Statins for people with type 1 diabetes: when should treatment start?

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Evidence-based clinical practice guidelines are systematically developed statements to assist practitioners and patients about health care for specific clinical circumstances. The evidence base should be obtained using an unbiased and transparent process of systematically reviewing, and appraising published clinical research, which is then synthesised into recommendations for clinical practice. There is a hierarchy of evidence, from meta-analyses or systematic reviews of randomised controlled trials, through case control or cohort studies, to expert opinion. Evidence-based guidelines have largely replaced consensus statements, where a group of experts would meet and produce a series of recommendations based on the consensus of the group.

A large evidence base supports the use of statins in people with type 2 diabetes, but there is very limited evidence for the use of statins in people with type 1 diabetes. A NICE guideline on the modification of lipids for the primary and secondary prevention of cardiovascular disease was published in 2014. This recommends considering statin treatment for the primary prevention of cardiovascular disease in all adults with type 1 diabetes, and recommends offering statin treatment to adults with type 1 diabetes who are older than 40 years of age, or who have had diabetes for more than 10 years, or who have established nephropathy, or other cardiovascular risk factors. It also recommends starting treatment with atorvastatin 20mg.

Is there any evidence behind these recommendations, and are these recommendations truly evidence based or another consensus statement from a group of experts?

Background
People with type 1 diabetes have an increased risk of cardiovascular disease. The relative risk of a cardiovascular event compared to age- and sex-matched non-diabetic control subjects is increased, particularly in women. In a publication from the Scottish Diabetes Research Network, the risk of a first cardiovascular event was doubled in men and trebled in women with type 1 diabetes compared to age- and sex-matched non-diabetic control subjects. Atherosclerotic cardiovascular disease, however, is uncommon in people under the age of 40 years so although the relative risk is high, the absolute risk of a cardiovascular event in people with diabetes in this age group is low. In the Scottish study, the most common causes of death in patients under 40 years of age were related to diabetes (coma, ketoacidosis) or other metabolic causes, whereas in those over 40 years of age circulatory causes were the most common causes of death. Interestingly, 39% of people with type 1 diabetes over 40 years of age were not on a statin.

Evidence base
The evidence base for cardiovascular risk reduction with statins in people with type 1 diabetes is very limited. A small number of people with type 1 diabetes were included in the diabetic subgroups in the large landmark secondary prevention statin trials, and most diabetic subjects were categorised as having type 2 diabetes. The Heart Protection Study (HPS) set out to recruit subjects that would not have been recruited to the earlier cardiology trials, so recruited people with peripheral vascular disease, strokes, or type 1 diabetes. There were 615 people with type 1 diabetes in HPS, and the reductions in cardiovascular events were not different from 5348 subjects with type 2 diabetes, but the confidence intervals were wide. The Cholesterol Treatment Trialists’ (CTT) Collaborators performed a meta-analysis of cholesterol-lowering therapy in 18,686 people with diabetes in 14 trials of statins, including HPS. All of these studies recruited people over the age of 40 years; 1466 subjects had type 1 diabetes, and 17,220 type 2 diabetes. There was a 21% relative risk reduction in major cardiovascular events in people with type 1 diabetes. This result did not individually reach statistical significance (95% confidence intervals 0.62–1.01) but no heterogeneity was found compared to subjects with type 2 diabetes.

Other guidelines
The Scottish Intercollegiate Guidelines Network (SIGN) guideline 116 on the management of diabetes from 2010 recommended simvastatin 40mg for people with type 1 diabetes over 40 years of age, as this was the dose that was used in HPS. A good practice point was added to consider the use of simvastatin 40mg in those under 40 years and with other important risk factors, for example microalbuminuria.

The long-awaited Joint British Societies’ consensus recommendations for the prevention of cardiovascular diseases (JBS3) were finally published in 2014. They recommended offering statins to all patients with type 1 diabetes over 50 years of age, and in the majority of patients aged 40–50. They also recommended statins in those aged 30–40 years with any of the following features: long duration of disease; poor control; persistent albuminuria or eGFR <60ml/min; proliferative retinopathy; treated hypertension; current smoking; autonomic neuropathy; raised total cholesterol or reduced HDL cholesterol; central obesity; or a family history of premature cardiovascular disease. The consensus recommendations do not indicate what proportion of patients this would be, but it must be approaching 100%! They also recommended statins for people aged 18–30 years who have type 1 diabetes and persistent albuminuria.
**NICE recommendations for future research**
The absence of an evidence base for the use of statins in people with type 1 diabetes is acknowledged in the section on research recommendations of the NICE guideline, and is recommended as an area for research.2 It states that the outcomes from the study could define the treatment recommendations made for lipid lowering in type 1 diabetes. It further acknowledges that type 1 diabetes can be diagnosed at a young age, and important questions exist as to when statins should be initiated and at what dose.

**Discussion**
It seems extraordinary that, in the absence of any substantial new evidence, the new NICE guideline extends the recommendations from an older guideline in 2004 where a much simpler approach was adopted and statins were recommended for people with type 1 diabetes over 40 years of age, or with established nephropathy, or who had diabetes for more than 10 years.3 The new guideline should have explicitly stated that there has been no new evidence since 2004 and that the present guideline writing group have come up with an expert opinion different from the group that wrote the previous guideline, although a more reasonable approach would have been to repeat the previous recommendations in the absence of any new evidence. It also seems extraordinary to recommend using atorvastatin 20mg when this dose of statins is untested in any cardiovascular outcome trial!

One reason for the confusion and contradictory recommendations in the guidelines is the concept that diabetes is not a cardiovascular disease equivalent and that there is not a general increase in cardiovascular risk in all people with diabetes.9 Some people with diabetes, probably the minority, have a risk of cardiovascular disease that is the same as that for people without diabetes, and so these people do not need to be treated with statins to reduce cardiovascular risk.

Data from Scotland indicate that many people with type 1 diabetes have suboptimal glycaemic control.5 The DCCCT demonstrated that intensive glycaemic control reduced microvascular outcomes, especially retinopathy and nephropathy.10 On epidemiological follow-up in the EDIC trial a reduction in macrovascular events was demonstrated,11 and recent data show that these reductions translate into a reduction in total mortality.12 In my expert opinion the focus of the management of adults under the age of 40 years with type 1 diabetes should be on improving glycaemic control, itself a very challenging task, and reducing the incidence of severe hypoglycaemia and diabetic ketoacidosis, as these are the causes of death in people of that age. The use of statins should be reserved until the patient reaches 40 years, when cardiovascular causes become the more common cause of morbidity and mortality, and where there is evidence that statins reduce cardiovascular risk.1

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**References**