

STATINS AND THE DEVELOPMENT OF DIABETES MELLITUS

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ABSTRACT

Objectives: To evaluate the impact of statins on the risk of developing new-onset diabetes mellitus (DM) through a meta-analysis of randomized, placebo-controlled trials and to discuss the possible mechanisms of these effects.

Research design and methods: A systematic literature search through March 20, 2009 was conducted to identify randomized, placebo-controlled trials of statins that report data on the incidence of new-onset diabetes mellitus. Incidence of new-onset DM was treated as a dichotomous variable. Weighted averages were reported as relative risks (RR) with associated 95% confidence intervals (CI). A random-effects model was used.

Results: Six prospective, randomized, placebo-controlled trials (n=57,593) were identified. Upon meta-analysis, the use of statins did not significantly increase the risk nor prevent the development of new-onset DM (relative risk 1.06; 95% confidence interval 0.93-1.22). Moderate statistical heterogeneity was observed in this analysis ($I^2=58%$, Q statistic $p=0.04$) arising from pravastatin's tendency towards a reduction in risk of developing diabetes and the other statins showing an increase in risk. There was also no significant impact on the incidence of new-onset DM with either high- or low-dose statin use (RR 1.13, 95% CI 0.95 to 1.35 for low-dose statin; RR 1.02, 95% CI 0.84 to 1.25 for high-dose statin).

Conclusions: Statins as a class did not demonstrate a statistically significant positive or negative impact on a patient's risk of developing new-onset DM. Randomized controlled trials of statin therapy with incidence of new-onset DM as a primary outcome are required to definitely determine its impact on the development of DM. The mechanisms by which these statins affect glucose metabolism also need to be studied further. However, the beneficial effects of statins in decreasing major vascular events and vascular mortality far outweigh the risks of any adverse effects of statin therapy on glucose metabolism.

INTRODUCTION

HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme A) reductase is the rate-limiting enzyme for cholesterol formation in the liver and other tissues. By inhibiting HMG-CoA reductase, statins or HMG-CoA reductase inhibitors reduce hepatocyte cholesterol content, stimulate expression of LDL (low-density lipoprotein) receptors, and ultimately enhance removal of LDL cholesterol from the circulation.¹ It has been established in several large-scale clinical trials that statin therapy for lowering blood cholesterol is beneficial in reducing the risk of cardiovascular diseases in a variety of patient populations.²⁻⁵ Diabetics (both type 1 and type 2) in particular, has been shown in several randomized clinical trials to benefit from statin therapy in terms of reducing major vascular events and vascular mortality.⁶ However, it has been a matter of recent concern whether statins as a class, has a potential adverse effect of glucose metabolism.

Since 2003, there have been several case reports in Japan of diabetic patients having deterioration in their blood glucose status associated with the use of atorvastatin.⁷ In 2005, there was a case report of a Japanese man who was diagnosed with diabetes mellitus (DM) after four months of atorvastatin treatment for hypercholesterolemia.⁸ In this case, hyperglycemia resolved after insulin therapy and discontinuation of atorvastatin and recurred with pravastatin use. During the American Heart Association (AHA) meeting in 2004, a substudy of the PROVE-IT TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22) trial involving patients with recent acute coronary syndrome was presented and concluded that compared to standard-dose pravastatin (40 mg/day), treatment with a high-dose atorvastatin (80 mg/day) appears to be associated with a significant worsening of glycemic control among diabetics and non-diabetics.⁹ In 2007, the ANDROMEDA (A raNdomized, Double-blind, double-dummy, multicentre, phase IIIb, parallel-group study to compare the efficacy and safety of Rosuvastatin

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[10 mg and 20 mg] and atorvastatin [10 Mg and 20 mg] in patients with type 2 Diabetes mellitus) study showed that rosuvastatin was associated with a significantly greater mean percentage increase in glycated hemoglobin (HbA_{1c}) from baseline over 16 weeks compared with the same dose of atorvastatin among type 2 diabetics.¹⁰ And in 2008, the JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) study revealed that rosuvastatin at 20 mg/day increased the incidence of physician-reported diabetes.¹¹ Therefore, we performed a meta-analysis of randomized controlled trials of statins to better evaluate their impact on the risk of developing new-onset DM and to discuss the possible mechanisms of these effects.

Research Design and Methods

We included all randomised controlled trials in humans of any statin against placebo which reported the incidence of new-onset DM. For this task, we searched for relevant articles in PubMed with the combination of “HMG-CoA reductase inhibitors”[MeSH], “Randomized Clinical Trials”[MeSH] and “Development of Diabetes Mellitus”[MeSH], and also MEDLINE with the following text key words: HMG-CoA reductase inhibitor, statin, new-onset diabetes mellitus, newly diagnosed diabetes mellitus, development of diabetes. We also used text words for all statins. The search was done on March 20, 2009. Related articles were also searched for by scanning the references quoted in the articles at hand. Three authors independently reviewed literature searches to identify relevant trials that met the inclusion criteria.

The incidence of new-onset DM was treated as a dichotomous variable. Weighted averages were reported as relative risks (RR) with associated 95% confidence intervals (CI). A random-effects model was used to calculate RR and 95% CI. Statistical heterogeneity was assessed using the I² and Q statistics.

RESULTS AND DISCUSSION

The search identified six randomized, placebo-controlled trials of statin therapy that reported the incidence of newly diagnosed diabetes as a post-hoc or tertiary endpoint. Each trial will be discussed in detail below.

The WOSCOPS (West of Scotland Coronary Prevention Study)¹² was the first clinical trial which investigated the risk of DM associated with statin treatment. It was a double-blind study originally designed to determine whether the administration of pravastatin to men with hypercholesterolemia and no history of myocardial infarction would reduce the combined incidence of nonfatal myocardial infarction and death from coronary heart disease. The study assigned 6,595 men, 45 to 64 years of age with hypercholesterolemia to receive pravastatin (40 mg each evening) or placebo for an average follow-up period of 4.9 years. In this study, treatment with pravastatin produced a significant reduction in the risk of the combined primary end point of nonfatal myocardial infarction and death from coronary heart disease (relative reduction in risk with pravastatin therapy 31%; 95% CI 0.17-0.43; $p < 0.001$). A post hoc analysis to examine the development of diabetes among the subjects was done. The incidence of diabetes mellitus was defined as at least two measurements of fasting blood glucose level of 7.0 mmol/L and at least one fasting blood glucose measurement of 2.0 mmol/L above the baseline level or newly started prescription of hypoglycemic agents (oral hypoglycemic agents or insulin). Subjects who self-reported diabetes at baseline or had a baseline glucose level of 7.0 mmol/L were excluded from the analysis. A total of 5,974 of the 6,595 randomized subjects were included in the analysis, and 139 subjects became diabetic during the study. After adjustment for body mass index, total and high-density lipoprotein (HDL) cholesterol, triglyceride, blood glucose, systolic blood pressure, and other characteristics at baseline, the subjects assigned to pravastatin therapy resulted in a 30% reduction (hazard ratio 0.70, 95% CI 0.50 to 0.99; $p = 0.042$) in the hazard of becoming diabetic.¹³

In the LIPID (Long-term Intervention with Pravastatin in Ischaemic Disease) study¹⁴, a total of 9,014 patients, aged 31 to 75 years with coronary heart disease and a broad range of initial cholesterol levels were randomly allocated to receive either 40 mg pravastatin daily or matching placebo over a mean follow-up period of 6.1 years. This study was designed to determine whether the administration of pravastatin in patients with coronary artery disease would reduce the mortality from coronary heart disease. The development of new-onset diabetes was defined as a fasting plasma glucose level of 7.0 mmol/L or reported use of oral hypoglycemic

medication or insulin in subjects without diabetes at baseline. In this study, pravastatin therapy significantly reduced the primary study end point of death from coronary heart disease (relative reduction in risk with pravastatin therapy 24%; 95% CI 0.12-0.35; $p < 0.001$). Among the 6,997 subjects with no history of diabetes and a normal fasting glucose (NFG; fasting plasma glucose 6.0 mmol/L) at study entry, there was no significant difference between the treatment groups in the numbers who were found to have developed diabetes during follow-up (126 [4.0%] in the pravastatin group versus 138 [4.5%] in the placebo group, $p = 0.32$).¹⁵ In the 940 subjects with no history of diabetes and an impaired fasting glucose (IFG; fasting plasma glucose 6.1-6.9 mmol/L) at study entry, there was again no significant difference between the treatment groups in the numbers who were found to have developed diabetes during follow-up (46 [9.7%] in the pravastatin group versus 43 [9.2%] in the placebo group, $p = 0.80$).

In the MRC/BHF Heart Protection Study,¹⁶ a total of 20,536 adults, aged 40-80 years with coronary disease, other occlusive arterial disease, or diabetes were randomly allocated to receive 40 mg simvastatin daily or matching placebo. Analyses were of the first occurrence of particular events, and compare all simvastatin-allocated versus all placebo-allocated subjects. Primary outcomes were mortality and fatal or non-fatal vascular events. The mean duration of follow-up was 4.8 years for all randomized subjects known to have diabetes at entry to the study, and 5.0 years for all the remaining subjects. The development of diabetes was predefined as initiation of hypoglycemic or insulin treatment, or a specific report of new diabetes, in subjects who had not had diabetes diagnosed prior to randomization. In this study, allocation to pravastatin significantly reduced the all-cause mortality (hazard ratio 0.87; 95% CI 0.81-0.94; $p = 0.0003$), due chiefly to a highly significant reduction in the death rate from vascular causes (781 [7.6%] in the simvastatin group versus 937 [9.1%] in the placebo group, $p < 0.0001$). Among the 14,573 subjects with no prior diabetes, there was no significant difference between the treatment groups in the numbers who were found to have developed diabetes during follow-up (335 [4.6%] in the simvastatin group versus 293 [4.0%] in the placebo group, $p = 0.10$).¹⁷

In the ASCOT study (Anglo-Scandinavian Cardiac Outcomes Trial),¹⁸ 19,342 hypertensive

patients aged 40-79 years with at least three other cardiovascular risk factors were randomized to either of two antihypertensive regimens (amlodipine plus perindopril versus atenolol plus bendroflumethiazide) and 10,305 subjects with non-fasting total cholesterol concentrations 6.5 mmol/L or less were further randomized to receive either atorvastatin 10 mg/day or matching placebo. The study was designed to assess the benefits of cholesterol lowering in the primary prevention of coronary heart disease in hypertensive patients who are not conventionally deemed dyslipidemic. The development of new-onset diabetes was a pre-specified tertiary end point and was predefined as a plasma glucose 7.0 mmol/L or a 2-hour plasma glucose level 11.1 mmol/L in subjects with no prior diabetes at baseline. Treatment was stopped after a median follow-up of 3.3 years. By that time, the primary endpoint of non-fatal myocardial infarction, including silent myocardial infarction, and fatal coronary heart disease was significantly lower by 36% (hazard ratio 0.64; 95% CI 0.50-0.83, $p = 0.0005$) in the atorvastatin group than in the placebo group. Furthermore, there was no significant difference in the development of diabetes mellitus between the two treatment groups (154 [3.0%] in the atorvastatin group versus 134 [2.6%] in the placebo group; hazard ratio 1.15, 95% CI 0.91 to 1.44; $p = 0.25$).

In the CORONA (Controlled Rosuvastatin in Multinational trial in Heart failure)¹⁹ study, a total of 5,011 patients at least 60 years of age with New York Heart Association class II, III, or IV ischemic, systolic heart failure were randomly assigned to receive 10 mg of rosuvastatin or placebo per day for a median follow-up 32.8 months. The primary composite outcome was death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. Secondary outcomes included death from any cause, and the number of cardiovascular hospitalizations. Newly diagnosed diabetes was a predefined tertiary outcome and was relied on physician or patient self-report to make the diagnosis. In this study, rosuvastatin did not reduce the primary outcome or the number of deaths from any cause, although the drug did reduce the number of cardiovascular hospitalizations (2,193 hospitalizations in the rosuvastatin group versus 2,564 hospitalizations in the placebo group, $p < 0.001$). Of the 3,534 subjects with no diabetes at baseline, 188 were reported to have newly diagnosed diabetes during follow-up with no significant difference between the two treatment group (100 [5.6%] in the rosuvastatin group versus 88 [5.0%] in the placebo group, $p = 0.40$).

In the JUPITER¹¹ study, a total of 17,802 apparently healthy men and women with LDL cholesterol levels of <130 mg/dl (3.4 mmol/L) and high-sensitivity C-reactive protein levels of 2.0 mg/L were randomly assigned in a 1:1 ratio to receive either rosuvastatin 20 mg/day or matching placebo. This study was designed to evaluate the benefit of statin treatment on people with elevated high-sensitivity C-reactive protein levels but without hyperlipidemia. The primary outcome was the occurrence of the first major cardiovascular event, defined as nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina, an arterial revascularization procedure, or confirmed death from cardiovascular causes. The trial was stopped after a median follow-up of 1.9 years. By that time, the rates of the primary endpoint were 0.77 and 1.36 per 100 person-years of follow-up in the rosuvastatin and placebo groups respectively (hazard ratio for rosuvastatin, 0.56; 95% CI 0.46 to 0.69; p<0.00001). In addition, protocol-specified measurements showed no significant differences between the study groups with respect to the fasting blood glucose level (98 mg/dL [5.4 mmol/L] in both groups; p=0.12) or newly diagnosed glycosuria (in 36 [0.5%] subjects in the roauvastatin group versus 32 [0.4%] in the placebo group; p=0.64). There was a minimal difference in the median glycated hemoglobin value (5.9% in the rosuvastatin group versus 5.8% in the placebo group; p=0.001). Physician-reported diabetes was more frequent in the rosuvastatin group (270 [3.0%] reports

of diabetes, versus 216 [2.4%] in the placebo group; p=0.01). However, physicians' reports of diabetes were not adjudicated by the end-point committee.

The six trials included a total of 57,593 patients without preexisting diabetes. The study population was diverse, mostly male, with mean age ranging from 55 to 73 years. The follow up of these patients ranges from 1.9 to 6.1 years. The definition of new-onset diabetes differed widely between the trials and was not a primary outcome. With the exception of the CORONA study, the other trials demonstrated significant reductions in vascular events and vascular mortality with the use of statins.

A total of 2,082 (3.6%) patients not having diabetes at enrollment developed new-onset DM during follow-up in these six clinical trials. Upon meta-analysis, the use of statins did not significantly increase the risk nor prevent the development of new-onset DM (RR 1.06; 95% confidence interval 0.93-1.22; see Figure 1). Moderate statistical heterogeneity was observed in this analysis (I²=58%, Q statistic p=0.04) arising from pravastatin's tendency towards a reduction in risk of developing diabetes and the other statins showing a tendency towards an increase in risk (see Figure 2). There was also no significant impact on the incidence of new-onset DM with either low- or high-dose statin use (RR 1.13, 95% CI 0.95 to 1.35 for low-dose statin and RR 1.02, 95% CI 0.84 to 1.25 for high-dose statin; see Table 1).

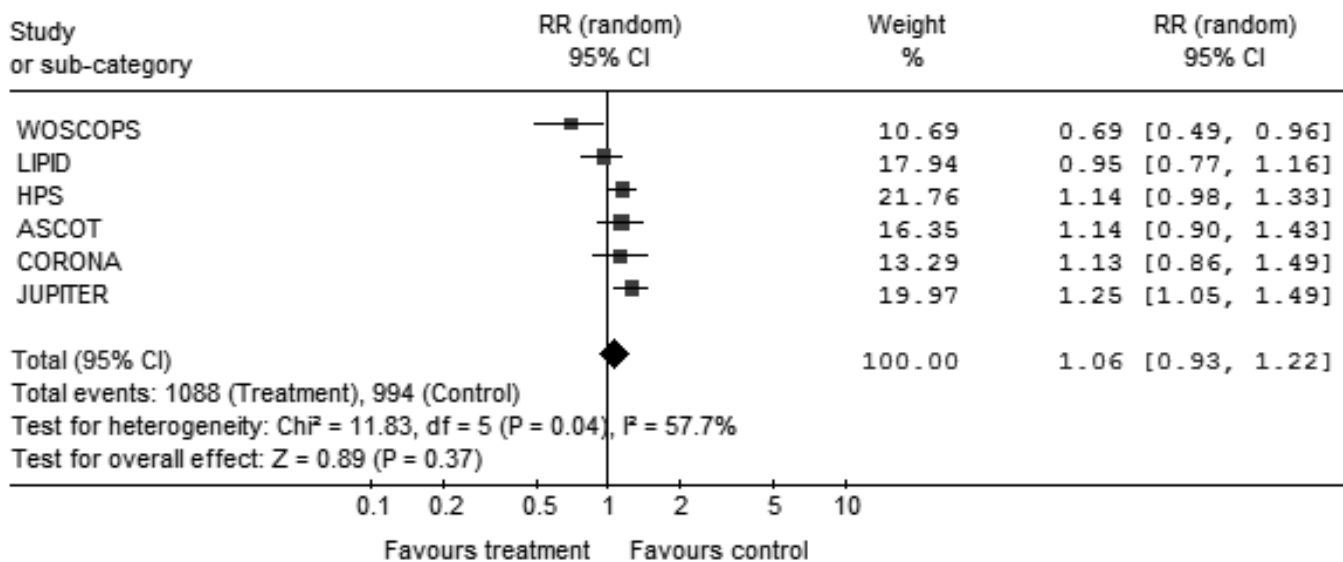


Fig. 1. Results of Meta-analysis of Randomized Placebo-Controlled Trials Evaluating Statins Effect on the Incidence of New-onset Diabetes Mellitus. RR=Relative Risk; CI=Confidence Interval

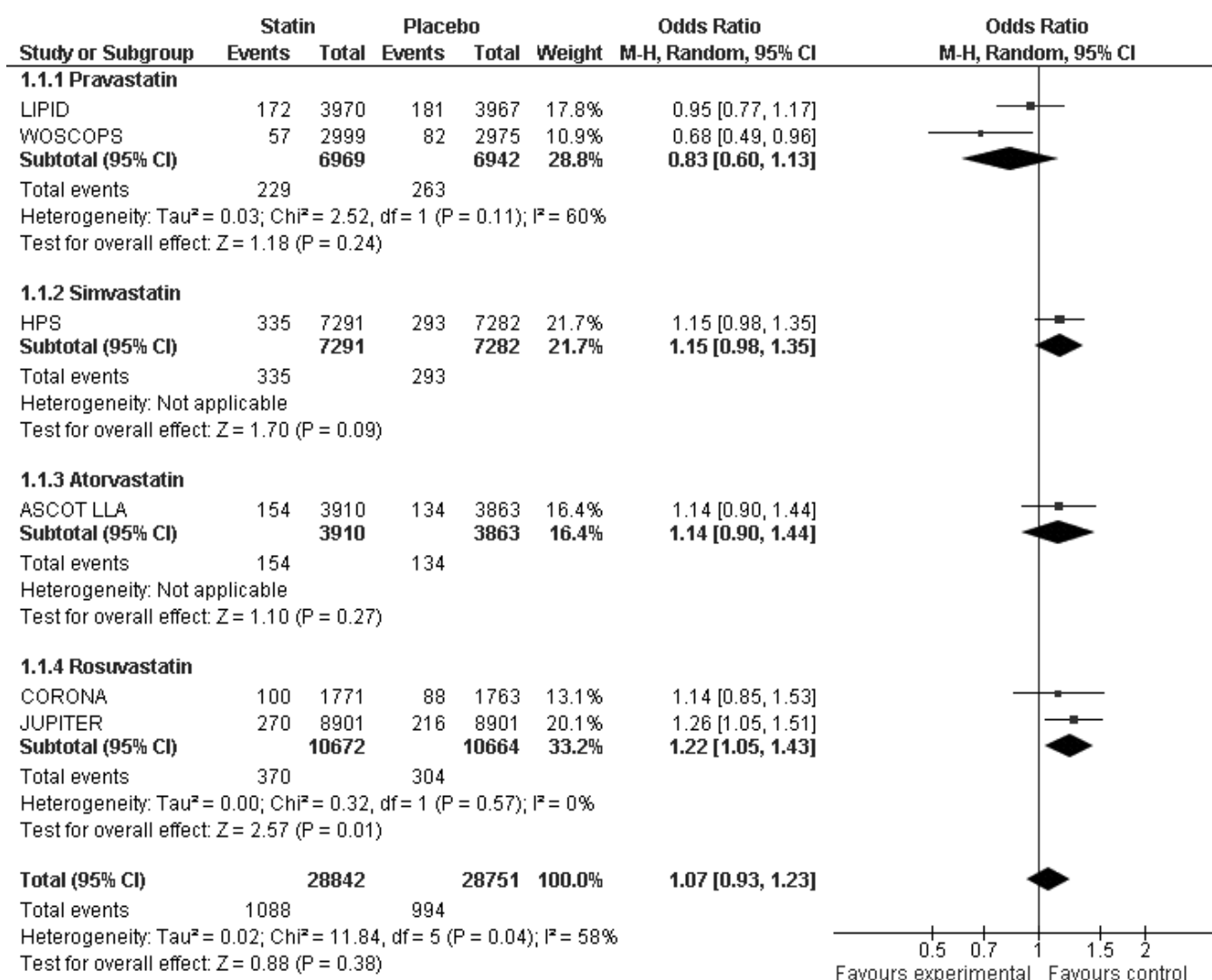


Fig. 2. Subgroup Analysis Evaluating the Effects of Different Statins on the Incidence of New-onset Diabetes Mellitus. RR=Relative Risk; CI=Confidence Interval

Table 1. Risk of New-Onset Diabetes Mellitus According to Statin Dose

Statin Dose	RR	95% CI
Low Dose (2 trials: ASCOT and CORONA)	1.13	0.95-1.35
High Dose (4 trials: WOSCOPS, LIPID, HPS and JUPITER)	1.02	0.84-1.25

RR=relative risk; CI=confidence interval

We could not determine the reasons for the conflicting results between the pravastatin trials and

the trials on other statins in terms of the incidence of new-onset DM, however, several possibilities exist. First, the population comprising the six trials was diverse and the different findings on the risks of development of diabetes could be plausibly related to variations in the population characteristics at baseline. Second, the criteria to define new-onset DM differed widely between the trials and may have caused varied effects on the outcome. And finally, it could also be possible that pravastatin is different from the other statins in terms of its pharmacodynamic and pharmacokinetic effects on glucose metabolism.

Mechanisms of the Effects of Statins on Glucose Metabolism

The mechanisms underlying the effects of statins on glucose metabolism is not yet fully understood and evidences are inconclusive and very limited at present. The anti-inflammatory effect of statins may play an important role on its effect on glucose metabolism. Pro-inflammatory cytokines such as tumor necrosis factor (TNF)- and leptin are secreted from adipocytes and have been implicated in mediating insulin resistance through their influences on the insulin receptor.^{20,21} It is speculated that pravastatin act on adipocytes and reduce the oversecretion of these cytokines that cause insulin resistance and may retard the development of diabetes.²² Furthermore, pravastatin therapy increases serum concentrations of adiponectin, an adipocyte-derived secreted protein that is associated with increased insulin sensitivity and glucose tolerance.²³ Using a variety of objective parameters to evaluate glucose metabolism, pravastatin was shown to improve insulin resistance in addition to reducing serum lipids and some inflammatory markers on nondiabetic dyslipidemic patients.^{24,25} It has also been reported that pravastatin improves endothelial-dependent coronary vasomotion, which may in turn lead to increased transport of glucose and insulin to peripheral tissues and thereby may possibly inhibit the progression of insulin resistance.²⁶

On the other hand, statins can also adversely affect glucose metabolism. Simvastatin, a lipophilic statin, has an ability to inhibit glucose-induced insulin secretion by inhibiting L-type Ca^{2+} channel and $[\text{Ca}^{2+}]_i$ signalling in pancreatic β -cells of rats.²⁷ Such inhibition was not observed with pravastatin, a hydrophilic statin. Atorvastatin, also a lipophilic statin, has been reported to significantly increase blood glucose levels of diabetic rats at several time points during OGTT (oral glucose tolerance test) whereas pravastatin did not.²⁸ Chen et al.²⁹ demonstrated that moderate lipid lowering therapy by pravastatin, but not intensive lipid therapy with atorvastatin, prevented new onset diabetes mellitus in a model of spontaneously developing type 2 DM, the OLETF (Otsuka Long-Evans Tokushima Fatty) rats. Mauser et al.³⁰ showed that treatment of terminally differentiated white adipocytes with atorvastatin resulted in a highly significant, dose-dependent reduction in insulin-induced glucose cellular uptake. When compared with pravastatin-pretreated 3T3L1 adipocytes, pretreatment with atorvastatin significantly reduced the glucose uptake induced by insulin treatment and is associated with the prevention of translocation of GLUT4 (glucose transporter-4),

a membrane transporter protein that plays a role in adipocyte glucose uptake, from intracellular vesicles into the plasma membrane.³¹ In a retrospective study comparing the effects of pravastatin and atorvastatin on glucose and lipid metabolism in 44 non-diabetic patients with hypercholesterolemia, pravastatin but not atorvastatin significantly reduced the fasting plasma glucose (FPG) from baseline after an average treatment period of 9.7 months.³²

The probable mechanism underlying these varied effects of statins on glucose metabolism is that lipophilic statins, such as simvastatin and atorvastatin, can easily enter into many extrahepatic tissues including the muscles, adipose tissues and pancreas, and thereby may decrease insulin secretion and exacerbate insulin resistance. In contrast, pravastatin, a hydrophilic statin, is more hepatocyte-specific and are not readily taken up by extrahepatic tissues. Isoprenoids are known to promote cellular glucose uptake by up-regulation of the insulin-responsive membrane transporter protein GLUT4. Inhibition of isoprenoid biosynthesis on adipocytes by a statin would cause insulin resistance by down-regulation of GLUT4 and mark inhibition of insulin-stimulated glucose transport.³³ Finally, statins inhibit biosynthesis of mevalonate, a precursor of both cholesterol and coenzyme Q10, a compound believed to be crucial for mitochondrial function and the provision of energy for cellular processes.³⁴ In this mechanism, the rate of ATP synthesis in pancreatic β -cells could be slowed by statins and possibly impairing insulin-secretion.

Based on these clinical studies, it is reasonable to suppose that the different effects on glucose metabolism of different statins maybe related to the drug's lipophilicity and inhibitory potency on HMG-CoA reductase. Pravastatin might be pharmacologically distinct from the other statins. However, rosuvastatin is also hydrophilic like pravastatin.³⁵ Simvastatin and pravastatin are both chemical modifications of lovastatin and as a result do not differ much in structure from lovastatin.³⁶ Further study will be needed to clarify the effects of statins on insulin resistance and the development of DM.

CONCLUSIONS

In this meta-analysis of six randomized, placebo-controlled trials, statins as a class did not demonstrate a statistically significant positive or negative impact on a patient's risk of developing new-onset DM. Randomized controlled trials of statin therapy with incidence of new-onset DM as a primary outcome are required to definitely

determine its impact on the development of DM. The mechanisms by which these statins affect glucose metabolism also need to be studied further. However, the beneficial effects of statins in decreasing major vascular events and vascular mortality far outweigh the risks of any adverse effects of statin therapy on glucose metabolism.

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