A GUIDE TO
deprescribing

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 in the order of 70-130.**

- **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 cardiovascular and cerebrovascular events.

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.

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 dwellings of 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

STATINS FOR PRIMARY PREVENTION

The majority of evidence in older patients is from subset analysis of larger trials. These are summarised in **Table 1** to the right. In a meta-analysis of primary prevention trials,[3] 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 risks 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**).

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.[10,11,12,13,14,15,16,17] 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.[15,18,19]

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.

- 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).[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).[12]

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

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

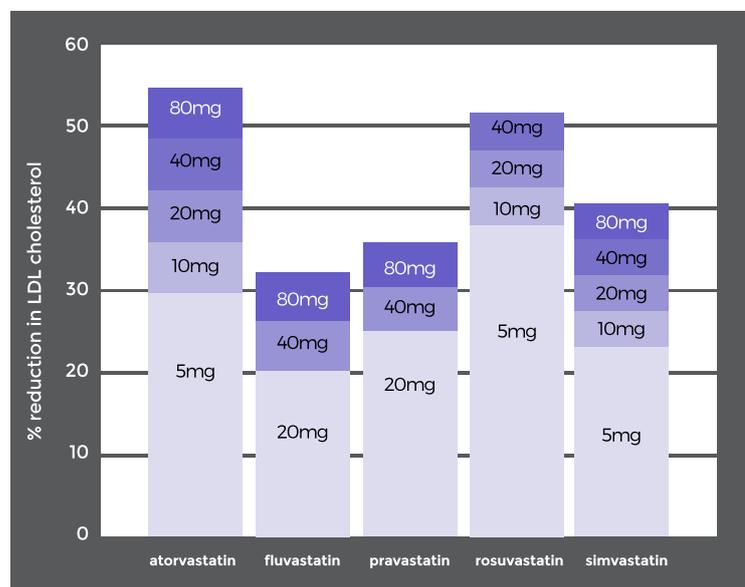Table 1: Statin Primary Prevention Studies in the Elderly

Figure 1: Effects of Statins and their doses[9]

ADVERSE EFFECTS

Safety data from clinical trials show relatively good tolerance of statins, even in the older age groups.[20,21] 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.[15] 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.[22,23] 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%).[22]

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.[24]

IMPACT ON MEMORY

A systematic review of the impact of statins on cognitive function was unable to find a clear association.[25] 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).[26] Other factors are renal and hepatic impairment, hypothyroidism, low body weight, interacting medications and intercurrent illnesses.[15, 27]

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.[28] 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."[28]

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.[29]

⊘ **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

- ☑ QUICK REFERENCE GUIDE
- ☑ GENERAL INFORMATION
- ☑ ALLOPURINOL
- ☑ ANTIHYPERTENSIVES
- ☑ ANTIPLATELET AGENTS
- ☑ ANTIPSYCHOTICS
- ☑ BENZODIAZEPINES
- ☑ BISPHOSPHONATES
- ☑ CHOLINESTERASE INHIBITORS
- ☑ GLAUCOMA EYE DROPS
- ☑ NSAIDS
- ☑ OPIOIDS
- ☑ PROTON PUMP INHIBITORS
- ☑ STATINS
- ☑ SULPHONYLUREAS
- ☑ VITAMIN D AND CALCIUM

AUTHORSHIP

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

MAY 2016

CPS CONSULTANT PHARMACY SERVICES

www.consultantpharmacyservices.com.au

Australian Government

phn TASMANIA
An Australian Government Initiative

While the Australian Government helped fund this document, it has not reviewed the content and is not responsible for any injury, loss or damage however arising from the use of or reliance on the information provided herein.

www.primaryhealthtas.com.au

REFERENCES

1. Morgan TK, Williamson M, Pirotta M, Stewart K, Myers SP, Barnes J. A national census of medicines use: 24 hour snapshot of Australians aged 50 years and older. Med J Aust 2012; 196: 50-53.
2. Gnjidic D, Wilson N, March L, Cumming RG, Cameron ID, Hilmer SN. Statin utilisation patterns in older Australians living in residential care: 1 year prevalence study. Intern Med J 2015 ; 45: 106-109
3. Savarese, G et al. Benefits of statins in elderly subjects without established cardiovascular disease: a meta-analysis. J Am Coll Cardiol 62(22), 2090-2099 (2013).
4. Downs JR, Clearfield M, Weis S, et al. Primary Prevention of Acute Coronary Events With Lovastatin in Men and Women With Average Cholesterol Levels Results of AFCAPS/TexCAPS. JAMA. 1998;279(20):1615-1622.
5. Sever PS, Dahlöf B, Poulter NR, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. Lancet. 2003;361(9364):1149-1158.
6. Neil HAW, DeMicco DA, Luo D, et al. Analysis of efficacy and safety in patients aged 65–75 years at randomization: Collaborative Atorvastatin Diabetes Study (CARDS). Diabetes Care. 2006;29(11):2378-2384.
7. Glynn RJ, Koenig W, Nordestgaard BG, Shepherd J, Ridker PM. Rosuvastatin for primary prevention in older persons with elevated C-reactive protein and low to average low-density lipoprotein cholesterol levels: exploratory analysis of a randomized trial. Ann Intern Med. 2010;152(8):488-496.
8. Nakaya N, Mizuno K, Ohashi Y, et al. Low-dose pravastatin and age-related differences in risk factors for cardiovascular disease in hypercholesterolaemic Japanese: analysis of the management of elevated cholesterol in the primary prevention group of adult Japanese (MEGA study). Drugs Aging. 2011;28(9):681-692.
9. Westaway, K.P. et al. Safe use of statin in elderly people. J Pharm Pract Res 44(3), 138-142 (2014)
10. Shepherd J. et al. for the PROSPER study group. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. Lancet 360, 1623-1630 (2002).
11. Miettinen, T.A. et al. Cholesterol-lowering therapy in women and elderly patients with myocardial infarction or angina pectoris: findings from the Scandinavian Simvastatin Survival Study (4S). Circulation 96. 4211-4218 (1997).
12. Heart Protection Collaborative Study Group/ MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet 360, 7-22 (2002).
13. Lewis, S.J. et al. Effect of pravastatin on cardiovascular events in older patients with myocardial infarction and cholesterol levels in the average range. Results of the Cholesterol and Recurrent Events (CARE) Trial. Ann. Intern. Med. 129, 681-689 (1998).
14. Hunt, D. et al. Benefits of pravastatin on cardiovascular events and mortality in older patients with coronary heart disease are equal to or exceed those seen in younger patients: results from the LIPID trial. Ann. Intern. Med. 134, 931-940 (2001).
15. Wenger, N.K., Lewis, S.J., Herrington, D.M., Bittner, V. & Welty, F.K. for the Treating to New Targets Study Steering Committee and Investigators. Outcomes of using high- or low- dose atorvastatin in patients 65 years of age or older with stable coronary heart disease. Ann. Intern. Med. 147, 1-9 (2007).
16. Deedwania, P. et al. Effects of intensive versus moderate lipid-lowering therapy on myocardial ischemia in older adults with coronary heart disease: results of the Study Assessing Goals in the Elderly (SAGE). Circulation 115, 700-707 (2007).
17. Olsson, A.G., Schwartz, G.G., Szarek, M., Luo, D. & Jamieson, M.J. Effects of high-dose atorvastatin in patients > or = 65 years of age with acute coronary syndrome (from the myocardial ischemia reduction with aggressive cholesterol lowering [MIRACL] study). Am. J. Cardiol. 99, 632-635 (2007).
18. Tikkanen, M.. et al. Comparison of efficacy and safety of atorvastatin (800mg) to simvastatin (20 to 40mg) in patients aged <65 versus > or = 65 years with coronary heart disease (from the incremental Decrease through Aggressive Lipid Lowering [IDEAL] study). Am JJ Cardiol 103(5), 577-582 (2009).
19. Amarenco, P. et al. High-dose atorvastatin after stroke or transient ischaemic attack. N Engl Med 355(6), 549-559 (2006).
20. Newman. C.B. et al. Safety of atorvastatin derived from analysis of 44 completed trials in 9,416 patients. Am Cardiol 92(6), 670-676 (2003).
21. Baigent C et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins Lancet. 2005 Oct 8;366(9493):1267-78.
22. Cohen JD, Brinton EA, Ito MK, Jacobson TA. Understanding Statin Use in America and Gaps in Patient Education (USAGE): An internet-based survey of 10,138 current and former statin users. J Clin Lipidol. 2012;6(3):208-215.
23. Jin H, Tang C, Wei Q, Chen L, Sun Q, Ma G, Liu N. Age-related differences in factors associated with the underuse of recommended medications in acute coronary syndrome patients at least one year after hospital discharge. BMC Cardiovasc Disord. 2014 Sep 24;14:127
24. Golomb BA et al. Effects of statins on energy and fatigue with exertion: results from a randomized controlled study. Arch Inten Med 2012; 172(15):1180-2.
25. Richardson K. et al. Statins and cognitive function: a systematic review. Annals of Internal Medicine 2013; 159: 688-697.
26. Bellosta S, Paoletti R, Corsini A. Safety of Statins Focus on Clinical Pharmacokinetics and Drug Interactions. Circulation. 2004;109(23 Suppl 1):III-50-III-57,
27. Hilmer S. Statin in older adults. Aust Prescriber 36(3), 79-82 (2013)
28. Robinson JG. Statins and diabetes risk: how real is it and what are the mechanisms? Curr Opin Lipidol. 2015 Jun;26(3):228-35.
29. Kutner, S. et al. Safety and benefit of discontinuing statin therapy in the setting of advanced, life-limiting illness: A randomised clinical trial. JAMA Internal Medicine published online 23rd March 2015