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Statins and type 2 diabetes: genetic studies on target

Published **Online** September 24, 2014 http://dx.doi.org/10.1016/S0140-6736(14)61639-1

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The topic of the side-effects of statin treatment is important and controversial. In *The Lancet*, Daniel Swerdlow and colleagues[1] used an updated meta-analysis of trials to investigate whether or not statins increased the risk of type 2 diabetes, and a genetic approach to address how statins might increase the risk of the disorder. Using data from 20 randomised controlled trials, they confirm findings from previous reports that statin treatment increased the risk of incident type 2 diabetes, with an odds ratio (OR) of 1·12 (95% CI 1·06–1·18) versus controls. In contrast to previous efforts, they then studied common genetic variants near the gene encoding the HMG-coenzyme A (HMGCoA) reductase protein—the enzyme inhibited by statins to lower LDL cholesterol. Genome-wide association studies had previously identified these variants as associated with altered circulating LDL cholesterol concentrations with robust levels of statistical confidence.[2] Using these genetic variants and a combination of their own and published data, the investigators provide evidence that reduced HMGCoA activity causes a slight increased risk of type 2 diabetes (rs17238484-G allele OR per allele 1·02, 95% CI 1·00–1·05; rs12916 allele 1·06, 1·03–1·09), and therefore surmise that an increased risk of type 2 diabetes is at least partly conferred by an on-target effect of statins.

These results are important because they suggest that any attempts to make statins more specific and reduce off-target effects will not reduce the risk of the diabetogenic side-effect. The investigators also provide

a new potential mechanism of statins' diabetogenic action—the alleles associated with lower circulating LDL cholesterol and increased type 2 diabetes risk were also associated with increased body-mass index (0·11 kg/m² higher with the rs17238484-G allele than in controls, 95% CI 0·07–0·14; $p=1·77\times10^{-7}$). Consistent with the genetic association, the investigators also described a subtle increase in weight caused by statins in the trial data (0·30 kg higher, 0·18–0·43; $p=3·15\times10^{-6}$).

Swerdlow and colleagues[1] provide a new angle to the debate about the adverse side-effects of statins. They used a genetic approach—mendelian randomisation—that has proven a valuable method to help understand disease mechanisms.[3,4] Mendelian randomisation is based on a fundamental principle of biology—that inherited DNA sequence variation is randomised during meiosis independently of the environment and disease processes. Mendelian randomisation approaches have been useful in understanding causality of potentially modifiable risk factors for cardiovascular disease. For example, several studies have used common genetic variants near the gene encoding C-reactive protein (CRP) to show that raised high-sensitivity CRP is unlikely to affect the risk of heart disease causally.[5] More recently, studies of genetic variants altering circulating HDL cholesterol concentrations have provided evidence that higher total HDL cholesterol concentrations are unlikely to reduce the risk of coronary artery disease, independently of any effects on LDL cholesterol or triglycerides.[6,7]

Of more direct relevance to the debate on statins, common genetic variants that alter LDL cholesterol concentrations are also associated with coronary artery disease.[7,8] The effect of common genetic variants is often subtle, but in some instances it provides great potential for improving mechanistic understanding. The genetic variants in the *HMGCR* gene have small effects on circulating LDL cholesterol (0·06 mmol/L) compared with other variants, which alter LDL concentrations by up to 0·36 mmol/L. Yet the variants in *HMGCR* provide proof of principle that genetics can be used to identify therapeutic targets.

Swerdlow and colleagues[1] used their own set of 26 236 cases and 164 021 controls as well as those from published studies. The results provide an important addition to a cascade of evidence that suggests a slight on-target type 2 diabetes side-effect of statins (figure). This cascade includes individual randomised controlled trials that provided some evidence of causality, although the different statins and definitions of diabetes used made results hard to interpret.[9,10] Observational associations between increased statin use and higher incidence of type 2 diabetes were consistent with the early trial data, but were probably heavily confounded by obesity and other factors.[10] Meta-analyses of randomised controlled trials followed[12] with, for example, an analysis of ten trials[11] showing an increased risk of type 2 diabetes. An analysis of intensive-dose versus moderate-dose statin treatment showed a dose–response effect, with individuals randomly assigned to intensive-dose treatment having a relative risk of 1·12 (95% CI 1·04–1·22) for diabetes compared with individuals assigned to moderate-dose treatment.[13] However, none of these studies could establish whether or not the diabetogenic effect of statins operated through the same pathway as the lipid-lowering HMGCoA-reductase effect or an off-target effect. Swerdlow and colleagues[1] answer this question—because the genetic variant lies near *HMGCR*, the diabetogenic effect of statins probably operates through the same mechanism as the lipid-lowering effect. The findings imply that new types of statin that more specifically target HMGCoA-reductase would not reduce the adverse side-effect of increased risk of type 2 diabetes.

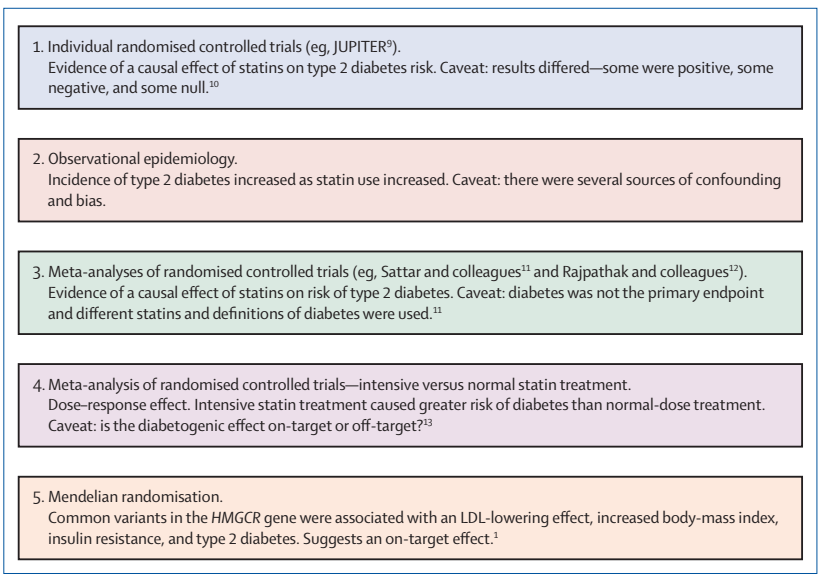

Figure: **Sequential evidence supporting a subtle diabetogenic effect of statin treatment**

There are some limitations to the study.[1] First, the subtle effects of the *HMGCR* variants meant that the investigators had to use large numbers of cases and controls, and the associations between the variants and type 2 diabetes are not statistically beyond reproach—more cases and controls would help confirm the findings. Second, we cannot be certain that the variants operate directly and solely through the *HMGCR* gene, although there is some evidence that these variants alter splicing of *HMGCR* transcripts.[14] Finally, genetic studies are not completely exempt from the confounders and biases of epidemiological studies—survival and index event biases can affect genetic studies, and further work with larger numbers of incident cases would provide more reassurance that the genetic associations with type 2 diabetes are real. However, the associations with body-mass index seem to be statistically robust and provide a mechanism downstream of the HMGCoA-reductase effect (increased body-mass index leading to increased insulin resistance, and to increased diabetes).

In summary, Swerdlow and colleagues[1] have used naturally occurring human genetic variation to provide another piece of evidence about the side-effects of statins, but have not cast any doubt on the evidence that the benefits of statins vastly outweigh their risks.

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I have consulted for Boehringer Ingelheim.

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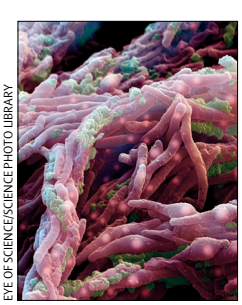
A collaborative strategy to tackle tuberculosis in England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Published Online
January 19, 2015
http://dx.doi.org/10.1016/S0140-6736(14)61638-X

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The UK has the second highest rate of tuberculosis among western European countries.[1] Tuberculosis clinics in London manage more cases a year than those in all other western European capital cities put together. Rates of tuberculosis are now nearly five times higher in the UK than in the USA.[2] Lack of progress with tuberculosis control in the UK does not just represent a risk to domestic public health,[3] but also an international embarrassment with examples of cases acquired in the UK leading to infections in other low-incidence countries. In recognition of this unacceptable trend, Public Health England has led a coalition of stakeholders to develop a forum, the national Tuberculosis Oversight Group, where innovation and good practice are shared between local, regional, and national health leaders. These discussions have led to local changes, with several areas establishing tuberculosis control boards and systematic cohort review, and the identification of tuberculosis as a major priority for Public Health England. However, the implementation of improved tuberculosis control measures has not been universal, and there is still unacceptable variation in the quality of clinical and public health measures across England.