Lipid lowering in the ageing population

Optimal care of older patients is a challenge for evidence-based medicine. In the past, older patients have tended to be under represented in clinical trials and are more vulnerable to harm from their medications. As age increases, patients tend to have difficulty participating in treatment decisions and concordance can be poor.

Mike Kirby **Visiting Professor, Faculty of Health & Human Sciences, Centre for Research in Primary & Community Care, University of Hertfordshire**
email **kirbym@globalnet.co.uk**

Cardiovascular disease (CVD) remains the main cause of death in the UK, accounting for almost 198,000 deaths each year.[1] The recognition of this fact led to the Department of Health placing the reduction in CVD as a priority in their initiative to reduce health inequalities relating to life expectancy. In 2009/2010, the NHS health check for people in England aged between 40 and 74 years was implemented. This is a universal vascular risk assessment and management programme.[2]

People over the age of 74 years, simply by virtue of their age, are at higher risk of cardiovascular events, and cardiovascular risk in elderly patients is generally underestimated according to non-age specific assessment.[3] As a general principle, target values for treatment decisions based on cholesterol levels in adults should be adopted without age limitation, especially in the otherwise healthy and independent individuals. Clearly, there are special considerations for the old (>75 years) and the very old (>85 years), because of comorbidity, dependency and end-stage dementia, which will limit life expectancy.[4] Life expectancy in this group of patients may also involve the consequences of competing causes of death, such as cancer and infection.[5,6] In such patients, addressing cholesterol levels is clearly unwarranted.

We know that raised levels of cholesterol in patients over the age of 50 years can be associated with increased cardiovascular risk and mortality, and there is a well proven, positive relationship between a certain cholesterol level and cardiovascular risk. Additionally, there is no evidence of a threshold below which lower cholesterol levels are not associated with a lower risk, and we have come to accept that cholesterol reduction is an effective approach for individuals at high cardiovascular risk regardless of their baseline cholesterol level.

The evidence base

There is evidence of benefit of cholesterol lowering in patients under the age of 80 years. For those patients older than 80 years, there is also some evidence of benefit from observational studies.[7] In one of these studies there was a trend towards benefit of statin therapy in those aged 80–85 years compared with those aged over 85 years. However, as age increases, the correlation between low-density lipoprotein (LDL) cholesterol and cardiovascular risk becomes attenuated, and more so in men than in women.[8] The benefit of lowering cholesterol in different age groups is to be found in the results from the Cholesterol Treatment Trialists' (CTT) Collaborators systematic, prospective meta-analysis. This study reported data from 14 randomised trials involving over 90,000 participants. The investigators concluded that those aged over 65 years had a 19% reduction in the risk of a major cardiovascular event compared with a 22% reduction in risk in those aged under 65 years.[9]

Clearly, both coronary and cerebrovascular atherosclerosis in older patients will be a growing clinical problem, because of demographic changes. Despite this fact, cardiovascular risk in elderly patients has, in the past, been under managed according to several epidemiological studies.[10-12] To compound this problem, in a North American study, elderly patients with coronary heart disease who were at the highest risk for recurrent disease appeared to be the least likely to receive preventative treatment.[12] This is set against the backdrop that cholesterol remains an important modifiable risk factor in patients older than 65 years.[13] Many of these patients will have concurrent conditions such as diabetes, hypertension and vascular disease and will benefit from statin therapy.

The evidence for the benefit of treating older patients has slowly accumulated. Prior to 2002, clinical evidence of the benefits of statins in patients older than 65 years of age came mainly from subgroup analysis of larger studies. A meta-analysis of older subgroups in the large statin trials indicated that relative risk reductions for older patients on statin therapy were similar to those for younger patients, although absolute risk reduction was greater for those aged over 65 years of age.[14] There was scepticism about applying this data to all elderly patients, because many of the trials defined an upper age limit of 75 years of age.

The Heart Protection Study included patients from 40 to 80 years of age, and the clinical benefit of statin treatment was consistent across subgroups defined by age. Of note, individuals aged 75–80 years of age at study entry benefited, the difference in the rate of major coronary events in the simvastatin group versus placebo was 21·3% versus 32·4% (p=0·0002).[15]

The PROSPER trial focused exclusively on an older cohort (70–83 years of age). All patients had a history of vascular disease or had a high-risk profile, and importantly, more than half the participants were women. After a mean follow-up of 3·2 years, pravastatin treatment reduced the relative risk of coronary death, non-fatal myocardial infarction (MI), and fatal or non-fatal stroke significantly by 15% (p=0·014) and coronary heart disease (CHD) death by 34% (p=0·043).[16] There was no reduction of risk for stroke in the PROSPER study,[16] whereas there was a proportional reduction in the rate of first stroke (25%) in the Heart Protection Study, regardless of the patients age.[15,17]

A further analysis of the PROSPER trial, published in 2005, concluded that in people over 70 years of age, high-density lipoprotein (HDL) cholesterol appeared to be a key predictor of risk and of treatment benefit with statins. The authors concluded that statin therapy could be usefully targeted for those with an HDL-cholesterol <1·15 mmol/l or an LDL-cholesterol/HDL-cholesterol ratio >3·3 mmol/l.[18]

A meta-analysis published in 2008 was designed to determine whether statins reduce all-cause mortality in elderly patients with CHD. It included nine trials encompassing 19,569 patients with an age range of 65–83 years. Pooled rates of all-cause mortality were 15·6% with statins and 18·7% with placebo. There was a relative risk reduction of 22% over five years. In addition to this, statins reduced CHD mortality by 30% and non-fatal MI by 26%. Revascularisation was reduced by 30% and stroke by 25%. The authors concluded that statins reduce all-cause mortality in elderly patients, and the magnitude of this effect is substantially larger than previously estimated.[19] Despite the evidence base, concerns have been raised because of limited data showing a reduction in all-cause mortality. However, in this meta-analysis, statins did reduce all-cause mortality by 22%, and the number needed to treat to save one older patient was 28.

Concordance issues

A major problem that needs to be addressed is long-term compliance[20,21] as muscular aches and pains are a common cause of discontinuation.[22] In very frail individuals, great caution is needed before embarking on lipid-lowering therapy with a statin, because of the probable increased risk of muscle disease and related side effects. Muscle problems increase with serum concentration of statin and many factors can potentially affect this concentration. These include body size and sex (volume of distribution), renal and hepatic function, age, hypothyroidism, debilitation, diabetes, concomitant medications and genetic factors. Concomitant medications that affect statin metabolism include fibrates, gemfibrozil in particular, and other medicines such as amiodarone,

azole antifungals, macrolide antibiotics, and even grapefruit juice.

Muscle problems associated with statins are nearly always reversible on withdrawal. Muscle pain is common in middle-aged patients and on the whole, unlikely to be due to statin treatment. Measurement of creatinine kinase in such patients can exclude myopathy and allow safe continuation of treatment. A trial of discontinuation can be helpful in establishing cause and effect. When intolerance occurs and lipid lowering is strongly indicated, the use of low-dose statin combined with ezetimibe or a trial of nicotinic acid with laropiprant can be a useful practical approach. Fibrates or anion exchange resins may also be considered if statins are not tolerated; however, the combination of an anion exchange resin, fibrate or nicotinic acid with a statin is not recommended in the NICE guidance due to the current lack of outcome studies.[23]

The decision to stop statins should not be taken without due consideration as discontinuation of statin therapy following an acute MI was associated with higher mortality in a study using the UK General Practice Research Database (GPRD) conducted between 2002 and 2004.[24]

Setoguchi et al have demonstrated clearly that medical therapy is very valuable after MI in a large cohort of community dwelling elderly patients whose mean age was 80 years and of whom 73% were women,[25] but persuading patients of this age to take the medication regularly is a major challenge. The American College of Cardiology and the American Heart Association advocate optimal medical therapy (OMT) as an appropriate initial management strategy regardless of age, and the data from the COURAGE trial support this approach in patients aged over 65 years.[26]

Additional benefits

In the Canadian Study of Health and Aging, lipid lowering therapy was associated with a lower risk of Alzheimer's disease in those younger than 80 years.[27] Statins also appear to be protective against non pathological fracture in older women and are compatible with the hypothesis that statins increase bone mineral density and may decrease the risk of osteoporotic fractures.[28] Subset analysis of the JUPITER trial, which involved apparently healthy older persons without hyperlipidaemia but with elevated high-sensitivity C-reactive protein (CRP), showed that in patients aged 70 years or over, rosuvastatin reduced the rate of major cardiovascular events and absolute reductions in event rates were greater in older persons.[29] In the SPARCL study, atorvastatin was shown to reduce stroke, transient ischaemic attack (TIA), cardiac events and revascularisation in elderly (65 years and older) patients with recent stroke or TIA.[30]

Conclusion

Cardiovascular disease is the leading cause of death in men and women older than 65 years. In public health terms prevention is a national priority. The approach should be multifactorial but dyslipidaemia contributes significantly to risk even in old age. The evidence supports lipid lowering therapy in older persons, but both healthcare provider and patient adherence to statins is suboptimal. Those most likely to benefit often seem the least likely to receive it. The key is as always, giving the right drug to the right patient at the right time, and making sure they take it.

I have received funding for research, advice, conference attendance, and lecturing from the pharmaceutical industry

References

1. Allender S, Peto V, Scarborough P et al (2008). Coronary heart disease statistics. BHF: London. Available at www.heartstats.org Accessed 06/08/10.
2. Department of Health. Vascular Programme briefing packs. Available at: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_098627 Accessed 06/08/10
3. D'Agostino RB, Russell MW, Huse DM, et al. Primary and subsequent coronary risk appraisal: new results from the Framingham Study. *Am Heart J* 2000;**139**: 272
4. Sinclair AJ. Diabetes in old age: changing concepts in the secondary care arena. *J Roy Coll Phys* 2000; **34**: 240–4
5. Schatz IJ, Masaki K, Yano K, et al. Cholesterol and all-cause mortality in elderly people from the Honolulu Heart Program: a cohort study. *Lancet* 2001; **358**: 351–55

6. Weverling-Rijnsburger AW, Blauw GJ, Lagaay AM, et al. Total cholesterol and the risk of mortality in the oldest old. *Lancet* 1997; **350**: 119–23
7. Aronow WS, Ahn C. Incidence of new coronary events in older persons with prior myocardial infarction and serum low-density lipoprotein cholesterol ≥125mg/dl treated with statins versus no lipid-lowering drug. *Am J Cardiol* 2002; **89**: 67–69
8. Anum EA, Adera T. Hypercholesterolaemia and coronary heart disease in the elderly: a meta-analysis. *Ann Epidemiol* 2004; **14**: 705–21
9. Baigent C, Keech A, Kearney PM, et al. The cholesterol Treatment Trialists' (CTT) Collaborators: 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
10. DeWilde S, Carey IM, Bremnar SA, et al. Evolution of statin prescribing 1994-2001: a case of agism but not of sexism? *Heart* 2003; **89**: 417–21
11. Gaw A. The care gap: underuse of statin therapy in the elderly. *Int J Clin Pract* 2004; **58**: 777–85
12. Ko DT, Mamdani M, Alter DA. Lipid-lowering therapy with statins in high-risk elderly patients: the treatment-risk paradox. *JAMA* 2004; **291**: 1864–70
13. Deedwania P, Stone PH, Bairey Merz CN, et al. Effects of intensive versus moderate lipid-lowering therapy on myocardial ischaemia in older patients with coronary heart disease: results of the Study Assessing Goals in the Elderly (SAGE). *Circulation* 2007; **115**: 700–707
14. LaRosa JC, He J, Vupputuri S. effect of statins on risk of coronary disease: a meta-analysis of randomized controlled trials. *JAMA* 1999; **282**: 2340–46
15. Collins R, Armitage J, Parish S, et al, for the Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet* 2003; **361**: 2005–16
16. Shepherd J, Blauw GJ, Murphy MB, et al, for the PROSPER Study Group: Prospective Study of Pravastatin in the Elderly at Risk: Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet* 2002; **360**: 1623–30
17. Heart Protection Study Collaborative Group. Effects of cholesterol-lowering with simvastatin on stroke and other major vascular events in 20,536 people with cerebrovascular disease or other high-risk conditions. *Lancet* 2004; **363**: 757–76
18. Packard CJ, Ford I, Robertson M, et al. Plasma lipoproteins and apolipoproteins as predictors of cardiovascular risk and treatment benefit in the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER). *Circulation* 2005; **112**: 3058–65
19. Afilalo J, Duque G, Steele R, et al. Statins for secondary prevention in elderly patients: a hierarchical Bayesian meta-analysis. *J Am Coll Cardiol* 2008; **51**: 37-45
20. Jackevicius CA, Mamdani M, Tu JV. Adherence with statin therapy in elderly patients with and without acute coronary syndromes. *JAMA* 2001; **288**: 462–67
21. Benner JS, Glynn RJ, Mogun H, et al. Long-term persistence in use of statin therapy in elderly patients. *JAMA* 2002; **288**: 455–61
22. Thompson PD, Clarkson P, Karas RH. Statin-associated myopathy. *JAMA* 2003;**289**: 1681–90
23. NICE guideline CG67. Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. May 2008 www.nice.org.uk Accessed 06/08/10
24. Daskalopoulou SS, Delaney JAC, Filion KB, et al. Discontinuation of statin therapy following an acute myocardial infarction: a population-based study. *Eur Heart J* 2008; **29**: 2083–91
25. Setoguchi S, Glynn RJ, Avorn J, et al. Improvements in long-term mortality after myocardial infarction and increased use of cardiovascular drugs after discharge: a 10-year trend analysis. *J Am Coll Cardiol* 2008; **51**: 1247–54
26. Koon TK, Sedlis SP, Boden WE, et al. Optimal medical therapy with or without percutaneous coronary intervention in older patients with stable coronary disease. *J Am Coll Cardiol* 2009; **54**: 1303–1308
27. Rockwood K, Kirkland S, Hogan DB, et al. Use of lipid-lowering agents, indication bias, and the risk of dementia in community-dwelling elderly people. *Arch Neurol* 2002; **59**: 223–27
28. Chan K, Andrade S, Boles M, et al. Inhibitors of hydroxymethylglutaryl-coenzyme A reductase and risk of fracture among older women. *Lancet* 2009; **355**: 2185–88
29. Glynn RJ, Koenig W, Nordestgaard BC, et al. 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**: 488–96
30. Chaturvedi S, Zivin J, Breazna A, et al. Effect of atorvastatin in elderly patients with a recent stroke or transient ischaemic attack. *Neurology* 2009; **72**: 688–94