ARTICLE

Statins in older adults

SUMMARY

Statin use in people over 65 years of age is high.

A meta-analysis of older patients included in randomised trials found good evidence that statins reduce vascular events and mortality in people with existing coronary heart disease.

In older adults, exposure to higher doses of statins or higher potency statins does not increase their effectiveness, but does increase the risk of adverse effects such as myopathy and cognitive impairment.

Increasing age is a risk factor for adverse events with statins. Older patients may be less resilient to these effects.

Older patients may have more comorbidities and be taking more concomitant drugs than the study populations in statin trials. Applying the evidence for statins to older individuals therefore requires frequent review and consideration of the therapeutic goals and potential benefits and harms.

Introduction

Statins (hydroxymethylglutaryl coenzyme A reductase inhibitors) are the most commonly used cholesterol-lowering drugs. They are being taken by more than 40% of Australians over 65 years of age.[1] Although the prevalence of statin use increases with age, the balance between evidence of their benefits and the risk of adverse effects such as myopathy or impaired cognition may change. In extreme old age, preserving function and avoiding frailty and injury in the short term may become more important than longer term goals such as preventing future cardiovascular events or even extending life.

Efficacy of statins

Older people have an increased risk of cardiovascular disease. However, epidemiological studies suggest that the relative risk for coronary heart disease associated with high cholesterol decreases with age.[2] In addition, in old age, there is an inverse relationship between high cholesterol and the risk of stroke[3] and there are conflicting data on the relationship between high cholesterol and non-cardiovascular mortality.

Cardiovascular events

Statins are most beneficial for preventing cardiovascular events in patients who already have coronary heart disease. A meta-analysis of patients with existing disease (aged 65–82 years) found that all-cause mortality was significantly lower with statins than with placebo (15.6% vs 18.7%) over five years.[4] This equates to a number needed to treat of 28 over five years to save one life. Approximately 25% of patients in the trials were female. Frail older patients may have been excluded because of comorbidity or organ dysfunction.

The role of statins in primary prevention of cardiovascular disease in older people is unclear. Their effects seem to increase over five years, with only minimal benefits over placebo seen in the first year.[5] It is therefore important to consider the patient's probable lifespan when deciding whether to start or continue a statin.

Studies of secondary prevention in patients with cerebrovascular disease suggest that statins are associated with a decrease in recurrent ischaemic stroke but an increase in haemorrhagic stroke.[5]

Other clinical outcomes

There are very limited data assessing the impact of statins on other outcomes such as frailty, physical and cognitive function and institutionalisation. Epidemiological data suggest that statins are not associated with an increase in the risk of developing frailty.[6] This is a condition of increased vulnerability to external stressors and an independent risk factor for adverse clinical outcomes. Symptoms and signs of frailty include complaints of fatigue, unintentional weight loss and low grip strength. We recently investigated the relationship between statins and institutionalisation and mortality, according to frailty in community-dwelling men aged 70 years and over. There was no association between statin use and institutionalisation or death in older men. Statins did not appear to improve mortality or delay institutionalisation.[7]

Observational studies report conflicting results on the association of statins and muscle mass, strength and function. Results of randomised trials on the effects of statins on cognition are conflicting.[8] In patients with dementia, statins do not significantly affect cognitive decline, global function, behaviour or activities of daily living.[9] A recent pilot study of statin withdrawal showed that statin reduction is associated

Sarah Hilmer
Staff specialist[1]
Associate professor[2]

Danijela Gnjidic
Lecturer[3]
Research fellow[1–4]

[1] Departments of Clinical Pharmacology and Aged Care
Royal North Shore Hospital
Sydney

[2] Sydney Medical School
University of Sydney

[3] Faculty of Pharmacy
University of Sydney

[4] Centre for Education and Research on Ageing
Concord Hospital
Sydney

Key words
ageing, deprescribing, HMG CoA reductase inhibitors, myopathy

Aust Prescr 2013;36:79–82

with improvements in cognitive function in patients with Alzheimer's disease. Moreover, rechallenge with statins was associated with a decline in cognition function.[10]

Statin dose

Meta-analyses suggest that 80% of the lipid-lowering effect of statins occurs at half the maximal statin dose.[11] In older patients, the efficacy of statins for secondary prevention of acute myocardial infarction and death appears to be a class effect, with no difference observed between high or low potency statins.[12] Surrogate markers, such as low density lipoprotein cholesterol, should be interpreted with care in older people. Epidemiological data indicate that lowering low density lipoprotein cholesterol has a smaller impact on the relative risk of coronary heart disease as age increases.[11]

Adverse effects of statins

Adverse effects appear to vary between types and doses of statins. The risk of common events such as myopathy and liver enzyme elevations increases with statin potency and exposure. The degree of statin exposure (area under the concentration–time curve) depends on dose, drug interactions and patient factors including genetic polymorphisms. With ageing, there is a decrease in body size, particularly in muscle mass, and in hepatic and renal function, so the same dose will result in a greater degree of exposure in older patients.

Muscle symptoms

The most common adverse effects that limit treatment with statins are muscle symptoms. These include myalgia, myositis and rhabdomyolysis (Table 1). The risks of muscle symptoms are related to the dose of the statin.

The risk of muscle damage with statins increases with age over 70 years, and with age-associated factors such as multiple medicines use, comorbidity and sarcopenia (low skeletal muscle mass and function) (Table 2).

Table 1 rows 1–3 should read creatine kinase, not creatinine kinase
Corrected July 2013

Table 1 **Muscle symptoms associated with statins**

Condition	Clinical presentation	Prevalence
Myalgia	Musculoskeletal pain without creatinine kinase increase	5–10% of patients in clinical trials
Myositis	Muscle symptoms with elevated creatinine kinase	0.1–0.2% of patients in clinical trials
Rhabdomyolysis	Severe muscle symptoms with creatinine kinase greater than 10 times the upper limit of normal, complicated by myoglobinuria and impaired renal function	Rare

Statin myopathy is likely to have a greater impact in older people, with limited musculoskeletal reserve, than in younger people, who generally have more muscle mass and strength and better mobility.

Liver enzyme increases

Elevated hepatic transaminases occur in 0.5–2% of patients treated with statins and are dose-dependent. Their clinical significance is uncertain and progression to liver failure is very rare. The transaminases may normalise if the statin dose is reduced and elevation does not always recur if the patient resumes the statin.[13] The effect of ageing on the risk of hepatic damage with statins is not known. In old age the risk of drug-induced liver injury appears to increase for some drugs, such as non-steroidal anti-inflammatory drugs, and decrease for others such as paracetamol. While drug-induced liver injury is commonly defined as moderate with an increase in liver enzymes over 2.5 times the upper limit of normal and severe at 5 times the upper limit of normal, these thresholds may be lower in older people because of their 30% decrease in liver mass.

Other adverse effects

The commonest adverse effects observed with statins are gastrointestinal, such as abdominal pain, constipation and nausea. A rare but serious adverse event is reversible peripheral neuropathy.

An increased risk of diabetes with statins was recently reported. Diabetes has also been found to be more common in older patients and those taking higher dose and higher potency statins.[14]

Studies have reported reversible cognitive impairment with statin use, both in patients with previously intact cognition and in those with pre-existing cognitive impairment.[15-17] This prompted the US Food and Drug Administration to change the prescribing information for statins* and has been noted by the Australian Therapeutic Goods Administration†.

A recent randomised controlled trial in younger patients suggested that compared to placebo, those prescribed statins were more likely to report a loss of energy and worsening exertional fatigue over six months of treatment.[18] This effect may have considerable impact on older patients with less functional reserve.

* www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm293623.htm [cited 2013 May 3]

† www.tga.gov.au/safety/alerts-medicines-statins-120302.htm [cited 2013 May 3]

Table 2 **Age-associated factors that increase the risk of rhabdomyolysis with statins**

Risk factor	Mechanism	Association with old age
Concomitant medicines	Pharmacokinetic drug–drug interactions increase exposure to statins (vary between statins) Pharmacodynamic interactions with other drugs that cause myopathy	Increased prevalence of polypharmacy
Comorbidity		
Renal and hepatic impairment	Increased exposure to statins	Decreased renal and hepatic function in old age
Hypothyroidism	Also causes myopathy	Increased prevalence and difficult clinical diagnosis in old age
Severe inter-current illness	Impaired metabolism results in increased exposure to statins and may also cause myopathy	Increased prevalence in old age
Low body weight	Increased exposure to statins and lower muscle mass	Weight decreases, particularly muscle mass, in old age and frailty

Adapted from Statins, macrolides and rhabdomyolysis. Medicines Safety Update No 5. Therapeutic Goods Administration; 2010 Oct.

Drug interactions

Gemfibrozil is the drug most commonly associated with statin-induced myopathy. When taken concomitantly it inhibits the hepatic uptake of statins (via the organic anion transporter polypeptide 1B1) and their biotransformation by glucuronidases. There is a smaller increase in the risk of myopathy with co-administration of other fibrates and statins because this pharmacokinetic interaction does not occur. The metabolism of atorvastatin and simvastatin is inhibited by cytochrome P450 3A4 inhibitors (for example macrolide antibiotics, amiodarone), increasing the risk of adverse effects (see Drug interactions: Fatal rhabdomyolysis following voriconazole and simvastatin, Aust Prescr 2012;35:88-9).

When should treatment be stopped?

When healthcare professionals and patients agree that there is no clinical benefit of treatment or the risks are greater than any potential benefit, treatment should be stopped. Withdrawal or deprescribing of statins should be considered when:

- the potential benefits are no longer clinically relevant. In patients with severe physical or cognitive impairments, or those in their last year of life, therapeutic aims often change from preventative to palliative and reducing the risk of vascular events or mortality may not be relevant.
- patients have serious adverse effects such as myositis, rhabdomyolysis or severe hepatic failure
- patients have symptoms or signs consistent with adverse effects in a temporal pattern consistent with statin exposure, such as myalgia, moderate or severe elevation of hepatic enzymes, cognitive impairment or fatigue
- patients need medicines that interact with statins (increasing the risk of toxicity).

Good opportunities to discuss withdrawal of statins include comprehensive health assessments by general practitioners or specialists, assessments on admission to or discharge from hospital or on entry to residential aged-care facilities, and after medication reviews by accredited pharmacists.

Conclusion

Evidence supports statin use for secondary prevention of coronary heart disease in older adults. However, this age group has an increased risk of adverse events from statins, particularly myopathy. The effect of these drugs on frailty, disability and institutionalisation is not well established. They are likely to decrease the risk of these outcomes by preventing vascular events, but to increase the risk by causing myopathy.

Randomised trials in older people (frail and robust) with clinically relevant endpoints are required to inform therapy in this large and growing patient population. Management of older adults relies on extrapolation of the available evidence and frequent reassessment as the patient's physiology, pathology, function and priorities change over time. ◁

Conflict of interest: none declared

Acknowledgement: Danijela Gnjidic is supported by a National Health and Medical Research Council Early Career Fellowship.

Q:

SELF-TEST QUESTIONS

True or false?

1. Statins are associated with a decrease in haemorrhagic stroke in secondary prevention studies of people with cerebrovascular disease.
2. Macrolides increase the risk of adverse effects with atorvastatin and simvastatin.

Answers on page 107

REFERENCES

1. Morgan TK, Williamson M, Pirotta M, Stewart K, Myers SP, Barnes J. A national census of medicines use: a 24-hour snapshot of Australians aged 50 years and older. Med J Aust 2012;196:50-3.
2. Kronmal RA, Cain KC, Ye Z, Omenn GS. Total serum cholesterol levels and mortality risk as a function of age. A report based on the Framingham data. Arch Intern Med 1993;153:1065-73.
3. Lewington S, Whitlock G, Clarke R, Sherliker P, Emberson J, Halsey J, et al. Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths. Lancet 2007;370:1829-39.

4. Afilalo J, Duque G, Steele R, Jukema JW, De Craen AJ, Eisenberg MJ. Statins for secondary prevention in elderly patients: a hierarchical Bayesian meta-analysis. J Am Coll Cardiol 2008;51:37-45.
5. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino 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;366:1267-78.
6. Lacroix AZ, Gray SL, Aragaki A, Cochrane BB, Newman AB, Kooperberg CL, et al. Statin use and incident frailty in women aged 65 years or older: prospective findings from the Women's Health Initiative Observational Study. J Gerontol A Biol Sci Med Sci 2008;63:369-75.
7. Gnjidic D, Le Couteur DG, Blyth FM, Travison T, Rogers K, Naganathan V, et al. Statin use and clinical outcomes in older men: a prospective population-based study. BMJ Open 2013;3:e002333.
8. McGuinness B, Craig D, Bullock R, Passmore P. Statins for the prevention of dementia. Cochrane Database Syst Rev 2009;2:CD003160.
9. McGuinness B, O'Hare J, Craig D, Bullock R, Malouf R, Passmore P. Statins for the treatment of dementia. Cochrane Database Syst Rev 2010;8:CD007514.
10. Padala KP, Padala PR, McNeilly DP, Geske JA, Sullivan DH, Potter JF. The effect of HMG-CoA reductase inhibitors on cognition in patients with Alzheimer's dementia: a prospective withdrawal and rechallenge pilot study. Am J Geriatr Pharmacother 2012;10:296-302.
11. Law MR, Wald NJ, Rudnicka AR. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. BMJ 2003;326:1423.
12. Zhou Z, Rahme E, Abrahamowicz M, Tu JV, Eisenberg MJ, Humphries K, et al. Effectiveness of statins for secondary prevention in elderly patients after acute myocardial infarction: an evaluation of class effect. CMAJ 2005;172:1187-94.
13. Pasternak RC, Smith SC Jr, Bairey-Merz CN, Grundy SM, Cleeman JI, Lenfant C. ACC/AHA/NHLBI clinical advisory on the use and safety of statins. Circulation 2002;106:1024-8.
14. Sattar N, Preiss D, Murray HM, Welsh P, Buckley BM, De Craen AJ, et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. Lancet 2010;375:735-42.
15. Evans MA, Golomb BA. Statin-associated adverse cognitive effects: survey results from 171 patients. Pharmacotherapy 2009;29:800-11.
16. King DS, Wilburn AJ, Wofford MR, Harrell TK, Lindley BJ, Jones DW. Cognitive impairment associated with atorvastatin and simvastatin. Pharmacotherapy 2003;23:1663-7.
17. Wagstaff LR, Mitton MW, Arvik BM, Doraiswamy PM. Statin-associated memory loss: analysis of 60 case reports and review of the literature. Pharmacotherapy 2003;23:871-80.
18. Golomb BA, Evans MA, Dimsdale JE, White HL. Effects of statins on energy and fatigue with exertion: results from a randomized controlled trial. Arch Intern Med 2012;172:1180-2.

FURTHER READING

Smith J. Appropriate primary prevention of cardiovascular disease: does this mean more or less statin use? Aust Prescr 2011;34:169-72.

Your questions to the PBAC

Gabapentin

Readers are invited to write in with their questions about decisions of the Pharmaceutical Benefits Advisory Committee (PBAC). *Australian Prescriber* publishes selected questions from readers, together with answers from the PBAC. Questions may address issues such as regulatory decisions, pharmaceutical benefits listings and withdrawals.

This exclusive arrangement helps *Australian Prescriber* readers understand how the contents of the Pharmaceutical Benefits Scheme (PBS, see www.pbs.gov.au) are determined.

Letters and responses are reviewed by the Editorial Executive Committee and may be edited before publication. It may not be possible to reply to all individual questions.

I noted with interest in the latest edition of NPS RADAR that pregabalin has been approved for neuropathic pain. The stated justification is 'non-inferior in efficacy and safety to amitriptyline and gabapentin (from indirect comparisons)'.[1]

Later it is stated that gabapentin is an effective treatment for neuropathic pain, but is not subsidised on the PBS for that indication. I would add that it has been available for many years and its dosage and adverse effects are well known to prescribers.

Many patients with neuropathic pain have been paying very high prices for their gabapentin for 10 years or more. The recent decision has created the illogical situation in which long-standing users of gabapentin, who are controlled on a well understood drug, will be paying more than patients being started on a much newer drug with less well established efficacy and safety.

Does the PBAC intend to rectify this scenario?

Gillian Shenfield
Clinical pharmacologist
Sydney

REFERENCE

1. Pregabalin (Lyrica) for neuropathic pain. NPS RADAR. 2012 Dec. Updated 2013 Apr.

PBAC response:

Gabapentin is currently available as a pharmaceutical benefit in Australia for the treatment of partial epileptic seizures which are not controlled satisfactorily by other antiepileptic drugs, however it is not listed for neuropathic pain. The PBAC has in the past rejected applications for the subsidy of gabapentin for the treatment of neuropathic pain.

The grounds for rejection were lack of evidence in the proposed population, as the clinical trial data did not reflect the population covered by the proposed PBS restriction, and uncertain cost-effectiveness in this patient group. Any re-submission must address those matters. It may provide new data or modify the previously requested indication.

In order to facilitate the listing of gabapentin for neuropathic pain, Professor Sansom, the former Chair of the PBAC, had held meetings with pain specialists. The Department of Health and Ageing is also in contact with sponsors of gabapentin to try to progress its listing for neuropathic pain. The PBAC would consider any submission proposing the listing of gabapentin as a pharmaceutical benefit for this condition on its merits.