Medicines Evidence Commentary

commentary on important new evidence from Medicines Awareness Weekly

Published: October 2013

Cardiovascular disease: risk of new onset diabetes with particular statins

Document as included in MAW

Consistent with evidence from randomised controlled trials, a large Canadian observational study has found an increased risk of new onset diabetes among statin users. This is small in absolute terms and is outweighed by the overall benefits of statins. The study suggests differences in the risk associated with particular statins, but limitations in the available data limit the conclusions that can be drawn. Health professionals should follow the [MHRA advice](#) about the risk of new onset diabetes, and use statins in accordance with [NICE guidance](#).

Overview and current advice

NICE guidance on [lipid modification](#) (currently being updated; expected publication date July 2014) recommends statin therapy as part of the management strategy for the primary prevention of cardiovascular disease (CVD) for adults who have a 20% or greater 10-year risk of developing CVD and for the secondary prevention of CVD. NICE also recommends statins for people with [type 1](#) and [type 2](#) diabetes (both of these guidelines are being updated; publication date to be confirmed). In addition NICE recommends statins as the initial treatment for all adults with [familial hypercholesterolaemia](#).

In 2010, a meta-analysis of 13 large placebo- and standard-care-controlled trials of statins found that their use was associated with an increased risk of new onset diabetes ([odds ratio](#) [OR] 1.09; 95% [confidence interval](#) [CI] 1.02 to 1.17). In absolute terms, this was equivalent to 1 additional case of diabetes per 255 (95% CI 150 to 852) people taking statins for 4 years. To set this in context, the meta-analysis authors calculated that statins are associated with a reduction in major coronary events of about 5 events per 255 people treated for 4 years (based on data from the Cholesterol Treatment Trialists’ meta-analysis of statin therapy and compared with control therapy for a 1 mmol/l reduction in LDL-cholesterol). This meta-analysis was discussed in the National Prescribing Centre MeReC Rapid Review [Statins and risk of diabetes](#).
In January 2012, the MHRA advised health professionals that statin use may be associated with a level of hyperglycaemia in some people where formal diabetes care is appropriate. The risk appears to be mainly in people already at increased risk of developing diabetes. However, the MHRA concluded that the overall benefits of statins strongly outweigh any risks, including in those at risk of developing diabetes or those with pre-existing diabetes.

New evidence

A Canadian retrospective cohort study has used healthcare records to examine the association between use of particular statins and new-onset diabetes. The researchers used data from several Ontario healthcare databases, anonymously linked by using encrypted individual health card numbers, relating to 471,250 people aged 66 years and older (median age at outset of treatment 73 years, 54% women) with no history of diabetes who were newly started on a statin (for primary prevention in 48% of people) between 1 August 1997 and 31 March 2010. The primary outcome was incident diabetes, defined as a diagnosis of diabetes in the Ontario Diabetes Database (a validated registry of all Ontarians diagnosed with diabetes).

The rate of new onset diabetes associated with each statin was compared with pravastatin, which has been found in some studies to be associated with a low risk of new onset diabetes. The authors adjusted for certain known confounders: age, sex, year of cohort entry, history of cardiac disease and cardiac procedures, Charlson comorbidity index and medication history, including use of drugs with an impact on glycaemic control (such as thiazide diuretics) in the previous 12 months.

Compared with people treated with pravastatin, the adjusted hazard ratio (HR) for new onset diabetes among those treated with atorvastatin was 1.22 (95% CI 1.15 to 1.29). Among those treated with rosuvastatin it was 1.18 (95% CI 1.10 to 1.26) and among those treated with simvastatin it was 1.10 (95% CI 1.04 to 1.17). In contrast, treatment with fluvastatin (adjusted HR 0.95, 95% CI 0.81 to 1.11) or lovastatin (adjusted HR 0.99, 95% CI 0.86 to 1.14) was not statistically significantly associated with an increased risk of new onset diabetes. Similar results were found when the results were stratified according to whether the statin was initiated for primary or secondary prevention, and in a sensitivity analysis that expanded the definition of diabetes to include any prescription for a diabetes drug or blood glucose test strips.

In absolute terms, there were about 23 new cases of diabetes per year per 1000 pravastatin users. The authors calculate that the observed increased risk was approximately equivalent to an additional 3 new cases per year per 1000 simvastatin users, 5 new cases per year per 1000 rosuvastatin users and 6 new cases per year per 1000 atorvastatin users, compared with pravastatin.

Commentary provided by the NICE Medicines and Prescribing Centre

The results of this retrospective cohort study are in keeping with evidence from randomised controlled trials, in that new onset diabetes was seen in people taking any of the statins examined (23 cases per 1000 patient years in the case of pravastatin, for example). It goes
further than this, in suggesting that there may be differences in risk between different statins. However, a single observational study, such as this one, can prove only association not causation. Observational studies are prone to confounding, which limits the conclusions that can be drawn. Unlike in the setting of a randomised controlled trial, in ‘real life’ treatment plans are chosen, changed, or actively not chosen in the light of individual patients’ risk factors, preferences and tolerability or responses to other drugs. Thus observed differences in outcomes may be due not only to the different treatments but also to differences among the patients.

In this study the authors adjusted for a number of such possible confounders but they accept that they could not adjust for important risk factors for diabetes such as weight, ethnicity and family history. In addition, data on blood lipids, glycated haemoglobin levels (HbA1c) and triglyceride concentrations were unavailable. The MHRA, in its 2012 review of the risk of new onset diabetes with statins, stated that the evidence suggests that the risk depends markedly on individual risk factors3. The risk appears to be mainly in people already at increased risk of developing diabetes: raised fasting blood glucose at baseline is a key factor in determining this increased risk and may be sufficient to identify those at risk3, but this was not taken into account in this study. Other risk factors include a history of hypertension, raised triglycerides and raised body mass index at baseline3. It is not clear if the analysis adjustment for cardiac disease included adjustment for a history of hypertension, and the analysis did not make adjustments for these other risk factors highlighted by the MHRA.

In addition, many more people were taking atorvastatin (268,254) than were taking pravastatin, the reference drug (38,470), rosuvastatin (76,774) or simvastatin (75,829), and very many more than were taking fluvastatin (5636) or lovastatin (6287). The small number of people taking fluvastatin or lovastatin and the correspondingly small number of events may explain the absence of a statistically significant effect on risk associated with these drugs – the study may simply have lacked statistical power.

Finally, although development of diabetes is clearly undesirable, we do not know what, if any, effect this had on the risk of macrovascular and microvascular outcomes among people taking statins who developed it compared with those taking statins who did not.

The results of this analysis do not suggest that health professionals should depart from the MHRA’s advice that steps should be taken to identify people who are at risk of new onset diabetes, to recognise it if it occurs, and to manage the condition appropriately3. People at risk should be monitored both clinically and biochemically according to NICE guidance3.

**Study sponsorship**

This cohort study was supported by a grant from the Ontario Ministry of Health and Long-Term Care (MOHLTC) Drug Innovation Fund and the Institute for Clinical Evaluative Sciences (ICES), a non-profit research institute sponsored by the Ontario MOHLTC.
References


About this Medicines Evidence Commentary

Medicines Evidence Commentaries form part of NICE’s Medicines Awareness Service and help contextualise important new evidence, highlighting areas that could signal a change in clinical practice. They do not constitute formal NICE guidance. The opinions of contributors do not necessarily reflect the views of NICE.

Visit Evidence Search

Copyright © 2013 National Institute for Health and Care Excellence. All Rights Reserved.