A GUIDE TO

deprescribing

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CPS Experts in Medicines
CONSULTANT PHARMACY SERVICES

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. Annualised Numbers Needed to Treat 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.**
- **The mortality benefit of statins is diminished if non-cardiovascular mortality is high.**
- **Adverse effects are related to dose (and levels) 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.**

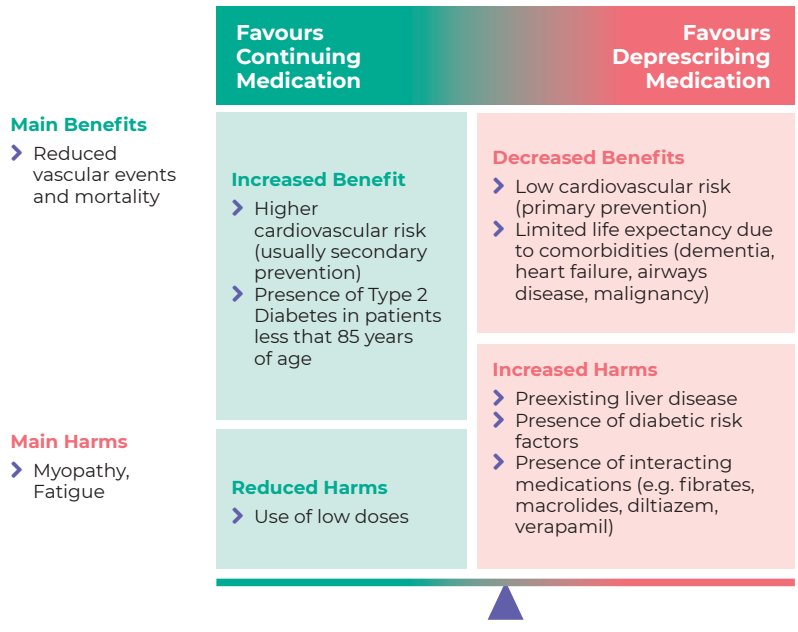
CONTEXT

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

RECOMMENDED DEPRESCRIBING STRATEGY

- Given the incremental benefits of statins with dose increases, and the increased risk of adverse effects, the first step in deprescribing a statin may be to minimise adverse effects by using the minimum dose of the statin.
- In appropriate patients with reduced life expectancy, a relatively low risk of cardiovascular events or who is 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.
- Statins can usually be stopped without the need for tapering.

BENEFIT VERSUS HARM



BACKGROUND

Statins are one of the most commonly used preventative medications in Australia, with established efficacy for the reduction of secondary cardiac and cerebral events.[1]

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]

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 of LDL that is reduced.[3] As can be seen in **Figure 1** the number of patients needed to treat to prevent a major vascular event reduces 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 comorbidities that may be the cause of their death. A review of the benefit of statins in patients with high non-cardiovascular mortality risk showed that the mortality benefit of statins was attenuated as non-cardiovascular mortality increased. They concluded that populations with a high non-cardiovascular mortality risk (>6%) had little reduction in total mortality.

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 2**).[23]

STATINS FOR 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.[5-12] 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.[10,13,14]

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 followup.

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.

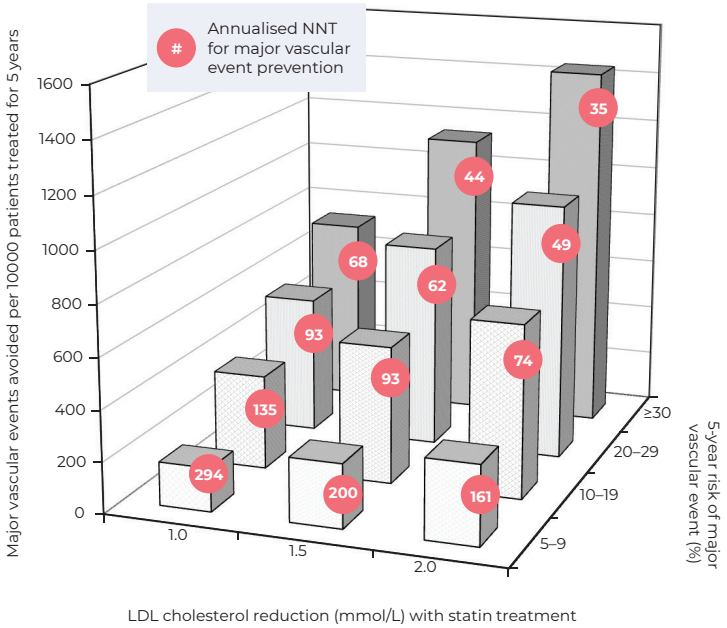


Figure 1: Numbers Needed to Treat (NNT) for prevention of major vascular events (calculated from ref 3)

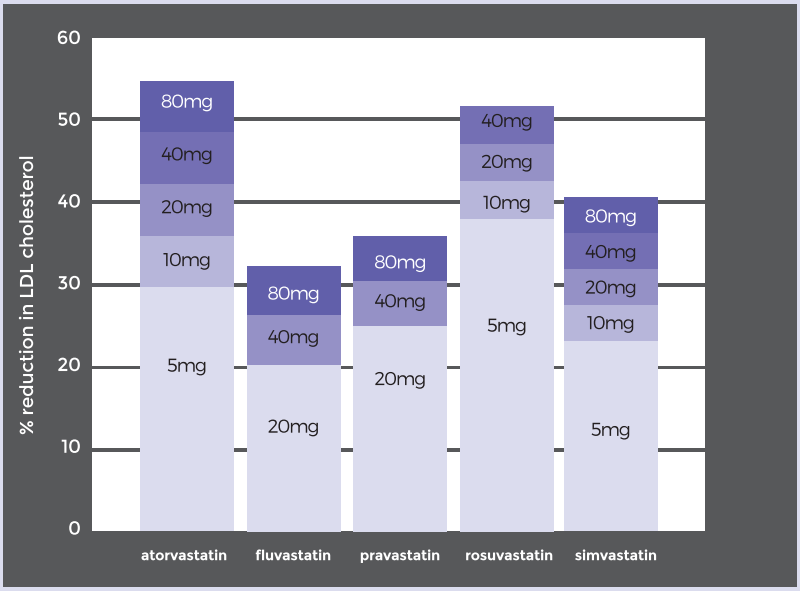


Figure 2: Effects of statins and their doses[23]

- 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 followup 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 year, annual **NNT = 74**).[5]
- 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, annual **NNT = 54**).[7]

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

STATINS FOR PRIMARY PREVENTION

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

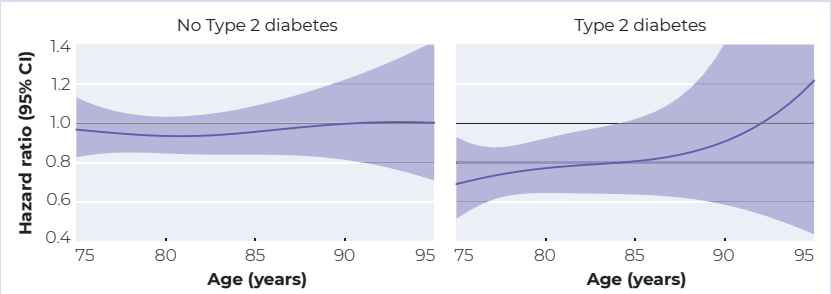
In a meta-analysis of primary prevention trials, the authors concluded that "In elderly subjects at high CV risk without established CV disease, statins significantly reduce the incidence of MI and stroke, but do not significantly prolong survival in the short-term."

- Statins, compared with placebo, significantly reduced the risk of MI (ARR 1.5%; (**Annual NNT=231**); p = 0.003) and the risk of stroke (ARR 0.9%; **Annual NNT=388**; p=0.006).
- The risk of all-cause death was not significantly reduced.

Primary prevention in old and very old patients has recently been studied in a retrospective cohort study.[22] 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 significantly related to 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 **Figures 2 and 3**).[22]

REF	PATIENTS/ CHARACTERISTICS/ TREATMENT/ AGE RANGE	ELDERLY SUBGROUP	RESULTS IN ELDERLY SUBGROUP (ENDPOINT; RATE [TREATMENT VS PLACEBO]; ARR; NNT; STATISTICAL SIGNIFICANCE)
PROSPER[5]	3239/ no previous vascular disease/ Pravastatin/ 70-82	100%	Fatal CHD, MI, Stroke; 11.4% vs 12.1%; p=0.19 **NS**
AFCAPS[16]	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[17]	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% over 3.2 years. Annualised **NNT 275**; p= 0.0027
CARDS[18]	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[19]	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[20]	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 [21]	12705/ 1 or more CV risk factors/ Rosuvastatin/>55	6350; >= 65.3 yo	MI, Stroke, CV death; 4.9% vs 6.4%; ARR 1.5% over 5.6 years; Annualised **NNT 378**; p =<0.05

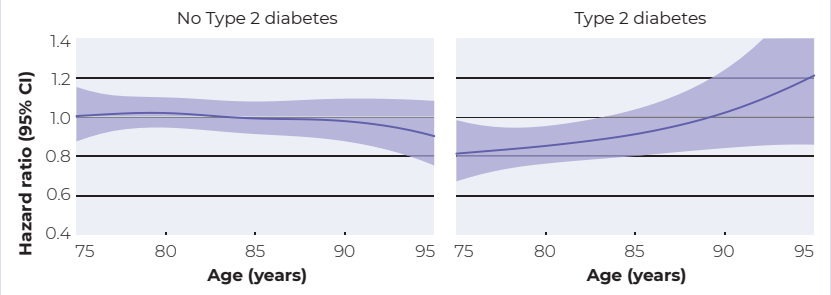
Table 1: Statin primary prevention studies in the elderly



Cardiovascular Events in Subjects WITHOUT Type 2 Diabetes			
Age Group	No Statin Use	Statin Use	NNT
75-84yo	1.78%	1.88%	Not Significant
85 or more	2.49%	3.06%	Not Significant

Cardiovascular Events in Subjects WITH Type 2 Diabetes			
Age Group	No Statin Use	Statin Use	NNT
75-84yo	2.92%	2.4%	164
85 or more	3.35%	3.06%	Not Significant

Figure 3: Hazard ratios and incidence rate for atherosclerotic disease for statin use, by age.



All Cause Mortality in Subjects WITHOUT Type 2 Diabetes			
Age Group	No Statin Use	Statin Use	NNT
75-84yo	3.7%	3.26%	Not Significant
85 or more	12%	11.6%	Not Significant

All Cause Mortality in Subjects WITH Type 2 Diabetes			
Age Group	No Statin Use	Statin Use	NNT
75-84yo	5.45%	4.15%	306
85 or more	13.7%	13.5%	Not Significant

Figure 4: Hazard ratios and incidence rate for all cause mortality for statin use, by age.

ADVERSE EFFECTS

Safety data from clinical trials show relatively good tolerance of statins, even in the older age groups.[24-26] 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.[10] 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.[27,28] 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%).[27]

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.[29]

IMPACT ON MEMORY

A systematic review of the impact of statins on cognitive function was unable to find a clear association.[30] 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 antihyperlidaemic 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).[31] Other factors are renal and hepatic impairment, hypothyroidism, low body weight, interacting medications and intercurrent illnesses.[10,32]

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.[33] 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."[33]

DISCONTINUATION SYNDROMES

None described

FACTORS TO CONSIDER

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, it improved quality of life.[34]
- **Poor overall functional status**
  Patients who or 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 (i.e. a recent event, coexisting poorly controlled diabetes, Aboriginal or Torres Strait Islanders, severe renal dysfunction).

RESOURCES

- GENERAL INFORMATION
- ALLOPURINOL
- ANTIHYPERGLYCAEMICS
- ANTIHYPERTENSIVES
- ANTIPSYCHOTICS
- ASPIRIN
- BENZODIAZEPINES
- BISPHOSPHONATES
- CHOLINESTERASE INHIBITORS
- GLAUCOMA EYE DROPS
- NSAIDS
- OPIOIDS
- PROTON PUMP INHIBITORS
- STATINS
- VITAMIN D AND CALCIUM

AUTHORSHIP

This guide was written by Dr Peter Tenni and Dr David Dunbabin in consultation with the Deprescribing Reference Group.

MAY 2019

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