Statin heart benefits outweigh diabetes risks

Treatment with high-intensity statins, such as atorvastatin 20 mg upwards, results in a 36% proportional increase in new type 2 diabetes diagnoses compared to placebo, with the majority of the new diabetes occurring in people already close to the diabetes glycaemic threshold, according to this meta-analysis of participant-level data from the Cholesterol Treatment Trialists' Collaboration published in *The Lancet Diabetes & Endocrinology*. A smaller 10% proportional increase occurs with low- or moderate-intensity statins. Although previous meta-analyses of summary data from the statin trials have highlighted this increased risk, they could not fully quantify the size and timing of increases or determine who is at greatest risk. People with pre-existing diabetes treated with statins are also at risk of worsening glycaemia, particularly with high-intensity statins. However, the benefits of statins in reducing cardiovascular events in those at high risk far outweigh the impact of these increases in incident type 2 diabetes, so this study should not change prescribing habits. Nonetheless, it reminds us of the importance of counselling regarding increasing glycaemia risk and of encouraging lifestyle discussions around weight, eating patterns, sleep and physical activity, which can not only reduce the risk of type 2 diabetes but also improve the cardiovascular risk the statin is being used to treat.

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People with diabetes are at increased risk of cardiovascular disease (CVD) due to high glucose levels. This is additional to other risk factors, such as atherogenic lipid profile (high triglycerides, low HDL cholesterol and high levels of small dense LDL particles) and high blood pressure; diabetes doubles the risk of mortality.

Statins are the first-line prescription to reduce cardiovascular events in those with and without diabetes who have high cardiovascular risk or established CVD. Although initially it was believed that pravastatin might reduce the risk of developing type 2 diabetes (Freeman et al, 2001), studies since 2008, including a 2010 meta-analysis (Sattar et al, 2010), have confirmed that statins increase this risk by causing small increases in blood glucose levels. Therefore, we counsel about this small increased risk when initiating statins in those who do not currently have type 2 diabetes.

Questions remain, and the present study by the Cholesterol Treatment Trialists' Collaboration, published in *The Lancet Diabetes & Endocrinology*, was designed to clarify the impact of statins on people with and without diabetes, including the impact of different doses and intensities of statins, length of treatment, and how quickly any rise in HbA_{1c} occurs and whether it continues to rise over time.

Study method

The authors analysed individual participant data from 154 664 people enrolled in 23 double-blind, randomised controlled trials, 19 of which compared statins with placebo (21% in people with pre-existing diabetes), with a median follow-up of 4.3 years. Four trials compared less intensive with more intensive statin therapy over a median of 4.9 years (17% with pre-existing diabetes).

Statins were classified into low-, moderate- and high-intensity according to their impact on lowering LDL cholesterol, as illustrated in *Table 1 (overleaf)*. The majority of people with diabetes will be on high-intensity statins (e.g. atorvastatin 20 mg or 40 mg) for primary prevention based on QRISK scores, and on atorvastatin 80 mg for secondary prevention.

Results

Low- or moderate-intensity statin use resulted in a 10% increase in new-onset diabetes, with an

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Table 1. Intensity and predicted LDL-lowering effects of various statin regimens (NHS England, 2024).

	Approximate reduction in LDL cholesterol				
Statin dose (mg/day)	**5 mg**	**10 mg**	**20 mg**	**40 mg**	**80 mg**
Fluvastatin			21%	27%	33%
Pravastatin		20%	24%	29%	
Simvastatin		27%	32%	37%	42%
Atorvastatin		37%	43%	49%	55%
Rosuvastatin	38%	43%	48%	53%	

Low-intensity statins will produce an LDL cholesterol reduction of 20–30%.
Medium-intensity statins will produce an LDL cholesterol reduction of 31–40%.
High-intensity statins will produce an LDL cholesterol reduction above 40%.
Simvastatin 80 mg is deemed high-intensity but is not recommended due to risk of muscle toxicity.

incidence of 1.3% per year compared to 1.2% in the placebo group. Those treated with a high-intensity statin had a larger, 36% proportional increase in new diabetes, with rates of 4.8% compared to 3.5% per year with placebo. The relative effects on new-onset diabetes were stable over time.

In participants without diabetes:

- Seven trials of statins versus placebo measured mean blood glucose at baseline and follow-up, while two trials measured HbA_{1c}:
  - Low- or moderate-intensity statins: Mean glucose increase of 0.04 mmol/L; mean HbA_{1c} increase of 0.06%.
  - High-intensity statins: Mean glucose increase of 0.04 mmol/L; mean HbA_{1c} increase of 0.08%.
- In those with pre-statin glucose measurements available, 62% of those developing new-onset diabetes were in the top quarter of the baseline glycaemia distribution and were already at high risk of developing type 2 diabetes before statin initiation.

In those with pre-existing diabetes:

- Low- or moderate-intensity statins resulted in a 10% relative increased risk in worsening glycaemia compared with placebo.
- High-intensity statins resulted in a 24% relative worsening of glycaemia compared with placebo.

Adding ezetimibe to statins does not appear to increase diabetes risk more than statins alone, whilst early data on bempedoic acid suggest it may reduce HbA_{1c} and weight by small amounts compared with placebo (Sattar, 2023). Two large studies comparing PCSK9 inhibitors with placebo (evolocumab [FOURIER trial] and alirocumab [ODYSSEY trial]) did not show any increased glycaemia or new-onset diabetes with the active drugs.

In an accompanying comment, Gerstein and Pigeyre (2024) remind us that it is not the new label of diabetes that is important but rather the degree and duration of elevated glucose. Although the diagnostic thresholds for type 2 diabetes are set at a fasting plasma glucose (FPG) level of 7.0 mmol/L or an HbA_{1c} of 48 mmol/mol (6.5%) – these being the levels where retinopathy risk increases – cardiovascular risk increases at lower glycaemia levels: above FPG 5.6 mmol/L and HbA_{1c} 39 mmol/mol (5.7%). Thus, many people without type 2 diabetes are already at elevated risk of CVD. Any increased risk of diabetes or higher glucose should be carefully balanced against the benefits of the drug causing the increase; in this case, statins significantly reduce CVD risk.

As yet, there is no clear mechanism for the increase in glycaemia with statins, although weight gain or changes in muscle mass may contribute (Sattar, 2023), and insulin resistance and gut microbiome dysbiosis may also be involved.

Implications for practice

Confirmation of the increased glycaemia and risk of new type 2 diabetes should not influence our decision to prescribe statins for their beneficial impact on cardiovascular events, as numbers needed to treat are low. Previous studies have demonstrated that 20 people without pre-existing CVD would need to be treated with a statin for 5 years to prevent one cardiovascular event, while the number needed to treat reduces to 10 to prevent one cardiovascular event in those with pre-existing CVD (secondary prevention).

In their supporting comment, Gerstein and Pigeyre (2024) emphasise the decreased absolute annual incidence of life-threatening cardiovascular outcomes with statins in people at high risk, which clearly exceeds the impact of the 0.1–1.3% increased absolute incidence of type 2

diabetes per year caused by statins. The increased cardiovascular risk due to increased glycaemia caused by the statin is already captured in the clinical trials and does little to affect the overall cardiovascular benefit observed.

Those at risk of CVD are often also at risk of type 2 diabetes; therefore, when starting statins, we should counsel about the small increased diabetes risk and remind of the importance of losing weight and increasing activity levels to reduce this risk. This study is likely to result in significant media coverage, possibly resulting in people choosing to discontinue or refuse statins. As clinicians, we have an important role in helping people understand that these small increases in type 2 diabetes risk or worsening glycaemia are more than offset by the benefits of statins in people at significant risk of cardiovascular events.

This study highlights that statin initiation and reviews are excellent opportunities to discuss lifestyle changes to counterbalance the small increases in glycaemia and reduce the risk of developing new type 2 diabetes. Helping people make lifestyle changes, such as reducing ultra-processed food intake, improving quantity and quality of sleep, increasing physical activity, and consuming less salt, will also help reduce their risk of CVD – which is our goal in prescribing the statin in the first place. Let's make every contact count, and find time to add lifestyle advice into our consultations!

Cholesterol Treatment Trialists' (CTT) Collaboration (2024) Effects of statin therapy on diagnoses of new-onset diabetes and worsening glycaemia in large-scale randomised blinded statin trials: An individual participant data meta-analysis. *Lancet Diabetes Endocrinol* 26 Mar [Epub ahead of print]. https://doi.org/10.1016/S2213-8587(24)00040-8

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Articles

Effects of statin therapy on diagnoses of new-onset diabetes and worsening glycaemia in large-scale randomised blinded statin trials: an individual participant data meta-analysis

Cholesterol Treatment Trialists' (CTT) Collaboration*

Summary

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