A GUIDE TO

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CONSULTANT PHARMACY SERVICES

STATINS

KEY POINTS

Statins are effective for secondary prevention of coronary, cerebro and peripheral arterial disease, although no specific studies exist for patients over the age of 80 years. Annualised numbers needed to treat for secondary prevention are in the 50-80 range

Statins are considerably less effective for primary prevention of cardiac and cerebral events, with annualised numbers needed to treat in the order of 150-300 for patients over 65 years.

The mortality benefit of statins is diminished if non-cardiovascular mortality is high.

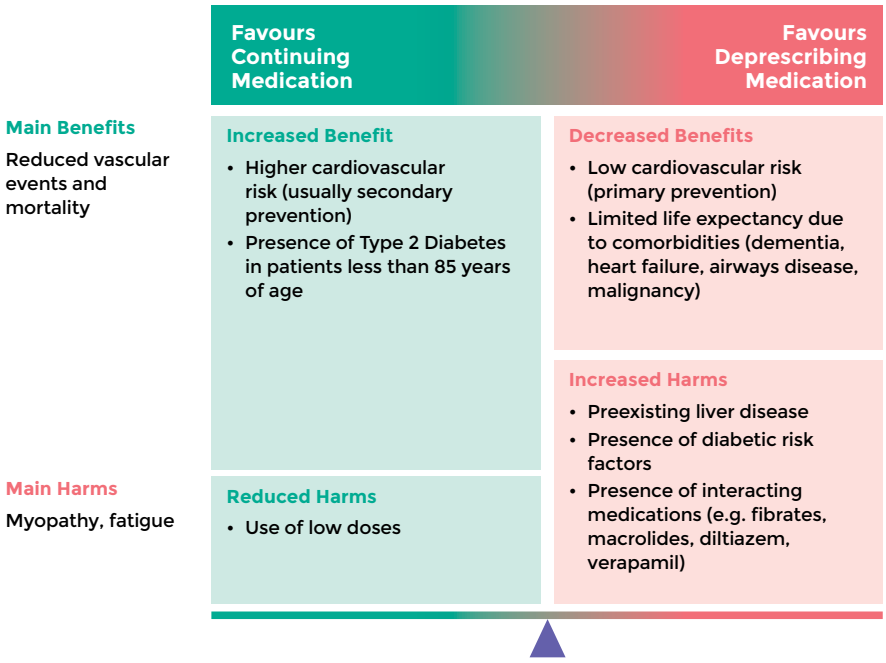
Adverse effects are related to dose and are more frequent in patients with interacting drugs or patients taking higher doses.

The majority of the reduction of LDL seen with all available statins is achieved at the minimum dose. There is incremental benefit in absolute risk reduction with higher doses.

CONTEXT

This guide considers the use of HMG-CoA Reductase inhibitors (statins) in the context of reducing the risk of vascular events in older people.

BENEFIT VERSUS HARM



RECOMMENDED DEPRESCRIBING STRATEGY

- The use of high-intensity statins for primary prevention should be reviewed.
- In appropriate patients with reduced life expectancy, a relatively low risk of cardiovascular events, or who are experiencing possible adverse effects the decision to stop (or a trial of cessation to see if adverse effects improve) may be considered.
- In patients with a limited prognosis, statins should be stopped.
- If cessation of statins is appropriate, this can usually be undertaken without the need for dose tapering

BACKGROUND

Statins are one of the most commonly used preventative medications in Australia, with established efficacy for secondary prevention in people with coronary, cerebro and peripheral arterial disease. While there is some evidence of benefit for their use in primary prevention, there is less absolute risk reduction of vascular events in this setting, and likely less benefit in an older population. In community dwelling patients 75 years of age or older, 43% are taking a statin.[1] In residential care, statin use was reported at 41% for patients 70-79 years old, 38.5% for those 80-89 years old and 17.7% for those 90 years old or over.[2] A study of nursing home residents found that up 34% of residents with limited life expectancy (life-limiting illnesses or life expectancy < 6 months) remained on statin therapy.[3]

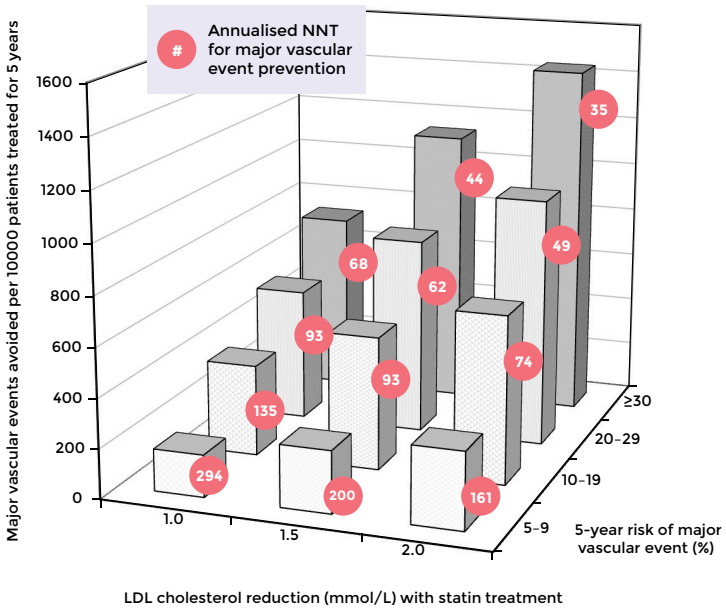


Figure 1: Numbers Needed to Treat for Prevention of Major Vascular Events (calculated from ref 3). This shows the number of vascular events avoided according to both baseline CV risk and degree of LDL reduction. This event rate is then calculated as an annualised NNT (inverse relationship).

EFFICACY

A major review of the evidence for efficacy of statin therapy has been published. These authors reviewed all available trials of statins for primary or secondary prevention. They concluded that the absolute benefits of statin therapy depend on an individuals' absolute risk of occlusive vascular events and the absolute reduction in LDL achieved. Statin therapy reduces the relative risk of major vascular events by ~25% for each mmol/L that LDL is reduced.[4] As can be seen in **Figure 1** the number of patients needed to treat (NNT) to prevent a major vascular event decreases (i.e. the likelihood of benefit increases) with both greater reduction of LDL and increased cardiovascular risk.

While effective for prevention of vascular events in patients at high risk, many patients taking statins have multiple non-vascular co-morbidities that may be the cause of their death. A review of the benefit of statins in patients with high risk of non-cardiovascular mortality showed that the mortality benefit of statins was attenuated as non-cardiovascular mortality increased. They concluded that populations with a high risk of non-cardiovascular mortality (>6%) statins had little impact to reduce total mortality.[5]

The efficacy of statins in terms of LDL reduction only increases modestly with each doubling of dose, and the use of the minimum dose provides over 50% of the LDL-lowering effect whichever statin is used (see **Figure 2**).[6] However, in a secondary prevention setting (with a focus on reduction of vascular events rather than LDL reduction), the use of higher doses and higher-intensity statins may offer incremental absolute benefits.[7]

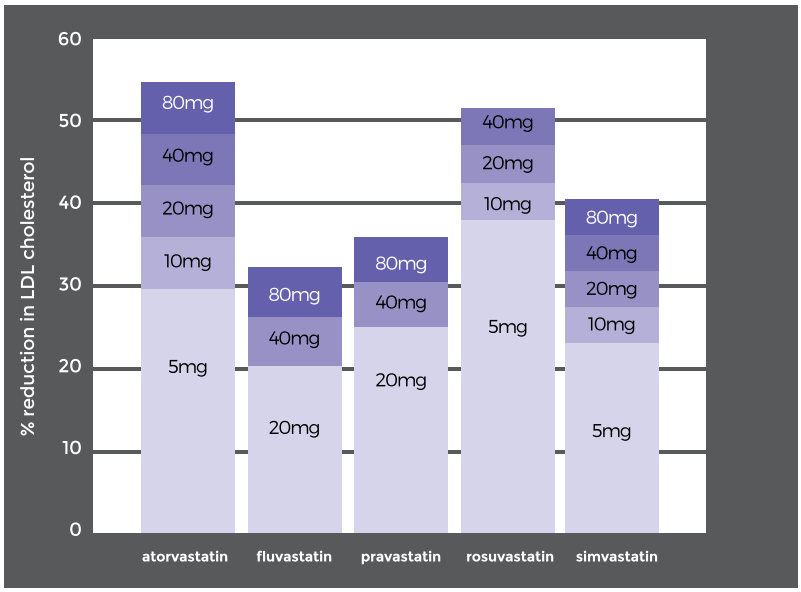


Figure 2: Effects of Statins and their doses[6]

STATINS FOR SECONDARY PREVENTION

Multiple large trials have demonstrated significant benefit with statins in terms of reduced mortality and various vascular events in patients over 65 years of age who have established cardiovascular disease.[8,9,10,11,12,13,14,15] In addition, subgroup analysis of older patients (over 65 years of age) from large trials have shown similar benefit to younger patients.[10,16,17]

Overall, these subgroup analyses consist of patients who are between 65 and 75 years old and the numbers needed to treat (NNT) 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.

- 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%) or the statin group and 273/1259 (21.7%) of the placebo group. Absolute risk reduction was 4.3% (**NNT 23.2** over 3.2 years).[8]
- Subset analysis of one study reported the results of statin use (40mg simvastatin) vs placebo n 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).[10]

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

STATINS FOR PRIMARY PREVENTION

The majority of evidence for statins in primary prevention in older patients is from subset analysis of larger trials. These are summarised in **Table 1**.

In a meta-analysis of primary prevention trials,[18] 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 or 231 annual; p = 0.003) and the risk of stroke (ARR 0.9%; **NNT 111** over 3.5 years or 388 annual; p=0.006).
- The risk of all-cause death was not significantly reduced.

The effect of statins for primary prevention in old and very old patients was reported in a retrospective cohort study in 2018.[26] Over a 7-year period, patients aged 74 or more who did not have atherosclerotic disease had their statin use documented and cardiovascular outcomes recorded. Statins were not associated with a reduction in atherosclerotic CVD or in all-cause mortality in participants without diabetes aged 75 years or older and free of clinical CVD. In participants with type 2 diabetes, however, statins were associated with a slight reduction in the incidence of atherosclerotic CVD and in all-cause mortality in patients less than 85 years old. This effect was substantially reduced after the age of 85 and disappeared in participants over 90 years of age (See **Figure 3**). [26]

REF	PATIENTS/ CHARACTERISTICS/ TREATMENT/ AGE RANGE	ELDERLY SUBGROUP	RESULTS IN ELDERLY SUBGROUP (ENDPOINT; RATE [TREATMENT VS PLACEBO]; ARR; NNT; STATISTICAL SIGNIFICANCE)
PROSPER[8]	3239/ no previous vascular disease/ Pravastatin/ 70-82	100%	Fatal CHD, MI, Stroke; 11.4% vs 12.1%; **p=0.19 NS**
AFCAPS[19]	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[20]	10305/hypertension + 3 or more other CVD risk factors/ Atorvastatin/ 40-79	6570 >60 yo	MI, fatal CHD; 2.2% vs 3.4%; ARR 1.2% over 3.2 years. Annualised **NNT 275; p= 0.0027**
CARDS[21]	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% over 3.9 years; Annualised **NNT 100 ; p= <0.05**
JUPITER[22]	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%; Annualised **NNT 130; p= < 0.001**
MEGA[23]	7832/ hypercholesterolaemia, no prior CVD/40-70	1814; > = 65yo	CHD;0.48% vs 0.72%; NS Mortality; 0.52% vs 0.73%; NS Stroke; 0.25% vs 0.58%; ARR 0.33%; Annualised **NNT 303; p = < 0.05**
HOPE-3[24]	12705/ 1 or more CV risk factors/Rosuvastatin/>55	6350; >= 65.3yo	MI, Stroke, CV death; 4.9% vs 6.4%; ARR 1.5% over 5.6 years; Annualised **NNT 378; p =<0.05**
ALLHAT-LLT[25]	2867/ hypertension, no CVD/>65	726; ≥75	All-cause mortality: 18.52% vs 24.53%; **p=0.07 NS**

Table 1: Statin primary prevention studies in the elderly

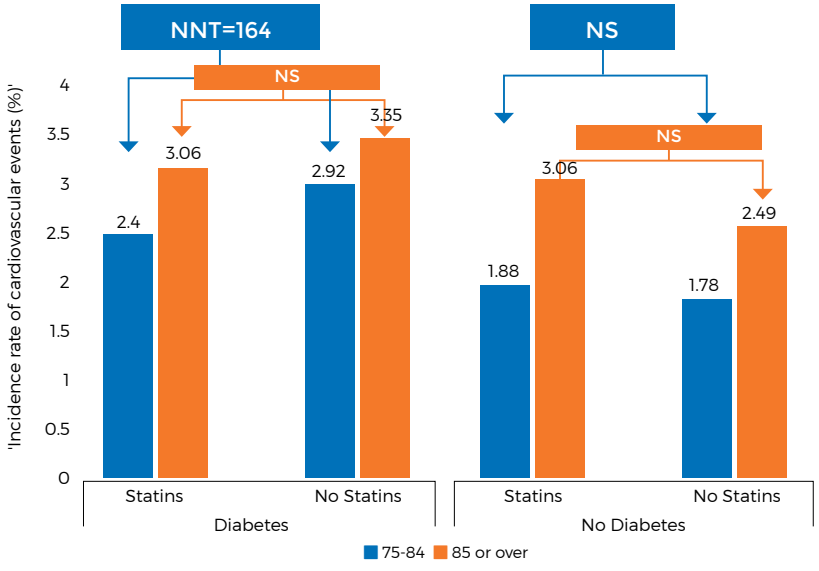


Figure 3: Incidence rate for cardiovascular disease by diabetes status and statin use (adapted from ref 26)

ADVERSE EFFECTS

Safety data from clinical trials show relatively good tolerability of statins, even in older age groups.[27,28] Adverse effects are dose related with lower doses are associated with a lower rate of adverse effects. The risk of dose-dependent adverse effects with simvastatin appears to be particularly unfavourable. 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.[13] Withdrawals due to adverse effects were also higher in the higher dose group (12.3% vs 9.5%).

In real world surveys, patients taking statins report higher rates of intolerance and discontinuation, due to adverse effects (predominantly muscle related) or cost.[29,30] 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 ($P < 0.05$). 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%).[29]

Many practitioners will, however, be aware of a range of adverse effects reported by patients taking statins. These include a variety of muscle effects, fatigue and impact on cognition/memory, that may not necessarily be due to their statin medication.

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 disproportionally affected.[31]

IMPACT ON MEMORY

Observational data from a post hoc analysis of ASPREE found no difference between statin users and non-statin users, for incidence of dementia (Hazard Ratio 1.16, 95% CI 0.97–1.40) or mild cognitive impairment (Hazard Ratio 0.97, 95% CI 0.77–1.22). No difference was found between lipophilic (e.g. atorvastatin, simvastatin) and hydrophilic (e.g. rosuvastatin) agents.[32]

A systematic review of the impact of statins on cognitive function was unable to find a clear association.[33] 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.

INTERACTING AGENT	STATIN	EFFECT	MAGNITUDE
Ciclosporin/ tacrolimus/ everolimus/ sirolimus*	Atorvastatin	Increased statin exposure through multiple mechanisms Increased risk for muscle-related toxicity	**Severe** 6- to 15-fold increase in AUC of atorvastatin
	Fluvastatin	Increased statin exposure through multiple mechanisms Increased risk for muscle-related toxicity	**Moderate** 2- to 4-fold increase in AUC of fluvastatin
	Pravastatin	Increased statin exposure through multiple mechanisms Increased risk for muscle-related toxicity	**Severe** 5- to 10-fold increase in AUC of pravastatin
	Rosuvastatin	Increased statin exposure through multiple mechanisms Increased risk for muscle-related toxicity	**Severe** 7-fold increase in AUC of rosuvastatin
	Simvastatin	Increased statin exposure through multiple mechanisms Increased risk for muscle-related toxicity	**Severe** 6- to 8-fold increase in AUC of simvastatin
Diltiazem	Simvastatin	Decreased metabolism of simvastatin leading to increased concentrations Increased risk of muscle-related toxicity	**Moderate** 4.6-fold increase in AUC of simvastatin
Gemfibrozil (Combination should be avoided)	Pravastatin	Decreased metabolism of pravastatin leading to increased concentrations Increased risk of muscle-related toxicity	**Moderate** 2.0-fold increase in AUC of pravastatin
	Simvastatin	Decreased metabolism of simvastatin leading to increased concentrations Increased risk of muscle-related toxicity	**Moderate** 2- to 3-fold increase in AUC of simvastatin
Ticagrelor	Simvastatin	Decreased metabolism of simvastatin leading to increased concentrations Increased risk of muscle-related toxicity	**Moderate** 2- to 3-fold increase in AUC
Verapamil	Simvastatin	Decreased metabolism of simvastatin leading to increased concentrations Increased risk of muscle-related toxicity	**Moderate** 2.5-fold increase in AUC
Warfarin	Fluvastatin	Increased INR/potential for increased bleeding	**Variable**
	Rosuvastatin	Increased INR/potential for increased bleeding	**Variable**
	Simvastatin	Increased INR/potential for increased bleeding	**Up to 30% change in INR**

Table 2: Significant drug interactions with Statins (adapted from ref 37)

DIABETES

There has been a rising awareness of an increase in the risk of diabetes in patients taking statins and this topic was recently reviewed and summarised.[34] 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 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.".[34]

MUSCLE EFFECTS

Muscle related adverse effects are dose related and can be increased by a range of drug interactions with common medications (see below). Other contributory factors include renal and hepatic impairment, hypothyroidism, low body weight and intercurrent illnesses. [15,35]

A recent meta-analysis of 62 studies was conducted looking for associations between statins used for primary prevention and adverse effects.[36] Statin use was associated with an increase in self-reported muscle symptoms, however there was no significant increase in clinically confirmed muscle disorders (diagnosed myopathy/rhabdomyolysis or creatine kinase elevation >10xULN). There was limited data for assessing event rates related to different doses of individual statins.

STATIN DRUG INTERACTIONS AND DOSE

Polypharmacy is common in older adults, potentially increasing the risk of drug-drug interactions. This may be one reason why these symptoms are reported more frequently in the elderly.[37] Statin concentrations can be affected by influx and efflux transporters (OATP and P-gp respectively), as well as by the actions of CYP 450 enzymes. In particular, simvastatin and atorvastatin are metabolised by CYP3A4, so concurrent use of 3A4 inhibitors may result in higher drug-concentrations and an increased risk of adverse muscle symptoms. Simvastatin is particularly sensitive to CYP3A4 changes and carries the highest risk of drug interactions, many of which include drugs commonly prescribed long-term for patients with cardiovascular disease. A summary of the key important interactions with statins is shown in **Table 2**.

Adverse events from the SEARCH trial have led the Therapeutics Goods Administration and several other international drug safety agencies to recommend avoiding or limiting the use of simvastatin at a dose of 80mg daily. Avoiding simvastatin is recommended in the presence of potent CYP3A4 inhibitors (e.g. clarithromycin, erythromycin, ketoconazole), gemfibrozil, and ciclosporin. Lower doses of simvastatin are recommended with a number of other drugs that are metabolised by or inhibit CYP including (but not limited to): verapamil, diltiazem, amlodipine, amiodarone, and colchicine.[38,39]

FACTORS TO CONSIDER

There are no randomised controlled trials of cessation of statins, however, in 2021 a population cohort study was published of all persons in Denmark ≥75 years who had been taking a statin for at least 5 consecutive years (67,418 people, 27,463 classed as primary prevention).[40] It assessed the rate of MACE between those continuing and discontinuing statins. For the primary prevention group, the absolute rate of difference was 0.9% (95% CI 0.5-1.2%) or a NNH of 112, i.e. one additional MACE per 112 people discontinuing statins (compared to a NNH of 77 in the secondary prevention arm). The trial authors noted that post-hoc analyses found a lower rate of vascular intervention (CABG) in the discontinuation group and suggested that statin discontinuation may be linked to poor patient health and frailty.

A 2019 French population-based cohort study involved 75 year olds using a statin for at least 2 years for primary prevention (120, 173 people). 17,204 people discontinued their statins and were followed-up over a mean duration of 2.4 years to assess the primary outcome of hospitalisation for cardiovascular events. A 33% increased risk was found, with 5396 admitted to hospital for a cardiovascular event (HR 1.33, 95% CI 1.18-1.50). No statistical difference was seen in the diabetic subset.[41]

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.[42]

Poor Overall functional status

Patients who are less independent and frailer tend to have a poorer prognosis and the benefits of statin therapy may be less relevant in this setting.

Low Cardiovascular Event Risk

Patients with a lower cardiovascular risk have a lower absolute benefit from statins (i.e. a larger number needed to treat).

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 reasonable life expectancy may derive ongoing benefit from the use of statins for secondary prevention.

Patients with a very high risk of recurrent events (i.e. a recent ACS, ischaemic stroke, severe PAD, coexisting poorly controlled diabetes, Aboriginal or Torres Strait Islanders, severe renal dysfunction) should be considered for ongoing statin therapy.

DISCONTINUATION SYNDROMES

None described. Statins can generally be ceased without tapering.

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