Lipid lowering: Known knowns and known unknowns

Colin Kenny

We know that primary care teams are now following a structured and systematic approach to reducing CV risk in people with diabetes, including the extensive use of lipid-lowering treatment. A series of important trials have informed contemporary guidance, as well as the treatment-to-target option of a total cholesterol level of 5 mmol/l in the nGMS contract.

Many guidelines are now suggesting benefits of even lower cholesterol levels in people with diabetes. In turn this has raised doubts about which lipid-lowering agents to use, how to escalate the doses, and whether or not to combine agents. Some areas remain unknown – for example: how to address CV risk across the age spectrum we encounter in people with diabetes; how to actively manage different lipid sub fractions with drug treatment; and whether statins have pleiotropic effects beyond their important effect on the LDL sub-fraction.

In an article in this issue of *Diabetes & Primary Care* (Evans, p138), the case is made for the active pursuit of aggressive total cholesterol and LDL-cholesterol targets for people with diabetes, especially in those with existing CV risk. This advice is reinforced by contemporary global guidance (British Cardiac Society et al, 2005; Buse et al, 2007), which recommend the setting of ambitious total and LDL-cholesterol targets (JBS 2: total cholesterol < 4 mmol/l, LDL-cholesterol < 2.0 mmol/l; ADA: LDL-cholesterol < 2.6 mmol/l) which are considerably lower than current NICE guidance of a total cholesterol level of 5 mmol/l; although this will be the subject of an appraisal by NICE later this year.

This debate is closely linked to which statin to choose and at what dose to start treatment. Many authorities report the utility and safety of statin therapy – and I believe that it could be used as a marker for overall adherence to pharmacological therapy. If we accept that people with diabetes who have not yet had a cardiac event should be managed in the same way as those without diabetes who have had a cardiac event, then the more aggressive targets outlined in JBS 2 appear to be optimal. Simvastatin is currently the most cost-effective statin, has an important evidence base in diabetes and is inevitably the preferred statin of local prescribing advisors; however it is perceived to be less potent than others. Updated NICE guidance, and perhaps altered nGMS contract targets, may open the debate as to whether to use the more potent and more expensive statins – atorvastatin and rosuvastatin – with their benefits of more consistently achieving lower cholesterol targets. Primary care diabetes teams may have to accept that this more aggressive approach to lipid lowering is the current direction of travel.

What then of the other lipid sub-fractions – HDL-cholesterol and triglycerides? Here the evidence of interventions is much less convincing, with fewer trials. We know that low HDL-cholesterol (< 1 mmol/l in men and < 1.2 mmol/l in women) and elevated fasting triglycerides (> 1.7 mmol/l) are markers for vascular risk. Primary care teams will need to decide whether to use niacin or a fibrate on a case-by-case basis depending on response to other agents, especially if there is an isolated high triglyceride level. HDL is a complex protein with many sub-fractions, and attempts to raise it by drug therapy have proved to be difficult and in the case of torcetrapib, associated with increased mortality. More data is awaited before we can make truly informed decisions about the appropriate treatment of these sub-fraction abnormalities.

What is the evidence to support treating people with diabetes with statins across a much wider age spectrum? Younger people with type 1 diabetes may have deceptively normal lipid profiles yet have considerable CV risk. Studies in this younger age group would be much harder to do because of the much longer follow up required and lower event rate. There is insufficient evidence for the safety of statins in women of child-bearing age and decisions need to be made on a case-by-case basis and may never be truly informed.

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A frequent mantra from primary care teams is that there is little contemporary trial evidence relating to the type of individual who they encounter daily. There is some trial evidence and guidance in older age groups (Deedwania et al, 2007; Gotto, 2007), but teams are making individual judgements to continue to treat lipid abnormalities in older people than are commonly recruited into trials, partially driven by the nGMS contract's lack of upper age limits.

Pleiotropic effects of a drug are actions other than those for which the agent was specifically developed. These effects may be related or unrelated to the primary mechanism of action of the drug, and they are usually unanticipated. Statin pleiotropic effects such as increased myocardial perfusion, increased bioavailabilty of nitrous oxide, anti-inflammatory and antioxidant effects, appear to operate independently of LDL-cholesterol reduction; correlate poorly or not at all with LDL-cholesterol changes; take place rapidly; and are rapidly reversible on discontinuation of the drug (Davignon, 2004). This makes a further and intriguing case for using them consistently.

Donald Rumsfeld won a Foot in Mouth award for his *known knowns* speech when he tried to make a serious point about a situation where the context is changing and strategies are emerging. Although *we know what we know* about treating lipid abnormalities in those with type 2 diabetes, there is still a lot that *we know we don't know*, about the optimum dose and type of statin. There may equally be much that *we don't know we don't know* about the complete effects of statins, which could change and improve diabetes management as a further decade evolves. What we do know is that statin therapy appears to be the treatment par excellence for reducing CV risk in diabetes. More aggressive targets are likely in the near future, although some UK and international guidance may remain at variance. ■

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