CME CREDIT ***EDUCATIONAL OBJECTIVE:*** Readers will compare the benefits and risks of statin therapy in patients at risk of cardiovascular disease

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Statins and diabetes risk: Fact, fiction, and clinical implications

ABSTRACT

Statin drugs now carry a US Food and Drug Administration warning that they may increase the risk of diabetes mellitus and may worsen glycemic control in patients who already have diabetes. Though the association is clear, until some contradictory observations can be resolved and plausible mechanisms of action elucidated, causality cannot be established. From a clinical standpoint, there is currently no evidence that elevations in blood glucose while taking lipid-lowering drugs are associated with an increased risk of cardiovascular events or that they attenuate the beneficial effects of the therapy. Until further study is done, statins should continue to be used based on a careful assessment of risk and benefit.

KEY POINTS

The evidence from individual clinical trials is mixed, but meta-analyses indicate that statin therapy is associated with approximately a 9% higher risk of diabetes (an absolute difference of about 0.4%).

We need to interpret this information cautiously. Many potentially confounding factors are involved, and rigorous prospective trials are needed to examine this issue.

The benefit of preventing serious cardiovascular events seems to outweigh the higher risks of diabetes and poorer glycemic control, and we should continue to give statins to patients at moderate to high risk, including those with diabetes, with vigilance for these side effects.

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On February 28, 2012, the US Food and Drug Administration (FDA) updated its labeling requirements for statins. In addition to revising its recommendations for monitoring liver function and its alerts about reports of memory loss, the FDA also warned of the possibility of new-onset diabetes mellitus and worse glycemic control in patients taking statin drugs.[1]

This change stoked an ongoing debate about the risk of diabetes with statin use and the implications of such an effect. To understand the clinical consequences of this alert and its effect on treatment decisions, we need to consider the degree to which statins lower the risk of cardiovascular disease in patients at high risk (including diabetic patients), the magnitude of the risk of developing new diabetes while on statin therapy, and the ratio of risk to benefit in treated populations.

This review will discuss the evidence for this possible adverse effect and the implications for clinical practice.

DO STATINS CAUSE DIABETES?

Individual controlled trials dating back more than a decade have had conflicting results about new diabetes and poorer diabetic control in patients taking statins.

The West of Scotland Coronary Prevention Study (WOSCOPS)[2] suggested that the incidence of diabetes was 30% *lower* in patients taking pravastatin (Pravachol) 40 mg/day than with placebo. However, this was not observed with atorvastatin (Lipitor) 10 mg/day in the Anglo-Scandinavian Cardiac Outcomes Trial–Lipid-Lowering Arm (ASCOT-LLA)[3] in hypertensive patients or in the Collaborative

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Meta-analysis: Statins are associated with a higher risk of new-onset diabetes

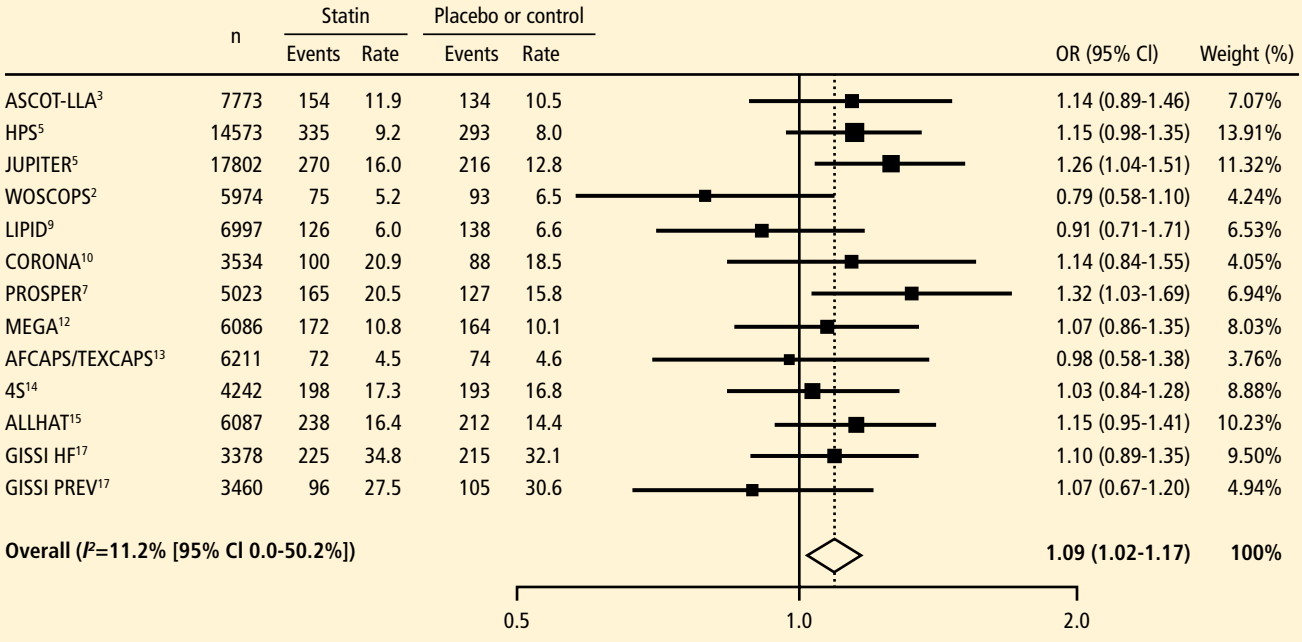


FIGURE 1. Individual odds ratio for new-onset diabetes in individual trials of statin therapy and overall results. Rates are per 1,000 patient-years. (OR = odds ratio, CI = confidence interval.)

REPRINTED FROM SATTAR N, PREISS D, MURRAY HM, ET AL. STATINS AND RISK OF INCIDENT DIABETES: A COLLABORATIVE META-ANALYSIS OF RANDOMISED STATIN TRIALS. LANCET 2010; 375:735–742, WITH PERMISSION FROM ELSEVIER. HTTP://WWW.SCIENCEDIRECT.COM/SCIENCE/JOURNAL/01406736

Atorvastatin Diabetes Study (CARDS)[4] in diabetic patients,[4] nor was it noted with simvastatin (Zocor) 40 mg/day in the Heart Protection Study (HPS).[5]

The Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER),[6] using the more potent agent rosuvastatin (Crestor) 20 mg/day in patients with elevated levels of C-reactive protein (CRP), was stopped early when an interim analysis found a 44% lower incidence of the primary end point. However, the trial also reported a 26% higher incidence of diabetes in follow-up of less than 2 years.

In the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER),[7] with a mean age at entry of 75, there was a 32% higher incidence of diabetes with pravastatin therapy.[7]

Results of meta-analyses

Several meta-analyses have addressed these differences.

Rajpathak et al[8] performed a meta-analysis, published in 2009, of six trials—WOSCOPS,[2] ASCOT-LLA,[3] JUPITER,[6] HPS,[5] the Long-term Intervention With Pravastatin in Ischaemic Disease (LIPID) study,[9] and the Controlled Rosuvastatin Multinational Study in Heart Failure (CORONA),[10] with a total of 57,593 patients. They calculated that the incidence of diabetes was 13% higher (an absolute difference of 0.5%) in statin recipients, which was statistically significant. In their initial analysis, the authors excluded WOSCOPS, describing it as hypothesis-generating. The relative increase in risk was less—6%—and was not statistically significant when WOSCOPS was included.

Sattar et al,[11] in a larger meta-analysis published in 2010, included 91,140 participants in 13 major statin trials conducted between 1994 and 2009; each trial had more than 1,000 patients and more than 1 year of follow-up.[2,3,5–7,9,10,12–17] New diabetes was de-

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fined as physician reporting of new diabetes, new diabetic medication use, or a fasting glucose greater than 7 mmol/L (126 mg/dL).

New diabetes occurred in 2,226 (4.89%) of the statin recipients and in 2,052 (4.5%) of the placebo recipients, an absolute difference of 0.39%, or 9% more (odds ratio [OR] 1.09; 95% confidence interval [CI] 1.02–1.17) (FIGURE 1).

The incidence of diabetes varied substantially among the 13 trials, with only JUPITER[6] and PROSPER[7] finding statistically significant increases in rates (26% and 32%, respectively). Of the other 11 trials, 4 had nonsignificant trends toward lower incidence,[2,9,13,17] while the 7 others had nonsignificant trends toward higher incidence.

Does the specific statin make a difference?

Questions have been raised as to whether the type of statin used, the intensity of therapy, or the population studied contributed to these differences. Various studies suggest that factors such as using hydrophilic vs lipophilic statins (hydrophilic statins include pravastatin and rosuvastatin; lipophilic statins include atorvastatin, lovastatin, and simvastatin), the dose, the extent of lowering of low-density lipoprotein cholesterol (LDL-C), and the age or clinical characteristics of the population studied may influence this relationship.[18–20]

Yamakawa et al[18] examined the effect of atorvastatin 10 mg/day, pravastatin 10 mg/day, and pitavastatin (Livalo) 2 mg/day on glycemic control over 3 months in a retrospective analysis. Random blood glucose and hemoglobin A_{1c} levels were increased in the atorvastatin group but not in the other two.[18]

A prospective comparison of atorvastatin 20 mg vs pitavastatin 4 mg in patients with type 2 diabetes, presented at the American College of Cardiology's 2011 annual meeting, reported a significant increase in fasting glucose levels with atorvastatin, particularly in women, but not with pitavastatin.[19]

In the Compare the Effect of Rosuvastatin With Atorvastatin on Apo B/Apo A-1 Ratio in Patients With Type 2 Diabetes Mellitus and Dyslipidaemia (CORALL) study,[20] both high-dose rosuvastatin (40 mg) and high-dose atorvastatin (80 mg) were associated with significant increases in hemoglobin A_{1c}, although the mean fasting glucose levels were not significantly different at 18 weeks of therapy.

A meta-analysis by Sattar et al[11] did not find a clear difference between lipophilic statins (OR 1.10 vs placebo) and hydrophilic statins (OR 1.08). In analysis by statin type, the combined rosuvastatin trials were statistically significant in favor of a higher diabetes risk (OR 1.18, 95% CI 1.04–1.44). Nonsignificant trends were noted for atorvastatin trials (OR 1.14) and simvastatin trials (OR 1.11) and less so for pravastatin (OR 1.03); the OR for lovastatin was 0.98. This may suggest that there is a stronger effect with more potent statins or with greater lowering of LDL-C.

Meta-regression analysis in this study demonstrated that diabetes risk with statins was higher in older patients but was not influenced by body mass index or by the extent that LDL-C was lowered.

Statin dose as a risk factor

Intensive-dose statin therapy has been shown to reduce cardiovascular risk more than low-dose or moderate-dose therapy, thus supporting more aggressive treatment of LDL-C in higher-risk patients. However, some controlled studies comparing more-potent with less-potent statin regimens suggest that there may also be a higher risk of incident diabetes at higher doses.[21–24]

We need to compare how much statins lower the risk of cardiovascular disease against the risk of new diabetes

In a post hoc analysis of the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 (PROVE-IT TIMI 22) trial,[21] patients who had experienced an acute coronary syndrome had a greater increase in hemoglobin A_{1c} if treated with atorvastatin 80 mg/day than with pravastatin 40 mg/day.

Waters et al[23] reported a higher risk of new diabetes with atorvastatin 80 mg than with placebo and a trend toward a higher risk with atorvastatin 80 mg than with atorvastatin 10 mg or simvastatin 20 mg.

In contrast, a review by Yousef et al[24] of the data from the Enhanced Feedback for Effective Cardiac Treatment (EFFECT) study did not find a higher diabetes risk with more intensive statin therapy based on the magnitude of LDL-C reduction. A propensity-matched examination of deaths, recurrent acute ischemic events, or new diabetes in patients previ-

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ously hospitalized with myocardial infarction found no differences in these end points each year out to 5 years. The risk of diabetes was in fact lower (but the difference was not statistically significant) in the high-dose groups out to 5 years. The risk of myocardial infarction or death was numerically different in the high-dose groups, but the difference was not statistically significant.

Preiss et al[25] in 2011 performed a meta-analysis of the impact of intensity of statin therapy on diabetes risk. They examined data from 32,752 participants without diabetes at baseline in five randomized controlled trials with more than 1,000 participants and more than 1 year of follow-up, comparing high-dose therapy against moderate-dose statin therapy.[21,22,26–28] New diabetes was considered present if there was an adverse event report of diabetes, if glucose-lowering drugs were started, or if two fasting plasma glucose measurements were higher than 7 mmol/L (126 mg/dL).

Diabetes developed in 1,449 (8.8%) of the intensive-therapy group and 1,300 (8.0%) of the moderate-therapy group (OR 1.12, 95% CI 1.04–1.22). In contrast, incident cardiovascular disease occurred in 3,134 (19.1%) of the intensive-therapy group and 3,550 (21.7%) of the moderate-therapy group (OR 0.84, 95% CI 0.75–0.94). Therefore, there was an 0.8% absolute increase in diabetes cases on high-dose statins and a 2.6% absolute reduction in adverse cardiovascular events.

The incidence of diabetes in meta-analysis of clinical trials: 4.89% on statins 4.5% on placebo

CAUTION IN INTERPRETING THESE DATA

There are many reasons for caution in interpreting these studies.

The trials were not designed to look for diabetes

The data supporting the relationship between statin therapy and higher risk of diabetes are primarily from observational studies. These studies were not prospectively designed to address this question, and we therefore need to view this as association and not as causation.

The definition of diabetes varied between trials, and new-onset diabetes was often not rigorously screened for. In many trials the outcome of diabetes was at least partially based on nonstandardized, nonadjudicated physician reporting.

Consequently, if statins reduce the risk of diabetes, the results from WOSCOPS may overstate the reduction, since this study used a nonstandard definition of incident diabetes (fasting plasma glucose > 126 mg/dL plus a > 36 mg/dL increase from baseline). When Sattar et al[11] reanalyzed WOSCOPS data using a more standard definition, they found a smaller effect.

On the other hand, nonstandardized physician reporting may overstate an adverse effect. Sattar et al[11] also found that when fasting plasma glucose levels alone were used as the definition for diabetes, the overall risk was attenuated and was no longer statistically significant (OR 1.07, 95% CI 0.97–1.17).

Perhaps statin therapy uncovers diabetes only in people at risk of diabetes

Perhaps statin therapy uncovers diabetes only in people at higher baseline risk of developing diabetes. Therefore, this adverse effect may be restricted to certain groups and not applicable to the general population.

In JUPITER, one of the two trials in which, on independent analysis, statin use was associated with new diabetes, 77% of patients in the rosuvastatin group who developed diabetes had impaired fasting glucose at entry and therefore were at higher risk of developing diabetes.[6]

Possibly, the relationship is driven by preexisting metabolic syndrome or other risk factors for diabetes. In the two studies that reported a statistically significantly higher incidence of new diabetes, more than 40% of patients in JUPITER met the criteria for metabolic syndrome, and metabolic syndrome, which increases in prevalence with age, was likely more prominent in the elderly population in PROSPER.

Waters et al[23] grouped patients according to whether they had risk factors for diabetes (impaired fasting glucose, obesity, elevated triglycerides, and hypertension) and found that those who had none or one of these risk factors had no difference in the rate of new-onset diabetes with either moderate or intensive statin therapy, but the risk was pronounced in those who had three or four risk factors.

Ridker et al[29] reanalyzed the JUPITER data from patients who did not have cardiovascular disease at baseline. Overall, for every 54

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new cases of diabetes in follow-up, 134 cardiovascular events or deaths were prevented. In subgroup analysis, those who had one or more risk factors for diabetes at baseline (metabolic syndrome, impaired fasting glucose, obesity, or hemoglobin A_{1c} > 6%) had a 39% reduction in the primary end point and a 28% increase in new diabetes. Those who had none of these risk factors had a 52% lower rate of cardiovascular events but no increase in diabetes.

Other confounding factors

Bias and confounding factors are difficult to control for in studies without prospectively defined, recognized, and analyzed outcomes.

Although it may be a bit of a stretch, residual confounding factors such as myalgia side effects while on statins may reduce exercise in the statin-treatment groups. Perhaps a change to a healthier lifestyle after cardiovascular events may be more common in placebo groups. Improved survival with statins may allow more people at risk of diabetes to live longer and present with the diagnosis.[30]

POSSIBLE EXPLANATIONS, BUT NO UNIFYING MECHANISM

If mechanisms could be identified to explain the association between statins and diabetes, this would strengthen the argument that it is a cause-and-effect relationship. Many explanations have been proposed as to how statins may influence glucose metabolism and insulin sensitivity.[31–34] These are *possible* explanations based on other observations.

In theory, statins may improve insulin sensitivity via their anti-inflammatory effect, since inflammatory markers and proinflammatory cytokines have been linked with insulin resistance. However, other effects of statins may adversely affect glycemic control.

In vivo analysis has shown that some but not all statins increase insulin levels and decrease insulin sensitivity in a dose-dependent fashion. Some statins decrease adiponectin and may worsen glycemic control through loss of adiponectin's proposed protective antiproliferative and antiangiogenic properties. In vitro studies and animal studies have demonstrated a decrease in expression of insulin-responsive glucose transporter 4 (GLUT4) with atorvastatin, and an increase in GLUT1. It has been hypothesized that reduction in isoprenoid biosynthesis or decreased insulin signaling may explain these effects and that changes in glucose transport in adipocytes may cause insulin resistance. Other studies suggest that dysregulation of cellular cholesterol may attenuate beta-cell function. Impaired biosynthesis of ubiquinones may result in delayed production of adenosine triphosphate and consequently diminish insulin release.

But different effects have been reported for atorvastatin, simvastatin, and pravastatin, arguing against a unifying explanation or, alternatively, suggesting that differences in lipophilicity and potency among statins are important. Hydrophilic statins may be less likely to be taken up by extrahepatic cells such as pancreatic cells and adipocytes, possibly lessening these effects. However, the strong association between rosuvastatin (which is hydrophilic) and new diabetes would not support this hypothesis.

Despite these speculations, lack of conformity in response to different statins and discrepancies in the clinical outcomes noted in trials fail to clearly identify a common causative mechanism.

For now, the higher rate of diabetes must be seen as an association, not cause and effect

OTHER COMMON THERAPIES MAY INFLUENCE GLYCEMIC CONTROL

Statins are not the first drugs for reducing cardiovascular risk that have been shown to affect glucose levels during treatment.

Niacin

Niacin has been known to increase glucose levels but has long been used as a treatment for dyslipidemia despite this caution. Reduced glycemic control during niacin treatment in diabetic patients does not seem to alter the beneficial effects of treatment.[35–37]

In a post hoc analysis of the Coronary Drug Project (CDP), in patient subgroups defined by baseline fasting plasma glucose and compared with placebo, niacin reduced the 6-year risk of recurrent myocardial infarction and the combined end point of coronary heart disease death or nonfatal myocardial infarction similarly (interactive *P* value nonsignificant) across all levels of baseline fasting plasma glu-

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cose, including levels of 126 mg/dL or higher at study entry.[36]

In another post hoc analysis of CDP patient subgroups defined by the change in glycemic status from baseline to 1 year, niacin reduced the 6-year risk of the same end points similarly (interactive *P* value nonsignificant) across all levels of change in fasting plasma glucose from baseline to year 1, whether baseline fasting plasma glucose levels decreased, stayed the same, or increased to 10 mg/dL or higher on niacin therapy.[36]

Therefore, the beneficial effect of niacin of reducing the rate of recurrent nonfatal myocardial infarction and coronary heart disease events was not significantly diminished when impaired fasting glucose or diabetes was present when therapy was started or by on-therapy increases from baseline fasting plasma glucose.

In addition, on-therapy changes in glycemic control may be dose-related and minimized by surveillance and therapy adjustments. The Assessment of Diabetes Control and Evaluation of the Efficacy of Niaspan Trial (ADVENT)[38] found that changes in glycemic control were minimal as measured by fasting glucose and hemoglobin A_{1c}; were associated with a higher niacin dose (1.5 g/day vs 1 g/day); and, when present, were successfully managed by adjusting the diabetes treatment regimen.

A meta-analysis found a higher risk of new diabetes with high-dose statin therapy (8.8%) than with moderate-dose therapy (8.4%)

Antihypertensive drugs

Diuretics as well as beta-blockers have been reported to increase the incidence of diabetes in patients with hypertension.[15,38–40]

A retrospective longitudinal cohort study[40] in 2009 examined the development of new-onset diabetes (defined as a new ICD-9 code for diabetes or initiation of diabetes treatment) in 24,688 treated hypertensive patients without diabetes at baseline; 4,385 (17.8%) of the patients developed diabetes. After adjusting for sex and age, the risk of new diabetes was significant in users of diuretics (OR 1.10), beta-blockers (OR 1.12), and calcium channel blockers (OR 1.10) compared with users of angiotensin-converting enzyme inhibitors, (OR 0.92), angiotensin receptor blockers (OR 0.90), or alpha-blockers (OR 0.88).

However, the increase in blood glucose does not seem to attenuate the beneficial effects of reducing cardiovascular events. In the Antihypertensive and Lipid-lowering Treatment to Prevent Heart Attack Trial (ALLHAT),[15] a long-term follow-up of those developing new-onset diabetes while taking chlorthalidone (Hygroton) found no difference in the risk of death from cardiovascular disease or from any cause (hazard ratio = 1.04).[15]

CLINICAL IMPLICATIONS

Balancing the benefits and risks of statins

It is important to examine how the 0.4% increase in absolute risk of new-onset diabetes as calculated in meta-analyses compares with the benefits of statin treatment in terms of cardiovascular risk reduction.

Using data from the Cholesterol Treatment Trialists (CTT) meta-analysis of statin trials in 71,370 participants, Sattar et al[11] estimated that statin treatment is associated with 5.4 fewer deaths from coronary heart disease and cases of nonfatal myocardial infarction per 255 patients treated over 4 years for each 1-mmol/L (39 mg/dL) reduction in LDL-C compared with controls. The benefit would be even greater if stroke, revascularization, and hospitalization are included as end points. This benefit is contrasted with the risk of developing 1 additional case of diabetes for every 255 patients treated with statins over the same period.

Preiss et al[25] calculated that there were 2 more cases of diabetes per 1,000 patient-years in patients receiving intensive doses than in those receiving moderate doses (18.9 vs 16.9), corresponding to 1 additional case of diabetes for every 498 patients treated per year. However, there were 6.5 fewer first major cardiovascular events per 1,000 patient-years (44.5 vs 51.0), corresponding to a number needed to treat per year to prevent 1 cardiovascular event of 155. Most of the benefit was due to fewer revascularizations, followed by nonfatal myocardial infarctions. The 12% increase in new diabetes with high-dose therapy contrasted with a 16% reduction in new cardiovascular disease combined events (OR 0.84, 95% CI 0.75–0.94).

As previously noted, in the JUPITER trial, the benefits of preventing cardiovascular events with statin therapy outweighed the risk of new diabetes in people both with and with-

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out baseline risk factors for diabetes.[29] Similar to the observations with niacin and some antihypertensive drugs, the increase in blood glucose with statins does not appear to reduce the benefits of cardiovascular risk reduction in these patients at moderate to high risk, even when used at high doses.

People with diabetes need aggressive lipid-lowering—with statins

Diabetes is a coronary heart disease risk equivalent and is associated with high risk of cardiovascular events.[41–46] Overall, the risk for these adverse events is two to four times greater in people with diabetes than without. Atherosclerosis-related events account for approximately 65% to 75% of all deaths in people with diabetes, and 75% of these events are coronary. Lipid abnormalities are strongly correlated with the risk of cardiovascular disease in people with diabetes, and aggressive treatment of risk factors, particularly lipid abnormalities, has been shown to reduce this risk.[47–49] And data from multiple clinical trials support the use of statins to lower LDL-C as the first-line therapy for dyslipidemia in people with diabetes, just as it is in the general population.[3–7,9,13,23,50–61]

Analyses of diabetic subgroups encompassing 18,000 to 20,000 patients in the large statin trials have clearly demonstrated the benefits of statin therapy. A recent meta-analysis of 10 placebo-controlled trials that included approximately 16,000 patients with diabetes and 54,000 without diabetes demonstrated a 30% reduction in coronary heart disease, a 19% reduction in strokes, and a 12% reduction in mortality.[54] Furthermore, in another meta-analysis of 14 trials, a similar 22% reduction in coronary heart disease was noted in people with diabetes whether or not they had a history of cardiovascular disease.[55]

Therefore, aggressive treatment of lipid abnormalities with statins as primary treatment has generally been adopted as a standard of care in diabetic patients, particularly those with clinical cardiovascular disease or one or more risk factors. The Adult Treatment Panel III guidelines recommend a minimum LDL-C goal of less than 100 mg/dL and a goal of less than 70 mg/dL as an option for patients with diabetes (TABLE 1).[41,62] Similar recommendations have been issued by the American Dia-

TABLE 1

Goals of lipid therapy by risk category: NCEP ATP III recommendations

RISK CATEGORY	LDL-C (mg/dL)	NON-HDL-C (mg/dL)
Coronary heart disease or coronary heart disease risk equivalent (10-year risk > 20%)	< 100 Optional: < 70	< 130 Optional: < 100
≥ 2 risk factors (10-year risk 10%–20%)	< 130	< 160
≥ 2 risk factors (10-year risk < 10%)	< 130	< 160
0–1 risk factor	< 160	< 190

Recommended goals for low-density and non-high-density lipoprotein cholesterol (LDL-C, non-HDL-C) by risk category. Diabetes is a coronary heart disease risk equivalent.

BASED ON GRUNDY SM, CLEEMAN JI, BAIREY MERZ CN, ET AL. IMPLICATIONS OF RECENT CLINICAL TRIALS FOR THE NATIONAL CHOLESTEROL EDUCATION PROGRAM ADULT TREATMENT PANEL III GUIDELINES. CIRCULATION 2004; 110:227–239.

TABLE 2

ACC/ADA suggested treatment goals in patients with cardiometabolic risk and lipoprotein abnormalities

	LDL-C (mg/dL)	Non-HDL-C (mg/dL)	ApoB (mg/dL)
Highest-risk patients, including those with: Known cardiovascular disease or Diabetes plus one or more additional major cardiovascular risk factors*	< 70	< 100	< 80
High-risk patients, including those with: No diabetes or known clinical cardiovascular disease but two or more additional major cardiovascular risk factors or Diabetes but no other major cardiovascular risk factors	< 100	< 130	< 90

*Other major risk factors (beyond dyslipoproteinemia) include smoking, hypertension, and a family history of premature coronary artery disease.
LDL-C = low-density lipoprotein cholesterol, non-HDL-C = non-high-density lipoprotein cholesterol, ApoB = apolipoprotein B

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betes Association together with the American College of Cardiology (TABLE 2),[30] the American Diabetes Association by itself,[63] and the American Academy of Pediatrics.[64]

Is new-onset diabetes as dangerous as established diabetes?

In studies to date, there did not appear to be more events in those who developed new-onset diabetes.

Waters et al,[24] evaluating three trials of high-dose atorvastatin therapy, found that major cardiovascular events occurred in 11.3% of those with new-onset diabetes, 10.8% of those without new-onset diabetes (HR 1.02, 95% CI 0.77–1.35), and 17.5% of those who had diabetes at baseline.

Therefore, it may not be appropriate to extrapolate the glucose changes seen on statin therapy to an equivalent increase in adverse cardiovascular events as seen in other diabetic patients. The beneficial reduction in cardiovascular events does not appear to be diminished in those developing diabetes. It is not clear that the increase in glucose on statins has the same implications of a new diagnosis of diabetes. Does this elevation in glucose represent true diabetes or some downstream effect? For example, thiazide diuretics have been known to increase blood glucose levels, but the levels drop when these drugs are discontinued, even after many years of treatment.

Patients at high risk of cardiovascular disease should not be denied the beneficial effects of statins on the basis of concerns about diabetes

On the other hand, it is possible that follow-up of 5 years or less in clinical trials has not allowed sufficient time to examine the influence of the increase in new-onset diabetes on future cardiovascular events. In addition, because of the widespread use of statins across a broad range of cardiovascular risk, even if the effect is small in absolute terms, the potential adverse effects are magnified, particularly in a low-risk population in which the cardiovascular benefits are smaller.

The association is real, but questions remain

In view of the evidence, it is difficult to refute that an association exits between statin use and new-onset diabetes, at least in some subgroups. The dose response noted in some studies further reinforces the conclusion that the association is real. However, many questions remain unanswered regarding mechanism of effect, whether there are differences depending on the particular statin or dose used, or differential effects in the populations treated (such as patients with metabolic syndrome or the elderly).

Until the contradictory observations can be resolved and plausible mechanisms of action elucidated, causality cannot be established. From a clinical standpoint there is no current evidence suggesting that the elevations in blood glucose seen while on lipid-lowering or blood-pressure-lowering therapy are associated with an increased risk of cardiovascular events or that they attenuate the beneficial effects of the therapy.

Statins should continue to be used in patients at high risk

Until further studies are done, statins should continue to be used, after assessing the risks and the benefits.

Primary prevention patients at moderate to high risk and secondary prevention patients stand to gain from statin therapy, and it should not be denied or doses reduced on the basis of concerns about the development of new-onset diabetes. The recognized modest risk of developing diabetes does not appear to blunt the cardioprotective effects of statin therapy in these moderate- to high-risk groups.

Rather than stop statins in patients at risk of diabetes such as the elderly or those with prediabetes, insulin resistance, or metabolic syndrome who are on therapy for appropriate reasons, it is reasonable to continue these drugs, monitoring glucose more closely and emphasizing the importance of weight reduction, diet, and aerobic exercise for preventing diabetes. The Diabetes Prevention Program Research Group, for example, reduced the incidence of diabetes by 58% over 2.8 years of follow-up with intensive lifestyle interventions (a low-calorie, low-fat diet plus moderate physical activity 150 minutes per week) vs usual care in at-risk populations.[65]

Should statins be used more cautiously in patients at lower risk?

The most recent Cholesterol Treatment Trialists meta-analysis of 27 randomized clinical trials (22 placebo-controlled, 134,537 people; 5 high-dose vs low-dose, 39,612 people) re-

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ported that reducing LDL-C with statins lowered cardiovascular risk even in low-risk patients.[66] Overall, there were 21% fewer major cardiovascular events (coronary heart disease, stroke, or coronary revascularization) for every 1-mmol/L reduction in LDL-C.

The proportional reduction in events was at least as large in the two lowest-risk groups (estimated 5-year risk of < 5% and 5% to < 10%, 53,152 people) as in the higher-risk groups. This was reflected mainly in fewer nonfatal myocardial infarctions and coronary revascularizations. In these groups, the absolute reduction in risk for each 1-mmol/L reduction in LDL-C was 11 per 1,000 patients over 5 years. Even in this low-risk population, the reduction in cardiovascular risk seems to compare favorably with the small estimated increase risk of diabetes.

However, even in the lowest-risk group studied, the average baseline LDL-C level was greater than 130 mg/dL.

Therefore, in groups in which the benefits of statins on cardiovascular risk reduction are less robust (eg, low-risk primary prevention groups without significant elevations in LDL-C, particularly the elderly), it would not be difficult to justify the case for more cautious use of statin therapy. If statins are used in these low-risk groups, restricting their use to those with at least moderate LDL-C elevation, using less aggressive LDL-C-lowering targets, and regular monitoring of fasting glucose seem reasonable until further information is available.

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