients treated with statins have a particularly high risk of developing drug-drug interactions, some of which may lead to drug discontinuations owing to adverse events.

Thus, it is crucial in medical decision making in cardiovascular prevention involving elderly patients to establish a therapeutic partnership with good communication aimed at assessing how they feel about their treatment regimen. In person interviews conducted with 356 community-living elderly patients with a mean age of 76 years and predominantly female (75%) examined their willingness to take a medication (i.e., a statin) for the primary prevention of myocardial infarction. Their willingness to take any medication hinged on the risk of side effects rather than the potential benefit that could be derived from taking a medication. For this reason, many older patients are reluctant to start taking a new medication.\(^\text{[82]}\)

### 5 Conclusions

Although evidence has demonstrated that statins are beneficial to the elderly, shared decision making is very important in old age. In primary prevention, each patient’s characteristics predisposing to adverse effects, as well as quality of life, should be considered in the decision to start treatment, balancing the probable benefits with the potential risks. More studies, education and representation of the elderly population are required to establish cost-effective interventions and systematic approaches to adherence that would help reduce cardiovascular morbidity and mortality in this specific population.

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