Statin therapy and dysglycaemia
Is this clinically important?

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The cardiovascular benefits of statin therapy in relevant patients greatly outweigh the adverse effects of the increased glycaemia these drugs cause, as shown in this discussion of relevant trials.

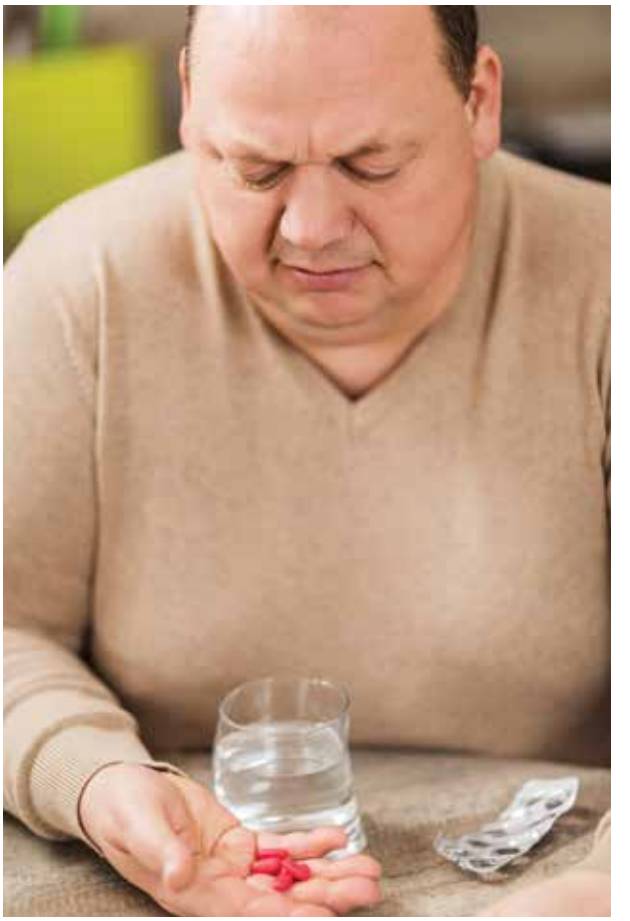
There is ample clinical evidence that statin therapy reduces future cardiovascular disease (CVD) risk in a variety of clinical situations. These include patients with or without prior CVD, those with higher or lower LDL-cholesterol levels, those with or without diabetes, men and women, and younger and older patients.[1,2] Statin therapy is generally safe and well tolerated, but a small proportion of patients taking statin drugs will experience muscle problems, and more rarely they may experience liver dysfunction or central nervous systems effects. It is acknowledged that some patients with dyslipidaemia can be adequately managed without drug therapy.

In recent years statins have been shown to increase glycaemia in both patients with and patients without diagnosed diabetes mellitus. This article addresses this important matter, ultimately to judge whether this effect is of clinical importance or not.

Randomised controlled trials with statins

Meta-analyses of randomised controlled trials have demonstrated an association between statin therapy and new-onset diabetes (NOD) that seems to be causally related.[3,4]

In an examination of 13 trials employing a variety of statins and involving 91,140 participants, 2.44% of those taking statins developed NOD, as did 2.25% of those taking placebo, over an average of four years.[3] This represented one additional case of NOD per 255 patients receiving a statin over four years. From published trial data it was



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Key points

- **The cardiovascular disease (CVD) benefits of statin therapy in relevant patients heavily outweigh adverse glycaemic effects.**
- **Patients using statins should be informed of the small increase in the risk of new-onset diabetes that taking statins involves, and that it may relate in part to an increase in bodyweight or the presence of other major risk factors for diabetes.**
- **These risk factors require regular monitoring, and weight gain should be avoided by attention to diet and exercise.**

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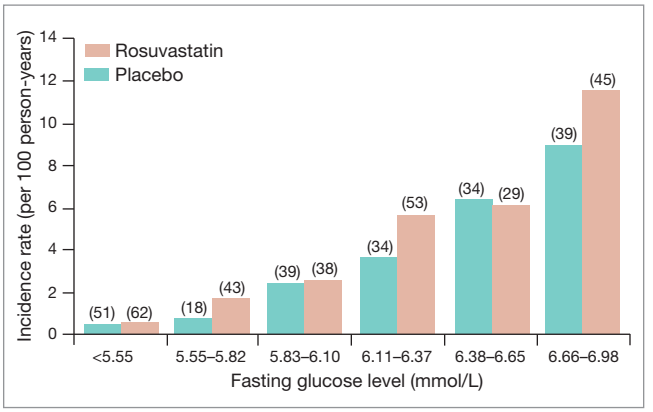

Figure 1. Incidence rates of physician-diagnosed diabetes in the JUPITER trial, by baseline fasting glucose concentration.
(Data are shown separately for participants allocated placebo and those allocated rosuvastatin. Numbers in parentheses are the absolute number of individuals who developed diabetes in each group.)
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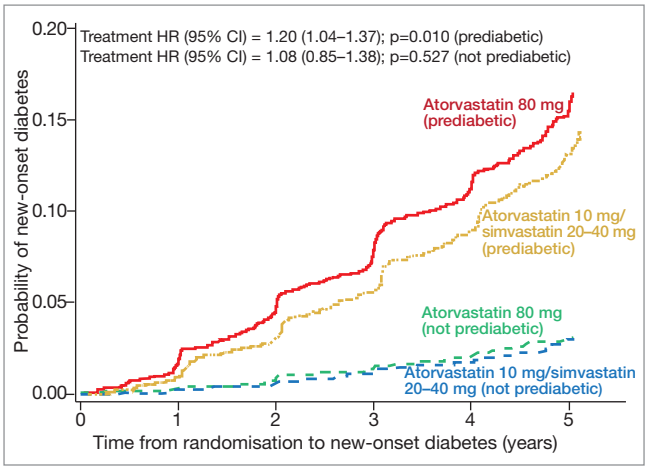

Figure 2. Effect of prediabetes on the incidence of new-onset diabetes in patients taking statins. Kaplan–Meier event-free survival curves from the Treating to New Targets (TNT) and the Incremental Decrease in Clinical Endpoints Through Aggressive Lipid Lowering (IDEAL) trials showing new-onset diabetes (NOD) in people with prediabetes and those without diabetes by treatment groups.
Abbreviations: CI = confidence interval; HR = hazard ratio.
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calculated that 5.4 coronary events would be prevented in 255 patients similarly treated for each 1 mmol/L reduction in LDL-cholesterol level (without taking into account other manifestations of CVD likely to be prevented).

A second meta-analysis of five statin trials compared intensive-dose statin therapy with moderate-dose statin therapy.[4] That is to say, all patients received some type of statin therapy. Intensive-dose statin therapy comprised atorvastatin 80 mg daily or simvastatin 40 or 80 mg daily. Among 32,752 participants treated for an average period of 4.9 years, 4.42% on intensive-dose statin developed NOD, 3.97% did so taking moderate-dose therapy. This represented one additional case of NOD in 498 patients receiving intensive-dose statin for one year. However, the parallel reduction in CVD events was demonstrated to be one event prevented in 155 patients for one year.

Effects of statin therapy in established diabetes

Information on the effect of statin therapy on glycaemic control in established diabetes is more limited and is conflicting.[5] A recent study examined the movement in HbA_{1c} in nine studies of statins that included patients with established diabetes, mostly type 2 diabetes.[5] In a pooled analysis involving 9696 participants with diabetes and an average follow up of 3.6 years, mean HbA_{1c} in those randomised to statins was significantly higher than in those randomised to a control group: mean difference was 0.12% (95% confidence interval [CI], 0.04–0.20) or 1.3 mmol/mol (95% CI, 0.4–2.2).

Clinically speaking, this is not a large mean change in glycaemic control and this will not be the last word on the matter. The study was limited to just three statins, atorvastatin, simvastatin and pravastatin, generally with moderate dosing. Not surprisingly, it seems that statin therapy increases glycaemia in both those patients with and those without established diabetes.

Mechanisms and pathways underlying effects on glycaemia

A randomised, primary prevention trial found an increased risk of developing NOD in patients receiving rosuvastatin compared with placebo, yet this effect was essentially confined to those participants with at least one of the four major risk factors for diabetes of metabolic syndrome, impaired fasting glucose, body mass index 30 kg/m^2 or higher or HbA_{1c} over 6% (42 mmol/mol).[6] The increased risk of NOD as baseline fasting glucose levels exceed 5.5 mmol/L levels is illustrated in Figure 1.[6] The point estimate of CVD risk associated with statin therapy in the small proportion who developed NOD was similar to that observed in the trial as a whole (hazard ratio of 0.63 *vs* 0.56; p>0.05).

A subsequent re-analysis of two studies comparing intensive-dose versus moderate-dose statin therapy contrasted the risk of developing NOD in patients with and without 'prediabetes'.[7] Prediabetes was defined as fasting glucose levels of 5.5 to 6.9 mmol/L. Of 15,056 patients at baseline without diabetes, 39% had prediabetes. During a mean follow up of five years, 14.2% of those with prediabetes developed NOD, 2.9% did so without prediabetes. The effect of statins in causing NOD was independent of the dose, but was essentially confined to patients with prediabetes (Figure 2).

This is a new paradigm – statins do seem to increase the risk of NOD, and the effect may not simply be a matter of statin dose.

The precise mechanism of this dysglycaemic effect of statins is not known, but some insight has come from a recent genetic study.[8] Several variants in the gene encoding 3-hydroxymethylglutaryl (HMG)-CoA reductase, the intended target of statin drugs, are

associated with reduced LDL-cholesterol levels but with higher bodyweight and waist circumference, higher plasma insulin and glucose levels, and increased risk of type 2 diabetes. This study also showed that statins are associated with a modest increase in bodyweight.[8] In other words, statin therapy through inhibition of HMG-CoA reductase may have additional on-target effects. It is possible that the NOD associated with statin therapy may be partially mediated by increased bodyweight.

What is the clinical significance of these findings?

Although there seems little doubt that statin therapy produces a small increase in the risk of NOD, this effect appears to be heavily outweighed by the parallel CVD prevention that follows. On the other hand, it would still be personally distressing when a patient without diabetes develops diabetes on statin therapy.

We need to inform patients using statins that this small risk of NOD does exist, and that it may relate in part to an increase in bodyweight or the presence of other major risk factors for diabetes. These risk factors require regular monitoring, and weight gain should be avoided by attention to diet and exercise. But the positive aspects of statin therapy need to be regularly reinforced. On balance, the CVD benefits of statin therapy in relevant patients heavily outweigh adverse glycaemic effects. **ET**

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