Maximising the benefits and minimising the harms of statins

Aseem Malhotra MRCP, **Andrew Apps** MRCP, **Simon Capewell** MD, DSc

Maximum dose statin therapy irrespective of total cholesterol is well established for the secondary prevention of cardiovascular events. After acute coronary syndrome (ACS) such therapy is shown to reduce all-cause mortality by an apparently impressive 22 per cent in two years.[1] The European Society of Cardiology thus recommends that all patients presenting with acute myocardial infarction receive high-intensity statins early during admission unless contraindicated.[2]

Discussing risk/benefit with patients

A potentially more useful way of understanding this evidence is the numbers needed to treat (NNT). Using relative risk reduction as opposed to absolute risk reduction or NNT is a common way of misleading the public. For example in those with established heart disease the NNT for mortality is 83 over five years.[3] But that doesn't mean that every patient benefits a little rather that 82 of those 83 patients will receive no mortality benefit over a five year period. Discussing the risk/benefit ratio in this detail with the patient affords better informed decision making. This may be crucial before contemplating a temporary cessation of therapy when new symptoms, possibly drug related, are encountered and which significantly impair quality of life. If we assume a constant but different risk over five years for those either on or not on statins, the risk of death from cessation of the drug per day in this cohort is approximately 1:150,026 or 1 in 10,787 over two weeks. Such information is potentially valuable to both patient and doctor in making informed decisions when concerns regarding possible side-effects are raised.

Statins for primary prevention

The potential benefits of statins in primary prevention raise very different issues. Statin mortality reduction diminishes as risk decreases. Recent recommendations by NICE to offer statins to those with a <20 per cent risk of cardiovascular disease (CVD) over 10 years have therefore generated controversy. Independent analysis of those individuals at low risk in the largest and most comprehensive meta-analysis, carried out by Cholesterol Treatment Trialists Collaboration, revealed no overall mortality benefit.[4] With zero survival benefit the question then moves to non-mortality benefits and harms. The same analysis demonstrated a 1 in 140 reduction in non-fatal heart attack or stroke over five years but no reduction in serious illness in those with a 10 per cent risk.

However, there are understandable limitations in relying purely on industry-sponsored RCTs which are primarily designed to determine the benefits of statins, particularly to actually determine the true incidence of side-effects. In part this is due to the fact that the clinical trial populations studied in pre-marketing trials are highly selected. For example, industry sponsored trials include pre-randomisation run-in periods where those individuals who fail to tolerate statins in addition to placebo non-compliers are excluded. RCT patients therefore do not often represent the true population, many of which have multiple co-morbidities, that will actually take the drugs in the real world. Such RCTs may thus seriously underestimate adverse effects such as muscle pain or cognitive impairment and also fail to detect drug interactions, *eg* amlodipine and statins.

A large uncontrolled observational study revealed that 17.4 per cent of patients had a 'statin adverse effect' documented but 85 per cent of those recommenced and were then able to tolerate a lower dose or different statin for at least a year.[5] The uncontrolled nature of this study is clearly not gold standard. But a recent article by Feingold *et al,* which concluded that there are no significant differences in rates between adverse effects of statins versus placebo in industry sponsored RCTs, is unhelpful.[6] This shows a clear lack of appreciation of critical issues mentioned above. A meta-analysis of RCTs that are not primarily designed to elucidate adverse effects simply adds false precision to biased estimates.[7]

Furthermore, the majority of RCTs have not systematically elicited information on many potential adverse effects such as fatigue or cognitive dysfunction, which are among the most commonly reported statin complaints by patients. A double blinded RCT published in the *Archives of Internal Medicine* involving 1016 low risk patients receiving simvastatin 20mg, pravastatin 40mg or placebo revealed that both drugs had a significant adverse effect on energy/fatigue exercise score with up to 40 per cent of women reporting reduced energy or fatigue with exertion.[8]

Pfizer's own patient leaflet of atorvastatin notes 'common side-effects that affect up to 1 in 10 patients' on the drug include 'sore throat, nausea, digestive problems, muscle and joint pain, and increase in blood sugar levels.'[9] Although the majority of these symptoms might well be reversible on cessation of the drug, the small increased 0.5–1.1 per cent risk of type 2 diabetes now directly attributed to statins should not be dismissed lightly.

Promoting healthy lifestyles

For some patients the chances of developing a life-altering medical condition at rates similar to preventing the most common benefit (developing a non-fatal heart attack) may guide the decision. Furthermore, a patient at low risk can still receive the same poten-

tial benefit of myocardial infarction risk reduction from eating an apple a day[10] and a 30 per cent reduction in a high risk group (NNT=61 for heart attack, stroke or death) by consuming a handful of nuts or four tablespoons of extra virgin olive oil daily.[11]

Indeed 80 per cent of CVD is attributable to lifestyle factors including an unhealthy diet, smoking and lack of physical activity. For those individuals at low risk it is clear that the benefits of statins are modest at best. They should not offer the illusion of protection that will enable many individuals to continue to engage in unhealthy lifestyle behaviours.[12] Rather than advocating the blanket prescription of statins to those at low risk of CVD, presenting information to patients through use of NNTs or absolute risk and away from scaremongering either through exaggerating the benefits of statins or risks of cessation when side-effects are disabling would instead advocate a more transparent approach to healthcare and a 'patient-centred view'. Professional societies aspire towards making recommendations free from commercial influence. However, moving the health system away from too much medicine may require a bottom up rather than a top down approach. Our patients deserve no less.

References

1. Bavry AA, *et al. Am J Cardiovasc Drugs* 2007;7(2):135–41.
2. European Society of Cardiology. *Essential messages from the European Society of Cardiology guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation.* 2012.
3. The NNT. Statins given for 5 years for heart disease prevention (with known heart disease). November 2013. http://bit.ly/1x5Xwmi.
4. Abramson John D, *et al. BMJ* 2013;347:f6123.
5. Zhang H, *et al. Ann Intern Med* 2013;158:526–34.
6. Finegold JA, *et al. Eur J Prev Cardiol* 2014;21(4):464–74.
7. Golomb BA. *Eur J Prev Cardiol* 2014 doi: 10.1177/ 2047487 314533085 .
8. Golomb BA, *et al. Arch Intern Med* 2012;172:1180–2.
9. Pfizer. *Lipitor. Patient Information Leaflet.* August 2013.
10. Briggs ADM, *et al. BMJ* 2013;347:f7267.
11. Estruch R, *et al. N Engl J Med* 2013;368:1279–90.
12. Redberg RF. *JAMA Intern Med* 2014;174:1046.

Declaration of interests

None to declare.

Dr Malhotra is honorary consultant cardiologist, Department of Cardiology Frimley Park Hospital, and consultant clinical associate to the Academy of Medical Royal Colleges, Dr Apps is cardiology registrar, Wycombe General Hospital, and Simon Capewell is professor of clinical epidemiology, University of Liverpool

Forthcoming events

The forthcoming events section highlights some of the many courses, meetings and conferences of interest to prescribers planned over the coming months

Dermatology half day

Date: 26 February
Venue: Wortley House, Scunthorpe
Tel: 0203 188 7786
Email: humberside@rcgp.org.uk
Website: www.rcgp.org.uk
A half-day dermatology course looking at common skin conditions such as eczema, psoriasis, red and spotty faces, non-melanoma skin cancer, and allergy.

BMJ masterclasses: GP general update

Date: 6–7 March
Venue: Etc Venues, Bishopsgate London
Tel: 0207 111 1106
Email: info.masterclasses@bmj.com
Website: http://masterclasses.bmj.com
The two days will focus on 12 core topics in primary care and collate the most recent guidelines, hottest evidence and expert advice. Topics include: cardiology, mental health, end-of-life care, endocrinology, contraception, diabetes, musculoskeletal medicine, paediatrics, respiratory medicine, and ophthalmology.

One day essentials: women's health

Date: 10 March
Venue: Macdonald Burlington Hotel, Birmingham
Tel: 0203 188 7658
Email: rcgpconferences@email.rcgp.org.uk
Website: www.rcgp.org.uk
A one-day conference providing expect specialist clinical training and essential information on women's health.

Essential dermatology

Date: 17 March
Venue: Rowley Mile Conference Centre, Newmarket
Tel: 01223 884417/324
Email: eanglia@rcgp.org.uk
Website: www.rcgp.org.uk
This day covers the essential information to enable a GP and dermatology nurse practitioners to cope with the vast majority of conditions encountered in day-to-day general practice.

Anyone who wishes to publicise details of events for GPs and pharmacists (at no charge) should e-mail them to: prescriber@wiley.com