

Statins in the elderly

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Learning objectives:

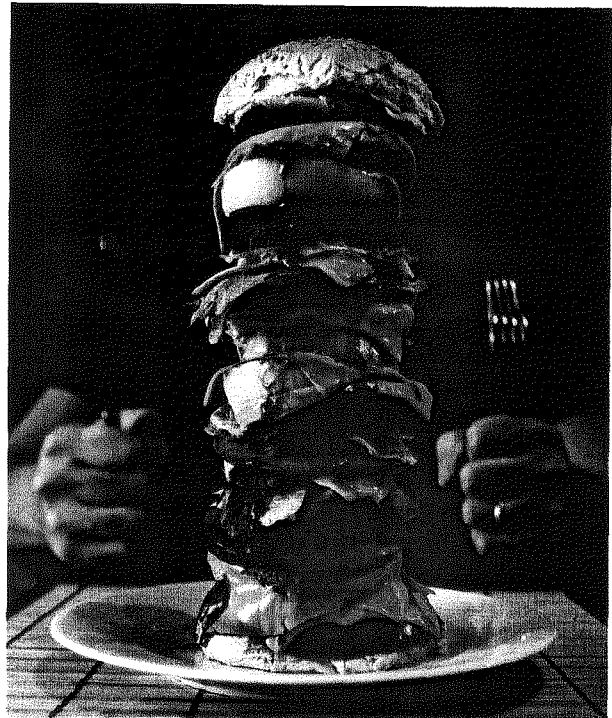
After reading this article, the reader should be able to:

- Discuss the use of statins for the primary and secondary prevention of coronary heart disease in the elderly;
- Consider the risk of adverse events related to the use of statins in the elderly; and
- Consider the potential benefits of statins, other than their effects in coronary heart disease.

Introduction

Coronary heart disease (CHD) is the leading cause of death among the elderly, with more than 80% of coronary deaths occurring in patients over the age of 65 years.¹ However, there is abundant evidence that older patients with CHD, or at high risk of CHD, are undertreated – possibly because of concerns regarding the increased likelihood of adverse events and drug interactions, or doubts regarding the cost-effectiveness of drug therapy in this population.² For example, in elderly patients with a recent myocardial infarction (MI), statin utilisation is only 40% to 60%.³⁻⁶ This is partly because evidence has not consistently shown that statins reduce mortality in the elderly.⁷⁻⁹ Given the high cost of therapy with statins (consuming approximately one-fifth of the total Pharmaceutical Benefits Scheme budget) and the obvious limit to society's health care resources, it is critical that the outcomes of lipid-lowering drug therapy are maximised.¹⁰

Elevated cholesterol levels remain a significant risk factor for CHD in the elderly, although coronary events are also known to occur in older adults who have none of the traditional cardiac risk factors, such as hyperlipidaemia, diabetes or hypertension.^{11,12} Ageing is accompanied by an increase in absolute risk of cardiovascular events as the frequency of CHD increases markedly with age.¹³ Whether this means that the elderly should be aggressively treated with lipid-lowering drug therapy or whether the elderly benefit as much as younger patients from pharmacological therapies directed at preventing coronary events has been long debated. The major problem has been the relative lack of research into reducing the risk of cardiovascular events in the elderly, so



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therapeutic decisions regarding the initiation of statin therapy are typically made on a case-by-case basis. This decision is dependent on the overall risk of cardiovascular events, particularly the presence or absence of established CHD, and the risk of adverse outcomes. This article will review the evidence for each of these considerations: statins for primary and secondary prevention of CHD in the elderly; and the risk of adverse events associated with statins in this population.

Statins for the primary prevention of CHD in the elderly

Partly due to the under-representation of elderly patients in randomised controlled trials (RCTs), there are no meta-analyses that specifically address the primary prevention of CHD in the elderly. The Cholesterol Treatment Trialists' Collaboration published a meta-analysis on the efficacy and safety of cholesterol-lowering treatment, and included a subgroup analysis of older adults.¹⁴ Over 90,000 patients were included in this analysis, with 16.6% of the 45,054 cardiovascular events in statin-treated groups occurring in those aged over 65 years, compared to 20.3% of 45,002 events in those over 65 years in the placebo group. The subgroup analysis of patients aged over 65 years (primary and secondary prevention), reported a 19% reduction in major cardiovascular events ($P < 0.01$). In those aged over 75 years, there was an 18% reduction in major cardiovascular events ($P < 0.01$). This analysis did not extract results specifically for the prevention of CHD in elderly people without a history of CHD.

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Continuing Professional Development

A number of trials have assessed the role of statins for the primary prevention of CHD (Table 1).^{9,15-19} An important issue when considering each of the RCTs, and its implications for clinical practice, is the number needed to treat (NNT) to prevent the incidence of one cardiovascular outcome over the course of the study (generally three to five years). ALLHAT-LLT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial)¹⁹ and ASCOT-LLA (Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm)¹⁸ were lipid studies conducted within clinical trials of hypertensive subjects. ALLHAT-LLT enrolled subjects who were over the age of 55 years, who were also enrolled in the blood pressure-lowering component of the study, the majority of whom had no prior history of CHD. However, many also had diabetes (35%). In this study, patients were randomised to pravastatin 40mg daily or usual care (rather than placebo). Statins were prescribed at the discretion of physicians in the usual care group, and by the end of the study, 26% of patients in the control group were receiving one. All-cause mortality did not differ between the groups, over a mean follow-up of almost five years, and there was also no difference between the groups in the rate of cardiovascular events overall, or among the elderly subgroup. In ASCOT-LLA, subjects had hypertension, without established hyperlipidaemia or substantially elevated low-density lipoprotein (LDL) levels. High-risk subjects were aged between 40 and 79 years without a known history of CHD, but multiple risk factors in addition to hypertension (excluding hyperlipidaemia). Patients were randomised to either atorvastatin 10mg daily or placebo. The trial was closed earlier than planned because of a significant reduction in the primary endpoint (fatal CHD and nonfatal MI) favouring atorvastatin (NNT = 94) in both the overall population and the elderly subgroup (> 60 years of

age). This result shifted primary prevention towards a focus on overall cardiac risk, rather than elevated lipid levels alone.

The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS)¹⁶ demonstrated that lovastatin 20-40mg daily, compared to placebo, reduced the risk of first coronary events in patients (including older individuals, aged > 65 years) with no known history of CHD, and with average total cholesterol and LDL-cholesterol, but below average high-density lipoprotein cholesterol. The incidence of major coronary events was reduced by 37% (NNT = 49) in the statin group. The Collaborative Atorvastatin Diabetes Study (CARDS)¹⁵ assessed statin use in older patients (mean age of 62 years) with type 2 diabetes. Enrolled patients had no history of CHD, but the majority (84%) had hypertension in addition to diabetes. Patients treated with atorvastatin 10mg daily (versus placebo) had a 35% risk reduction in major cardiovascular events (NNT = 52). Therefore, data from CARDS indicated that statins reduce the risk of first CHD event in patients with type 2 diabetes.

The Heart Protection Study (HPS)¹⁷ investigated statin treatment in individuals aged between 40 and 80 years with considerable 5-year CHD risk based on an individual review of risk factors. In this study, simvastatin 40mg daily achieved a 26% reduction in the incidence of fatal coronary event or nonfatal MI, regardless of age or the presence of prior CHD at randomisation compared to placebo (NNT = 32). This risk reduction also appeared to be independent of the pre-treatment cholesterol level.

The Pravastatin in the Elderly at Risk (PROSPER) study⁹ assessed the effects of pravastatin (40 mg/day) versus placebo in 2,804 men and 3,000 women, aged 70 to 82 years, who

Table 1: Summary of RCTs for the primary prevention of CHD with statins (modified from Ali, *et al.* 2007)²¹

| Study | Intervention compared to placebo unless otherwise indicated | Mean duration of follow-up (years) | Number of subjects | Mean age (years) | Number in elderly subgroup (%); age cutoff (years) | % at baseline with no history of vascular disease | Selected Outcome | RRR, % | ARR, % | NNT |
|----------------|---|------------------------------------|--------------------|------------------|--|---|---|--------|--------|-----|
| ALLHAT-LLT | Pravastatin 40mg (compared to usual care) | 4.8 | 10,355 | 66 | 55; ≥65 | 89 | Fatal CHD and nonfatal MI | 10.6 | 1.1 | 91 |
| ASCOT-LLA | Atorvastatin 10mg | 3.3 | 10,305 | 63 | 64; >60 | 86 | Fatal CHD and nonfatal MI | 36 | 1.1 | 94 |
| AFCAPS/TexCAPS | Lovastatin 20-40mg | 5.3 | 6,605 | 58 | 21; >65 | 97 | Fatal or nonfatal MI, unstable angina, sudden cardiac death | 37 | 2.0 | 49 |
| CARDS | Atorvastatin 10mg | 3.9 | 2,838 | 62 | 62; >60 | 96 | Acute coronary events | 35 | 1.9 | 52 |
| HPS | Simvastatin 40mg | 5.0 | 20,536 | NR | 28; >70 | 35 | Fatal CHD and nonfatal MI | 26 | 3.1 | 32 |
| PROSPER | Pravastatin 40mg | 3.2 | 5,804 | 75 | 100; >70 | 56 | Fatal CHD and nonfatal MI | 17.3 | 2.1 | 47 |

RRR = relative risk reduction; ARR = absolute risk reduction; NNT = Number Needed to Treat; CHD = coronary heart disease; MI = myocardial infarction

either had pre-existing vascular disease or were at significant risk for developing it because of smoking, hypertension, or diabetes. Pravastatin significantly reduced the incidence of the primary endpoint by 15%. Coronary death and nonfatal MI risk was also reduced by 17% (NNT = 47), and mortality from CHD fell by 24%. The risk for stroke, however, was unaffected. The investigators attributed the lack of an effect on strokes to the relatively short duration of the study. Recent publications suggest that stroke benefit from statins does not begin to appear until after three years of treatment.²⁰ CHD death and MI risk reduction in elderly patients by pravastatin in the PROSPER study was similar to the benefit of statins in middle-aged populations in other studies.

As a result of this body of research, primary prevention has moved beyond a focus on lipid lowering alone. There is no evidence that advanced age should preclude patients from receiving therapy or achieving benefits from risk reduction.²¹ The available evidence from the RCTs discussed suggests that the use of statins for the primary prevention of CHD in the elderly should focus on the individual's global risk (rather than cholesterol levels alone), and suggests a beneficial effect of statin treatment in those at high risk. It is worth noting that the studies that included more patients with a history of vascular disease (HPS¹⁷ and PROSPER⁹) resulted in lower numbers needed to treat than the other trials (which all involved greater than 85% patients without a history of vascular disease); this needs to be taken into account in their interpretation (see Table 1). However, CHD often occurs in the elderly in the absence of traditional risk factors (e.g. hyperlipidaemia, diabetes, hypertension and smoking).^{11,12} Studies are now also investigating the role of inflammation in the development of CHD and, in particular, the inflammatory marker, high-sensitivity C-reactive protein (hs-CRP).²² CRP is an acute phase reactant and is thought to be involved in the initiation and progression of atherosclerosis.²³ Consequently, it has been suggested that hs-CRP levels could be included after CHD risk assessment for primary prevention to improve risk stratification.^{22,24} The JUPITER (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin) study²⁵ recruited men aged over 55 years and women aged over 65 years with low LDL cholesterol levels, but elevated hs-CRP. This study was stopped prematurely

because patients treated with rosuvastatin 20mg had a significantly lower rate of CHD morbidity and mortality compared to patients receiving placebo.

Statins for the secondary prevention of CHD in the elderly

Recently, a meta-analysis was conducted to ascertain the effectiveness of statins in elderly patients with known CHD. Included in this meta-analysis were nine RCTs, which enrolled patients between the ages of 65 and 82 years with documented cardiac disease.²⁶ Compared to placebo, statin treatment resulted in a significantly reduced rate of all-cause mortality (22% risk reduction over 5 years, NNT = 28). Statin treatment also reduced CHD mortality by 30% (NNT = 34), nonfatal MI by 26% (NNT = 38), need for revascularisation by 30% (NNT = 24) and stroke by 25% (NNT = 58).²⁶ A key finding was that the magnitude of benefit was substantially larger than previously reported and increased with age, with a 50% reduction in mortality observed in those over the age of 80 years. Table 2 shows the expected benefits of statin therapy in the secondary prevention of CHD, based on the results of the meta-analysis and using a previously published survival model,²⁷ to demonstrate the practical implications of these results. According to the meta-analysis and the survival model, an 85 year-old man with known CHD has a greater annual baseline mortality risk (18.8% versus 1.3%), and therefore obtains a greater benefit from statin treatment compared to an otherwise similar 55 year-old man. Although the absolute survival is lower in the older man (2.1 versus 4.3 years), in relative terms (i.e. relative to the expected survival following a CHD event) it is proportionally greater (75% versus 23%).²⁸ According to Diamond, *et al.*:

*'All things being equal, then, the older we become, the more value we should ascribe to each additional year of life (and to the treatment that provides it).'*²⁸

The risk of adverse events in elderly patients taking statins

The statins are generally well tolerated. However, fear of muscle toxicity remains a major reason that patients with risk factors for CHD, or established CHD, are undertreated,²⁹ and

Table 2: Expected benefit of statins for secondary prevention of cardiovascular events (modified from Diamond, *et al.* 2008)²⁸

| Age (years) | Expected survival (years) | Absolute annual mortality without statin (%) | Absolute mortality reduction with statin (%) | NNT for 5 years to prevent 1 death | Absolute survival gain with statin (years) | Relative survival gain with statin (%) |
|-------------|---------------------------|--|--|------------------------------------|--|--|
| 85 | 2.8 | 18.8 | 8.9 | 11 | 2.1 | 75 |
| 70 | 8.3 | 5.0 | 2.2 | 45 | 4.1 | 49 |
| 55 | 18.8 | 1.3 | 0.4 | 250 | 4.3 | 23 |



Of major importance to pharmacists is that persistence with statin therapy is poor.

the incidence of statin-induced rhabdomyolysis is higher in practice than in controlled trials in which high-risk patients are excluded.³⁰ The risk of myopathy with statin treatment increases with co-administration of drugs that inhibit statin metabolism (Box 1).³¹ In fact, when muscle damage does occur with statins, it is commonly the result of drug interactions rather than a specific adverse response to statin monotherapy.³² Such interactions inevitably result in higher plasma concentrations of a statin and thereby an increased risk of myopathy. Multiple drug use, drug interactions and altered drug metabolism may put the elderly patient at increased risk of myopathy when statins are administered.³² Some caution is therefore advocated in the use of these drugs in elderly patients.³³ Accepted risk factors for rhabdomyolysis include age (particularly > 80 years of age); small body frame and frailty; renal, hepatic and thyroid dysfunction; and hypertriglyceridaemia.²⁹ Recent data also suggests that exercise, Asian race and peri-operative status may also increase the risk of muscle toxicity.²⁹ Some patients may also be genetically predisposed to statin rhabdomyolysis. The incidence of rhabdomyolysis seems similar among patients taking atorvastatin, pravastatin and simvastatin, although no study has been powered to provide a definite comparison.^{30,34} Controversy exists in this area, with some analyses suggesting that simvastatin and rosuvastatin may have higher rates of

Box 1: Concomitant medications that increase risk of statin-associated myopathy (modified from Thompson, *et al.* 2003)³¹

- | |
|--|
| Fibric acid derivatives, especially gemfibrozil Niacin Cyclosporin Azole antifungals Macrolide antibiotics HIV protease inhibitors Verapamil and diltiazem Amiodarone Grapefruit juice, >1 glass/day |
|--|

muscle toxicity.³⁵⁻³⁷ However, because rhabdomyolysis is rare (0.0042% per year for statin monotherapy)³⁰ and can also be prevented through screening and monitoring, other muscle complaints, including cramping, aching and weakness are likely to be more relevant adverse effects in the clinical setting, and may necessitate statin cessation.³⁸

In the PROSPER study,⁹ new cancers were more frequent amongst pravastatin-treated individuals (25% increased risk; P = 0.02). Much of this slight excess occurred early after the start of therapy and it was not confined to any particular site, which suggests it may have been due to chance.²⁰ Incorporation of the new data in a meta-analysis of all pravastatin and all statin trials revealed no overall increase of cancer risk.³⁹

Additional beneficial effects of statins in the elderly

It is worth noting that in addition to the extensive research in the chronic prevention of CHD, recent studies have also suggested that statins possess a range of other beneficial attributes, including effects on measures of inflammation, immunity, oxidative stress, thrombosis, and vascular and renal function.^{40,41} Pleiotropic effects of statins have also been implicated in:⁴¹

- Reductions in heart failure⁴²
- Myocardial ischaemia⁴³
- Periprocedural MI⁴⁴
- Inflammatory responses to sepsis⁴⁵
- Neuroprotection⁴⁶
- Rheumatoid arthritis⁴⁷ and
- Multiple sclerosis.⁴⁸

Summary

- The available evidence from RCTs suggests that the use of statins for the primary prevention of CHD in the elderly should focus on the individual's global risk (rather than cholesterol levels alone), and suggests a beneficial effect of statin treatment in those at high risk. As the elderly may suffer from CHD in the absence of traditional risk factors, additional markers such as hs-CRP may be used in the future to direct preventive treatment, particularly for those at intermediate risk.
- There is less data regarding the use of statins in the primary prevention of CHD in patients aged over 80 years and, in fact, a case has been made for not treating octogenarians with statins for the primary prevention of CHD.⁴⁹
- It should also be remembered that smoking cessation, regular physical activity and healthy diet are, as in younger individuals, appropriate and effective measures for preventing CHD in the elderly.⁵⁰

- For the secondary prevention of CHD, statins reduce overall mortality, the occurrence of cardiovascular events and stroke in the elderly and the magnitude of this effect is much larger than has been previously estimated.
- Although the risk of myopathy in controlled trials with statins is low, it is higher in real-world patients, and may necessitate treatment discontinuation in some patients.
- Of major importance to pharmacists is that persistence with statin therapy is poor. For example, in Australia it is estimated that approximately 30% of patients (~26% of those aged > 68 years) discontinue statin treatment within six months of initiation.⁵¹ Community pharmacists are well placed to identify poor medication adherence and non-persistence and implement strategies to combat these important issues.

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