Statins and Diabetes

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KEYWORDS

• Statins • High intensity statins • Diabetes mellitus • Glucose • Glycemia • Dyslipidemia
• Cardiovascular disease • Coronary heart disease

KEY POINTS

- Statin use is associated with a modest increase in risk for new-onset type 2 diabetes mellitus compared with placebo or usual care.
- The risk for diabetes seems to be greater for intensive-dosage statin therapy, and to be most evident in those with major risk factors for diabetes.
- The cardiovascular benefits of statin therapy outweigh the potential risk for diabetes development, with several cardiovascular events generally prevented for each excess case of diabetes.
- No changes to clinical practice have been recommended, other than measuring glycated hemoglobin or fasting glucose in patients at elevated diabetes risk before and within 1 year of initiating therapy.
- The American Diabetes Association guidelines should be followed for screening and diagnosis, and lifestyle modification is emphasized for the prevention or delay of diabetes mellitus.

INTRODUCTION

Statins are first-line drug therapy for the management of dyslipidemia and have been shown to reduce the risks for myocardial infarction, stroke, and cardiovascular death,[1–3] but clinical trial data suggest a modest, yet statistically significant, increase in the incidence of new-onset type 2 diabetes mellitus (T2DM) with statin use.[4–10] Diabetes mellitus is a common condition affecting nearly 10% of the US population[11] and is increasing in prevalence worldwide.[12] In 2012, the US Food and Drug Administration added a statement to the labels of statin medications indicating that increases in glycated hemoglobin (HbA_{1C}) and fasting glucose levels have been reported with statin use.[13] In 2014, the National Lipid Association Statin Diabetes Safety Task Force reviewed the published evidence relating statin use to the hazard of diabetes mellitus or worsening glycemia, and provided practical guidance on how to manage this issue in clinical practice.[10] This paper provides a brief overview of the literature regarding statin use and T2DM risk and summarizes the findings and guidance from the National Lipid Association Expert Panel. The terms T2DM and diabetes are used synonymously throughout the article.

CLINICAL TRIAL EVIDENCE REGARDING STATIN USE AND DIABETES

West of Scotland Coronary Prevention Study

The West of Scotland Coronary Prevention Study (WOSCOPS) was one of the first clinical trials to draw attention to a possible association, albeit inverse in that trial, between T2DM risk and statin use.[14] An examination of the incidence of new-onset diabetes mellitus among 5974 subjects receiving pravastatin in WOSCOPS indicated that

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pravastatin therapy was associated with a lesser risk for development of diabetes mellitus, defined as a blood glucose level of 7.0 mmol/L or greater (126 mg/dL).[14] Subjects assigned to receive pravastatin had a 30% reduction in the risk for developing diabetes, compared with placebo, in multivariate analysis (hazard ratio [HR], 0.70; 95% CI, 0.50–0.99; $P = .042$). Because these analyses were post hoc and not predefined, it was acknowledged that they should be considered hypothesis generating and interpreted with caution.

Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin

The WOSCOPS results sparked interest in pursuing a formal, prospective analysis of the relationship between T2DM risk and statin use. The Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) was a study of 17,802 apparently healthy men and women with low-density lipoprotein cholesterol levels of less than 130 mg/dL and high-sensitivity C-reactive protein levels of 2.0 mg/L or more treated with rosuvastatin 20 mg/d or placebo (n = 8901 in each group) and followed for a median of 1.9 years.[4] The study included protocol-specified comparisons of glucose changes and physician-reported T2DM incidence between treatments. The results of JUPITER indicated that there were no differences between treatment groups in incidence of newly diagnosed glycosuria (rosuvastatin, n = 36; placebo, n = 32) or fasting blood glucose concentrations. A difference between groups in median HbA_{1C} concentration, although small, was detected, with a significantly higher value observed in the rosuvastatin group (5.9% vs 5.8% in the placebo group; $P = .001$). Furthermore, in the rosuvastatin group, there were significantly ($P = .01$) more cases of physician-reported diabetes (not adjudicated by the endpoint committee) among subjects receiving rosuvastatin (270 reports) versus subjects receiving placebo (216 reports; **Table 1**).

A follow-up analysis from JUPITER included stratification of participants on the basis of whether they had none or at least 1 of the following 4 major risk factors for developing diabetes: the metabolic syndrome, impaired fasting glucose, body mass index of 30 kg/m^2 or greater, or HbA_{1C} of greater than 6% (see **Table 1**).[5] Of the participants, 6095 had no major diabetes mellitus risk factors and 11,508 had at least 1 diabetes risk factor. During follow-up, there were 54 more new cases of T2DM in rosuvastatin-treated subjects with at least 1 diabetes risk factor compared with placebo-treated subjects with at least 1 diabetes risk factor (258 and 204 cases, respectively; $P = .01$). Importantly, all of the excess cases of T2DM with rosuvastatin occurred in patients with at least 1 major diabetes risk factor. There was no difference between treatment groups in the number of new T2DM cases among subjects with no diabetes risk factors (12 cases in each). The HRs (95% CIs) for developing diabetes associated with rosuvastatin use compared with placebo among subjects with none versus at least 1 diabetes risk factor were 0.99 (0.45–2.21) and 1.28 (1.07–1.54), respectively. These results suggest that risk for developing diabetes while on statin therapy may be limited to those with major T2DM risk factors.

Although the risk for developing diabetes was increased modestly, the risk for the primary

Table 1
Risk for developing T2DM with rosuvastatin treatment according to the number of diabetes risk factors in JUPITER

Event and Hazard Ratio	Placebo (n = 8901)	Rosuvastatin (n = 8901)	Difference	*P*-Value
New T2DM (All)	216 (2.4%)	270 (3.0%)	+54	.01
New T2DM (0 DM RF)	12 (0.2%)	12 (0.2%)	0	.99
New T2DM (≥1 DM RF)	204 (1.7%)	258 (2.1%)	+54	.01
HR (95% CI) 0 DM RF	—	0.99 (0.45, 2.21)	−1%	—
HR (95% CI) ≥1 DM RF	—	1.28 (1.07, 1.54)	+28%	—

There were 6095 patients with no major diabetes mellitus risk factors and 11,508 with ≥1 risk factor. Diabetes mellitus risk factors included the metabolic syndrome, impaired fasting glucose, body mass index of ≥30 kg/m^2, and glycated hemoglobin of >6%.

Abbreviations: CI, confidence interval; HR, hazard ratio; JUPITER, Justification for Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; RF, risk factors; T2DM, type 2 diabetes mellitus.

Data from Ridker PM, Pradhan A, MacFadyen JG, et al. Cardiovascular benefits and diabetes risks of statin therapy in primary prevention: an analysis from the JUPITER trial. Lancet 2012;380:565–71.