

STATINS

KEY POINTS

- Statins are effective for secondary prevention of cerebral and cardiac events, although no specific studies exist for patients over the age of 80 years. Numbers needed to treat for secondary prevention are in the 20-40 range (for 5 years of treatment).
- Statins are considerably less effective for primary prevention of cardiac and cerebral events with numbers needed to treat of the order of 70-130.
- Adverse effects are related to dose and are more frequent in patients with interacting drugs or patients taking higher doses.
- The majority of the reduction of LDL seen with all available statins is achieved at the minimum dose.

CONTEXT

This guide considers the use of statins in the elderly under the distinct categories of primary and secondary prevention of cardiovascular events.

RECOMMENDED DEPRESCRIBING STRATEGY

- 1 The first step in deprescribing a statin may be to minimise adverse effects by using the minimum dose of the statin.
- 2 In appropriate patients with reduced life expectancy, a relatively low risk of cardiovascular events or who are experiencing possible adverse effects, a trial cessation may be considered.
- 3 In patients with a limited prognosis, statins should be stopped.
- 4 Statins can usually be stopped without the need for tapering.

EFFICACY

PRIMARY PREVENTION

The majority of evidence in older patients is from subset analysis of larger trials. These are summarised in [Table 1](#).

In a meta analysis of primary prevention trials,¹¹ the authors concluded that "In elderly subjects at high CV risk without established CV disease, statins significantly reduce the incidence of MI and stroke, but do not significantly prolong survival in the short-term."

- Statins, compared with placebo, significantly reduced the risk of MI (ARR 1.5%; NNT 66 over 3.5 years; $p = 0.003$) and the risk of stroke (ARR 0.9%; NNT 111 over 3.5 years; $p=0.006$).

- The risk of all-cause death were not significantly reduced.

No specific randomised trials or subset analysis for patients over 80 years of age have been identified.

The efficacy of the statins (at least in terms of LDL reduction) only increases incrementally with dose increases, and the use of the minimum dose of whichever statin provides the majority of the LDL reduction benefit (see [Figure 1 on page 2](#)).

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REF	PATIENTS/ CHARACTERISTICS/ TREATMENT/ AGE RANGE	ELDERLY SUBGROUP	RESULTS IN ELDERLY SUBGROUP (ENDPOINT; RATE [TREATMENT VS PLACEBO]; ARR; NNT; STATISTICAL SIGNIFICANCE)
PROSPER ¹	3239/ no previous vascular disease/ Pravastatin/ 70-82	100%	Fatal CHD, MI, Stroke; 11.4% vs 12.1%; p=0.19 NS
AFCAPS ¹²	6605/ no previous cardiac or vascular disease, no hyperlipidaemia/ Lovastatin/ 45-73	3180 (males over 57, Females over 63)	MI,USA,SCD; 4.9% vs 7.0%;NS
ASCOT- LLA ¹³	10305/hypertension + 3 or more other CVD risk factors/ Atorvastatin/ 40-79	6570 >60yo	MI, fatal CHD; 2.2% vs 3.4%; ARR 1.2%; NNT 83.3 over 3.3 years; p= 0.0027
CARDS ¹⁴	3249/T2DM, no previous CVD, +1 or more CVD risk factors/Atorvastatin/ 40-75	1129; >= 65yo	ACS, Stroke; 7.2% vs 11.1%; ARR 3.9%; NNT 25.6 over 3.9 years; p= <0.05
JUPITER ¹⁵	17802/no hyperlipidaemia, no CVD, elevated hsCRP / Rosuvastatin/ 60-71	5695; 70-97yo	MI, Stroke, USA, CVD death; 1.22% vs 1.99%; ARR 0.77%; NNT 130 annual; p= < 0.001
MEGA ¹⁶	7832/ hypercholesterolaemia, no prior CVD/40-70	1814; > = 65yo	CHD;4.8% vs 7.2%; NS Mortality; 5.2% vs 7.3%; NS Stroke; 2.5% vs 5.8%; ARR 3.3%; NNT 68 annual; p = < 0.05

Table 1: Statin Primary Prevention Studies in the Elderly

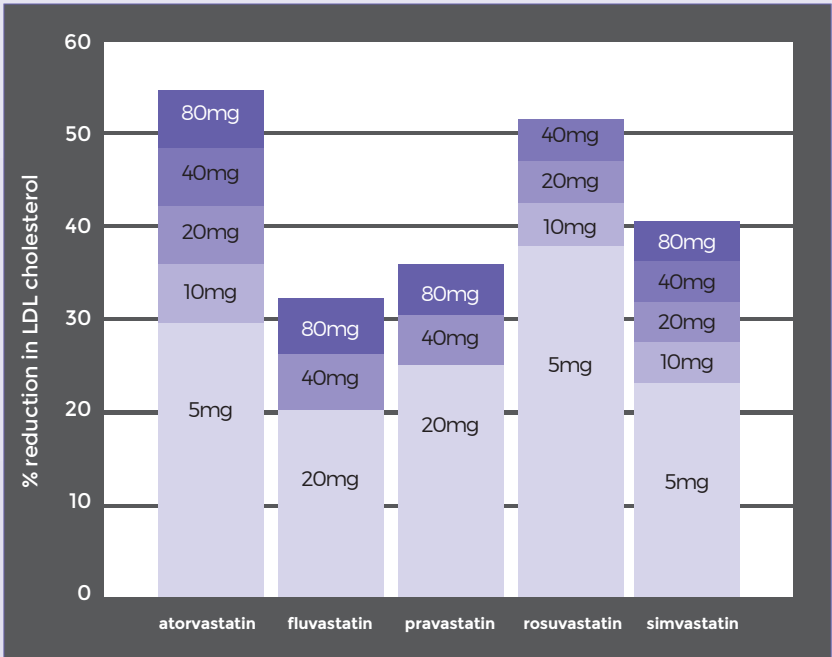


Figure 1: Effects of Statins and their doses¹⁷

EFFICACY continued from page 1

SECONDARY PREVENTION

Significant benefit has been demonstrated in terms of mortality and number of cardiovascular events in patients over 65 years of age with established cardiovascular disease in multiple large trials.^{1, 2, 3, 4, 5, 6, 7, 8}

In addition, subgroup analysis of older patients (over 65 years of age) from large trials have shown similar benefit to younger patients in the same trials.^{6, 9, 10}

Overall, these subgroup analyses consist of patients who are between 65 and 75 years old and the numbers needed to treat (for mortality or a major primary end point of MI, stroke or revascularisation) are between 16 and 43 at approximately 5 years of follow-up.

There is only limited evidence, from one specific trial and subset analysis of a larger trial, for benefit of statins vs placebo in patients over 75 years old.

No specific trials or subset analysis for patients over 80 years of age have been identified.

- The PROSPER study randomised patients 70-82 years of age (mean age 75.4) with cardiovascular disease or risk factors for cardiovascular disease to receive pravastatin or placebo with an average follow-up of 3.2 years. For patients with prior vascular disease, the primary end point of coronary death, MI or stroke occurred in 227/1306 (17.4%) of the placebo group and 273/1259 (21.7%) of the statin group. Absolute risk reduction was 4.3% (NNT 23.2 over 3.2 years).¹
- Subset analysis of one study reported the results of statin use (40mg simvastatin) vs placebo in 1263 CVD patients aged 75-80 years at study entry. They were followed for 5 years and 142/615 (23.1%) of the statin group and 209/648 (32.3%) of the placebo group had major cardiovascular events (stroke, revascularisation or infarction) over 5 years. Absolute risk reduction was 9.2% (NNT ~11 over 5 years).³



ADVERSE EFFECTS

Safety data from clinical trials show relatively good tolerance of statins, even in the older age groups.^{18, 19} Adverse effects are dose/level related and lower doses are associated with a lower rate of adverse effects. In the subgroup analysis of the TNT trial, Persistent AST or ALT elevations more than 3x normal occurred 24 times (1.3%) in 1937 patients taking 80mg of atorvastatin compared to once (0.1%) in 1872 patients taking 10mg of atorvastatin.⁶ Withdrawals due to adverse effects were also higher in the higher dose group (12.3% vs 9.5%).

Many practitioners will, however, be aware of multiple adverse effects reported by patients taking statins. These include a variety of muscle effects, fatigue and impact on cognition/memory.

In real world surveys of patients taking statins report higher rates of intolerance and discontinuation, due to adverse effects (predominantly muscle related), cost or perceived ineffectiveness/lack of necessity.^{20, 21} Rates in these studies were high, as the methodology involved an internet based survey. Muscle-related side effects were reported by 60% and 25% of former and current users, respectively ($P < .05$). Nearly half of all respondents switched statins at least once. The primary reason for switching by current users was cost (32%) and the primary reason for discontinuation was side effects (62%).²⁰

FATIGUE/ENERGY

In a randomised study of the effects of statins on energy and fatigue, both pravastatin and simvastatin reduced energy levels and increased fatigue, with women being disproportionately affected.²²

IMPACT ON MEMORY

A systematic review of the impact of statins on cognitive function was unable to find a clear association.²³ The authors stated that the level of evidence available was of low quality and that measurements of cognitive function should be included in any future trials of antihyperlipidaemic treatments.

MUSCLE EFFECTS

Muscle related adverse effects are dose (and therefore level) related and are increased by range of drug interactions with common medications. This may be one reason why these symptoms are reported more frequently in the elderly (as they take more medication).²⁴ Other factors are renal and hepatic impairment, hypothyroidism, low body weight and intercurrent illnesses.^{6, 25}

DIABETES

There has been some attention to an increase in the risk of diabetes in patients taking statins. This area was recently reviewed and summarised.²⁶ The excess risk of diabetes appears to be confined to those who are already at risk for developing diabetes. Diabetes is diagnosed only 2-4 months earlier in statin-treated patients and therefore is unlikely to have no long-term adverse consequences. The author concluded that "the clinical impact of statin-associated diabetes is likely unimportant. The cardiovascular risk reduction benefit from statins far outweighs the potential for adverse effects in all but the very lowest risk individuals."²⁷



FACTORS TO CONSIDER BEFORE DEPRESCRIBING

IN FAVOUR OF DEPRESCRIBING

SHORT ESTIMATED LIFE EXPECTANCY

- ✓ A recent randomised trial of discontinuing statin therapy in patients with life limiting illness suggested that cessation was not only safe, but that it improved quality of life.²⁷

POOR OVERALL FUNCTIONAL STATUS

- ✓ Patients who are more independent and generally functional tend to have a longer prognosis and the benefits of statin therapy may be more relevant in this setting.

LOW CARDIOVASCULAR EVENT RISK

- ✓ Patients with a higher cardiovascular risk would have a greater absolute benefit from statins.

PRESENCE OF SUSPECTED ADVERSE EFFECT

- ✓ Adverse effects may be unrecognised and a trial of cessation of statin may clarify whether non-specific muscular pains, issues with cognition or lethargy are related to the use of the agents.

AGAINST DEPRESCRIBING

- ✗ Patients who are well and functionally independent and have a five or more year life expectancy may derive ongoing benefit from the use of statins.
- ✗ Patients with a very high risk of recurrent events (ie a recent event, coexisting poorly controlled diabetes, Aborigines or Torres Strait Islanders, severe renal dysfunction).



DISCONTINUATION SYNDROMES

None.

RESOURCES

- ☒ QUICK REFERENCE GUIDE
- ☒ ANTIHYPERTENSIVES GUIDE
- ☒ ANTIPLATELET AGENTS GUIDE
- ☒ ANTIPSYCHOTICS GUIDE
- ☒ BENZODIAZEPINES GUIDE
- ☒ BISPHOSPHONATES GUIDE
- ☒ STATINS GUIDE
- ☒ VITAMIN D & CALCIUM GUIDE

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