Statins in the prevention of cardiovascular disease

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Since their launch in the late 1980s, statins have become the most prescribed drugs worldwide. However, the 2014 NICE guidance extending their use to lower-risk patients triggered controversy over their side-effects and alleged overprescribing. This article gathers the views of clinicians and opinion leaders on the current place of statins in the prevention of cardiovascular disease.

The NHS spent £150 million on statins last year and if every one of the cholesterol-lowering tablets was taken as prescribed they would have been used at the astounding rate of 124 per minute. But, at around 3p each thanks to the drugs going off patent, they are widely regarded as a safe and cost-effective way of reducing harmful levels of low-density lipoprotein (LDL) cholesterol to mitigate the risk of strokes and heart attacks.

Statins inhibit the enzyme HMG-CoA reductase, which controls cholesterol production in the liver, thus lowering circulating levels of LDL cholesterol and, as clinical evidence has shown a clear correlation between reduction in LDL cholesterol and the lowering of cardiovascular risk, they are seen as an efficient way to combat one of the nation’s greatest health threats.

A 2015 study, commissioned by the BHF, showed a 44.4 per cent drop in death rates among men and a 43.6 per cent drop among women in the UK from cardiovascular disease in the 10 years to 2011.¹ That triumph was not driven by statins alone as smoking cessation and improved diet and lifestyle played important roles. But they have been viewed as a tried and tested frontline weapon against heart disease and the mounting jeopardy inflicted by obesity and type 2 diabetes. The success in reducing cardiovascular mortality was tempered by a rise in morbidity.

Prescribing controversy
There is, however, a schism over the role of statins in controlling cardiovascular disease (CVD), which was ignited after the latest NICE clinical guidance, delivered in July 2014, that offered atorvastatin 20mg for primary prevention for anyone with a 10 per cent risk of CVD over the next decade, extending the reach from people with a 20 per cent risk.² In theory, this took the number who could take statins in the UK from seven million to around 12 million – approaching 40 per
cent of the adult population – and drew alarmed calls that the nation was being overmedicated and even placed in harm’s way from a greater risk of adverse effects than previously accepted. Clinicians have challenged statins’ reputation, alleging that an “epidemic of misinformation” surrounds these drugs.

Figures from the Health and Social Care Information Centre show only a modest rise of 3.5 million pills3 prescribed in the first year since the guidance, up to 65,320,625, and a study by GPs showed just a 10 per cent increase in prescribing to the new group. The NICE offer appears yet to alter the statin landscape and many clinicians believe the right people are getting statins thanks to good practice and the NHS Health Check programme, which identifies need from its health MOT for patients aged between 40 and 74 years old.

Efficacy and safety
Professor Sir Rory Collins, head of Nuffield Department of Population Health and BHF Professor of Medicine and Epidemiology at the University of Oxford, is confident that wide-ranging trials have, in the first instance, proved the link between lowering LDL cholesterol and reducing cardiovascular risk and that statins play a key role.

His view is anchored in a reservoir of research but that opinion, shared by many, has come under increasing contention from doctors who believe that the side-effects of taking statins – typically muscle pain, blood disorders, fatigue, vision problems and diabetes – mean we should put a brake on prescription.

Professor Collins maintains that the exacting multiple trials, conducted over five years and with compelling 10-year follow-up evidence, confirm the efficacy and safety of statins. He oversaw the Cholesterol Treatment Trialists Collaboration, which performed a meta-analysis of 170,000 patients, who took part in 26 randomised controlled trials that helped researchers show that every 1mmol per litre reduction in cholesterol could result in a 20 per cent reduction in risk of major vascular events such as heart attack or stroke.4

“I do find it difficult to understand why there is controversy around it,” he says. “Part of it is, I think, that people don’t understand the strengths of the randomised evidence and in general don’t understand why randomised, placebo-controlled trials are much more reliable than observational trials.

“My view is that if you look in terms of the epidemiology and the trials then the risk reduction you see with the statins is entirely consistent with it being largely if not wholly in reducing LDL cholesterol.

“It is a concern that there is a failure of understanding of the evaluation of evidence. If it can happen with something as important from a public health point of view as statins, then it is worrying. We’ve had one of the best data sets created and to see those data misunderstood and dismissed and data from observational studies, with all their problems, being used as a basis to make claims dismays me because it misleads doctors and their patients in a way that has an impact on public health. This kind of misleading coverage in the media has an impact on what people do – they actually stop taking the treatments that help prevent heart attacks and strokes.”

He also highlights that the NICE guidance offers statins to the extended group rather than it being a blanket recommendation to prescribe and, significantly, no Quality and Outcomes Framework (QOF) incentive was attached to the guidance.

He says debate about the use of statins for low-risk patients was “perfectly reasonable” but adds: “It is an offer to these people and they can choose to take them or not. What is unacceptable is to provide misleading data or claims on side-effects in order to make the argument against them choosing statins.”

Use in lower-risk patients
The antistatin lobby is concerned about pharmaceutical industry funding and that other studies show a greater incidence of side-effects. There is accross the use of statins for those at high-risk such as patients who have type 2 diabetes or have had a heart attack or stroke, but the battle lines get drawn when statins are applied to those with moderate or mild risk.

A group of nine clinicians wrote an open letter to Professor David Haslam, chair of NICE, copying in Health Secretary Jeremy Hunt, in June 2014, listing six key points including results from a double-blind randomised controlled trial that compared 1016 low-risk patients on 20mg simvastatin or 40mg pravastatin with placebo that showed an adverse effect on energy and fatigue after exertion.5 Another observational study involving 153,840 postmenopausal women, aged 50 to 80 years old, found that statins were associated with a 48 per cent increased risk of developing diabetes.6

Professor Collins adds: “I completely understand why there is confusion among GPs, they are on the front line and have to deal with patients coming in with media reports. GPs have to base their practice on the evaluations being provided to them, but when those evaluations are poorly done and misleading then it doesn’t serve them well and they cannot therefore serve their patients well. The scientific community needs to make it very clear how evidence is evaluated generally and for statins, specifically.”

The BHF is clear that statins have been key to the reduction in cardiovascular disease in the UK. “Statins have played a huge role and there is no denying that since they have been available in the 1990s, the number of people dying from heart disease has significantly reduced,” says Maureen Talbot, senior cardiac nurse with the BHF. “But we also need to acknowledge that there is now a greater understanding of healthier lifestyles and the role of better physical exercise in increasing HDL cholesterol along with a continuing decrease in the number of smokers. The BHF advises anyone with factors that lead to an increased risk of cardiovascular disease to concentrate on lifestyle factors first in discussion with their healthcare professional.”

But the charity, which runs an advice line for the public and healthcare professionals (tel: 0300 330 3311) is concerned that patients have been discontinuing medication after media reports on side-effects. “Statins have a unique ability to divide opinion,” Ms Talbot adds. “But I have a concern over people making medical decisions from something they have read or heard. They should consult with their doctor, practice nurse or specialist. There are risks in stopping medica-
Understanding side-effects
Robert Cramb, consultant chemical pathologist for HEART UK (www.heartuk.org.uk), says: “The Cholesterol Treatment Trialists’ Collaboration work showed that statins do not have long-term deleterious effects on individuals. The data convincingly shows, after grouping all the large clinical trials together and pooling results, that statins reduce the risk of cardiovascular disease and there are no harmful effects, particularly from cancer.

“There are side-effects for statins but this is true of all drugs. Statins produce the biggest cholesterol-lowering effect and the greatest reduction in cardiovascular events concomitant with maximum dose. This does have to be balanced with the incidence of side-effects.”

But the use of statins has become clouded by a statistics arms race with both sides saluting a march past of ever-increasingly powerful research data. Ranged against the pro-statin big research guns are studies that claim to show a mortality benefit for only one in 83 patients with established CVD and that 75 per cent of patients stop their statins regimen in the first year with 62 per cent citing side-effects as the main reason. Even among high-risk patients, there is significant noncompliance.

Dr Aseem Malhotra, a London-based NHS consultant cardiologist and a signatory of the letter to NICE on the 2014 clinical guidance, believes greater transparency and shared decision-making between patients and clinicians is needed to lift the fog of war. “We have an epidemic of misinformation on statins in terms of how beneficial they are and the under-reporting of side-effects,” he says. “Statins are just one example of many drugs in modern medicine that we have to critically analyse ourselves on how beneficial they are in terms of the questions that are important to patients.

“We have enough information to present in a transparent way rather than saying you must or you mustn’t take statins. I’m not saying I’m against statins, I’m saying let’s agree this is the information we have and make decisions based on that.”

The path to an agreed medical understanding will be long, he says, adding: “A key component is an inability of doctors and patients to understand risk. You have misinformed doctors and misled and misinformed patients.” Dr Malhotra believes the spotlight on statins needs to get even brighter and more searching before any chance of peace between the warring factions.

An extra consideration is those patients who cannot tolerate statins and a report in the European Journal of Preventive Cardiology in 2014, defending placebo-controlled trials, stated: “A significant number of patients stop prescribed statins, or can take only a reduced dose, because of adverse events attributed to the statin, and are then considered statin-intolerant.”

But it argued that statin-associated muscle symptoms could be attributed to the high prevalence of those symptoms that occur generally in the statin-taking population and that media misinformation raises patient expectation that the drugs will cause problems – known as the “nocebo” effect, the opposite of the placebo effect. It echoed proposals by the European Atherosclerosis Consensus Panel to offer lower doses and longer dosing intervals to help these patients remain on statins.

The history of statins
The fault lines were not that obvious in the early history of a class of drugs that came to revolutionise the approach to the global scourge of heart disease. Cholesterol, which is essential for human function, was first isolated from gallstones in 1784 and its role has beguiled scientists ever since. A century of detailed investigation helped crystallise the importance of cholesterol in maintaining cell membranes, producing key hormones and vitamin D and pinpointed its good and bad properties.

Cholesterol’s association with atherosclerosis was first reported in 1910. In the 1950s, research in California established a link between elevated levels of LDL cholesterol and heart attacks while also reporting that heart attacks were less frequent when the blood contained higher levels of high-density lipoprotein (HDL) cholesterol.

Pioneering Japanese scientist Akira Endo, working at the Sankyo company’s laboratories in Tokyo, created the first statin, mevastatin, also known as compactin, in 1972 after culturing moulds and subjecting them to 6000 different tests. Research and refinement continued into the 1980s until the first clinical trials
with patients with familial hypercholesterolemia – the inherited genetic condition that causes people to be born with abnormally high levels of cholesterol. The first commercial statin was given FDA approval in the USA in 1987.

The floodgates opened and pharmaceutical companies enjoyed booming balance sheets as statins became the most prescribed drugs in the world with Pfizer’s Lipitor (atorvastatin) peaking at annual sales of $13.3 billion (£9.3 billion).

Mr Endo, writing in the Proceedings of the Japan Academy journal in 2010, stated: “Statins have now been tested in many large-scale clinical trials, involving 90,000 subjects who were followed for five years. The results in all these studies have been consistent: treatment with statins lowers plasma LDL levels by 25–35 per cent and reduces the frequency of heart attacks by 25–30 per cent.”

Weighing up benefits and risks

The big companies have a stake in the statin market and many have funded research reinforcing their efficacy and safety, which has caused unease, but Dr Terry McCormack, a GP in Whitby and secretary of the British Hypertension Society, says: “There is confusion on both sides of the argument but my belief is that these trials were properly conducted because it would have to amount to something on a criminal level to misreport.

“The most reported side-effects are muscle pain and disturbed sleep but my experience is that they are mild and, in 30 years of practice, I have only ever come across one person who had serious side-effects with rhabdomyolysis but he was also given amiodarone and it was the co-prescription that caused problems. He had been on statins for years and was fine.

“The vast majority of the people who I prescribe statins for do very well. There is good evidence of the benefit for people at high risk but the evidence is much weaker where people are at low risk.”

Dr McCormack believes it is vital to understand the difference between absolute and relative risk when handling statin prescriptions. “If you are a fit and healthy 55-year-old nonsmoker and your risk is 10 per cent then you’d probably be the fittest 55-year-old in town and I don’t think you’d get any benefit from taking statins,” he explains. “But if you are a 40-year-old with a 10 per cent risk, you’d be a very unfit 40-year-old and would benefit from taking statins.”

He adds that a recent public talk about the benefits and risks divided an audience of GPs almost 50/50. “GPs have mixed views and people are entitled to make their own minds up – the information is all there,” says Dr McCormack.

“But headlines about statins being good one day and terrible the next do not help. Debate is good but invariably when there is controversy, people at high risk stop taking their statins because they misunderstand the argument. There is a need for responsible reporting and a responsible attitude from doctors.

“You have to look at the reduction of heart attacks over the last 10 years. Stopping smoking and improved lifestyles are the main drivers but statins are a player and are therefore important.”

New therapies to challenge statins

The lack of alternatives has concentrated the issue but two new therapies, alirocumab and evolocumab, delivered by fortnightly injections could challenge oral statins. They are monoclonal antibodies that inhibit pro-protein convertase subtilisin/kexin type 9 (PCSK9) in the liver leading to increased LDL-receptor expression and hence lowering LDL cholesterol in the bloodstream.

Results of large clinical trials presented at last year’s American College of Cardiology and published in the New England Journal of Medicine revealed that PCSK9 inhibitors could lower LDL cholesterol levels by about 60 per cent over a year,11,12 compared to statins that achieve around a 30 per cent reduction.

But the breakthrough comes with a high price tag, estimated at £6000 per patient per year, and the BHF believes the new injectables may be principally used as an alternative for patients who cannot tolerate statins and those with familial hypercholesterolemia before the cost stabilises to affordable levels for the NHS.

Trials of another new potential therapy, cholesteryl ester transfer protein inhibitors (CETP), which boost HDL cholesterol, have been dogged by Phase III trial failures but one, anacetrapib, is still pushing forward.

In the meantime, the battle to conquer cardiovascular disease in the face of rising levels of obesity and type 2 diabetes continues to be fought in GP surgeries, hospitals and laboratories every day.

References


Declaration of interests

See http://www.mjaauk.org/author/bucklandd/

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