



## Q/ Do statins increase the risk of developing diabetes?

### EVIDENCE-BASED ANSWER

**A** | **Yes.** Statin therapy produces a small increase in the incidence of diabetes: one additional case per 255 patients taking statins over 4 years (strength of recommendation [SOR]: **A**, meta-anal-

ysis). Intensive statin therapy, compared with moderate therapy, produces an additional 2 cases of diabetes per 1000 patient years (SOR: **B**, meta-analysis with significant heterogeneity among trials).

### Evidence summary

A meta-analysis of 13 randomized, placebo- or standard of care-controlled statin trials (113,148 patients, 81% without diabetes at enrollment, mean ages 55-76 years) found that statin therapy increased the incidence of diabetes by 9% over 4 years (odds ratio [OR]=1.09; 95% confidence interval [CI], 1.02-1.17), or one additional case per 255 patients.<sup>1</sup> The increased risk was similar for lipophilic (pravastatin, rosuvastatin) and hydrophilic (atorvastatin, simvastatin, lovastatin) statins, although the analysis wasn't adjusted for doses used.

In a meta-regression analysis, baseline body mass index or percentage change in low-density lipoprotein cholesterol didn't appear to confer additional risk. The risk of diabetes with statins was generally higher in studies with older patients (data given graphically).

### Higher statin doses mean higher risk

A meta-analysis of 5 placebo and standard-of-care randomized controlled trials (39,612 patients, 83% without diabetes at enrollment, mean age 58-64 years) found that the risk of diabetes was higher with higher-dose statins.<sup>2</sup> Therapy with atorvastatin 80 mg or simvastatin 40 to 80 mg was defined as intensive. Treatment with simvastatin

20 to 40 mg, atorvastatin 10 mg, or pravastatin 40 mg was defined as moderate.

At a mean follow-up of 4.9 years, intensive statin therapy was associated with a higher risk of developing diabetes than moderate therapy (OR=1.12; 95% CI, 1.04-1.22) with 2 additional cases of diabetes per 1000 patient-years in the intensive therapy group. The authors noted significant heterogeneity between trials with regard to major cardiovascular events.

Similar results were found in a subsequent population-based cohort study of 471,250 non-diabetic patients older than 66 years who were newly prescribed a statin.<sup>3</sup> The study authors used the incidence of new diabetes in patients taking pravastatin as the baseline, since it had been associated with reduced rates of diabetes in a large cardiovascular prevention trial.<sup>4</sup> Without adjusting for dose, patients were at significantly higher risk of diabetes if prescribed atorvastatin (hazard ratio [HR]=1.22; 95% CI, 1.15-1.29), rosuvastatin (HR=1.18; 95% CI, 1.10-1.26), or simvastatin (HR=1.10; 95% CI, 1.04-1.17) compared with pravastatin. The risk with fluvastatin and lovastatin was similar to pravastatin.

A subanalysis that compared moderate- and high-dose statin therapy with low-dose therapy (atorvastatin <20 mg, rosuvastatin <10 mg, simvastatin <80 mg, or any dose of fluvastatin, lovastatin, or pravastatin) found

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a 22% increased risk of diabetes (HR=1.22; 95% CI, 1.19-1.26) for moderate-dose therapy (atorvastatin 20-79 mg, rosuvastatin 10-39 mg, or simvastatin >80 mg) and a 30% increased risk (HR=1.3; 95% CI, 1.2-1.4) for high-dose therapy (atorvastatin ≥80 mg or rosuvastatin ≥40 mg).

### A cohort trial also shows increased diabetes risk

A smaller subsequent cohort trial based on data from Taiwan National Health Insurance records compared 8412 nondiabetic adult patients (mean age 63 years) taking statins with 33,648 age- and risk-matched controls not taking statins over a mean duration of 7.2 years.<sup>5</sup> Statin use was associated with

a 15% higher risk of developing diabetes (HR=1.15; 95% CI, 1.08-1.22).

### Recommendations

The 2013 American College of Cardiology/American Heart Association guidelines for lipid-lowering therapy recommend that patients taking statins be screened for diabetes according to current screening recommendations.<sup>6</sup> The guidelines advise encouraging patients who develop diabetes while on statin therapy to adhere to a heart-healthy dietary pattern, engage in physical activity, achieve and maintain a healthy body weight, cease tobacco use, and continue statin therapy to reduce the risk of cardiovascular events. **JFP**

### References

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