REVIEW

Byron J. Hoogwerf, MD, FACP, FACE
Clinical Professor of Endocrinology/Medical Sciences Discipline, Central Michigan University College of Medicine, Mount Pleasant, MI; Emeritus, Department of Endocrinology, Diabetes, and Metabolism, Cleveland Clinic, Cleveland, OH

Statins may increase diabetes, but benefit still outweighs risk

ABSTRACT

Data have been accumulating on the risk of developing type 2 diabetes in patients receiving statins and on the potential adverse effects of these drugs on glycemic control in patients who already have type 2 diabetes. This article reviews data linking statin use and new-onset diabetes mellitus, the effects of statins on glycemic control in type 2 diabetes, the benefit-risk considerations of statin use and type 2 diabetes, and how these factors affect patient management.

KEY POINTS

The weight of the evidence suggests that statin use is associated with an increased risk of new-onset diabetes mellitus, but the magnitude of the effect has varied across studies, including differences between randomized controlled trials and observational studies.

The risk is generally greater with high-intensity statin therapy and higher statin doses. However, many other variables are also involved, including prediabetes, genetics, central obesity, dyslipidemia, hypertension, lifestyle, and other medications, most notably glucocorticoids.

In patients with type 2 diabetes mellitus, statin use is associated with a small increase in hemoglobin A1c, and this effect may be greater with atorvastatin than with other statins. However, the benefits of statins in preventing atherosclerotic cardiovascular disease outweigh their adverse effects on glycemic control.

Pitavastatin has been associated with a lower risk of new-onset diabetes mellitus, but it lacks data on cardiovascular outcomes from large trials in patients with diabetes.

doi:10.3949/ccjm.90a.22069

After the first of the statins was introduced in 1987, a number of clinical trials demonstrated that these drugs, which effectively lower low-density lipoprotein cholesterol (LDL-C) levels, consistently reduce the risk of atherosclerotic cardiovascular disease events in many types of patients, including those with type 2 diabetes mellitus.[1] One of these trials—the West of Scotland Coronary Prevention Study (WOSCOPS),[2] with 5,974 patients—even reported that statins decreased the risk of new-onset diabetes.

Then, a larger trial—Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER)[3] with 17,802 participants treated with rosuvastatin or placebo—found a higher incidence of diabetes in the rosuvastatin group.

This observation raised questions and stimulated efforts to find answers. Do statins cause diabetes? If they do, is it true for all statins? Is the risk a function of the potency and dose of the statin? Are there other risk factors for this effect? In patients who already have diabetes, do statins worsen glycemic control? Most importantly, do the benefits of statin use in reducing cardiovascular risk outweigh any increased risk of new-onset diabetes mellitus?

Two caveats are warranted. First, in most studies, new-onset diabetes was diagnosed by the individual investigators and not according to any protocol. It was probably underdiagnosed, but in double-blind trials, the amount of underdiagnosis was likely about the same in each treatment group. Second, there are not enough data on microvascular complications of diabetes mellitus in statin-treated patients to warrant

Downloaded from www.ccjm.org on April 20, 2024. For personal use only. All other uses require permission.

TABLE 1
Statins and diabetes: Results of 13 trials

Trial and statin	Risk of diabetes with statin use
Trial of atorvastatin	
ASCOT-LLA (Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm)	Higher
Trials of simvastatin	
HPS (Heart Protection Study)	Higher
4S (Scandinavian Simvastatin Survival Study)	Higher
Trials of rosuvastatin	
JUPITER (Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin)	Higher
CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure)	Higher
GISSI HF (*Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico*–Heart Failure)	Higher
Trials of pravastatin	
WOSCOPS (West of Scotland Coronary Prevention Study	Lower
LIPID (Long-Term Intervention with Pravastatin in Ischaemic Disease)	Lower
MEGA (Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese)	Higher
ALLHAT-LLT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial)	Higher
GISSI PREVENZIONE (*Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico–Prevenzione*)	Lower
PROSPER (Prospective Study of Pravastatin in the Elderly at Risk)	Higher
Trial of lovastatin	
AFCAPS/TexCAPS (Air Force/Texas Coronary Atherosclerosis Prevention Study)	Lower

Based on information from reference 5.

any discussion of risk vs benefit. The available results are limited and inconsistent regarding statin benefit or harm for microvascular complications, and they vary for retinopathy, nephropathy, and neuropathy.

DO STATINS CAUSE DIABETES? A NEW LOOK AT OLD TRIALS

Investigators have examined data from a number of trials of statin therapy in preventing cardiovascular disease events to look for effects on the incidence of new-onset diabetes mellitus.

The JUPITER trial[3] reported the incidence of physician-reported new-onset diabetes mellitus during the 1.9-year trial duration as 3.0% in the rosuvastatin group and 2.4% in the placebo group ($P < .01$).

Rajpathak et al[4] performed a meta-analysis of 6 trials, including JUPITER[3] and WOSCOPS.[2] The risk of new-onset diabetes mellitus was increased by 6% when WOSCOPS was included (P = NS) and by 13% ($P = .008$) when WOSCOPS was excluded.[4]

Sattar et al[5] performed another meta-analysis of the same 6 trials plus 7 more, for a total of 13. The results varied widely across trials (**Table 1**).[5] In 4 trials, the incidence of new-onset diabetes was higher in the control group than in the statin group, while it was higher in the statin group in the other 9.[5] Individually, none of the findings was statistically significant, but combined, the odds ratio for new-onset diabetes was 1.09 with statins, which was statistically significant (95% confidence interval [CI] 1.02–1.17). The investigators calculated that 255 patients would need

Downloaded from www.ccjm.org on April 20, 2024. For personal use only. All other uses require permission.

to be treated with statins for 4 years to observe 1 extra case of diabetes.[5]

The Women's Health Initiative[6] recruited 161,808 postmenopausal women without diabetes mellitus at baseline, of whom 153,840 had enough data to be analyzed post hoc. Statin therapy was associated with a 71% higher risk of new-onset diabetes mellitus (self-reported). After adjustment for age, body mass index, family history of diabetes, and other variables, the risk was still 48% higher in statin users.[6]

Lin et al[7] used a database of more than 30,000 patients who had undergone percutaneous intervention for acute coronary syndromes. Propensity score matching (n = 9,043 in each group) was used to evaluate the effects of statin use vs no statin use on new-onset diabetes. In the unmatched cohort, statin use was actually associated with a lower risk of diabetes. However, in the matched cohort the risk of new-onset diabetes was higher in statin users than in nonusers (adjusted hazard ratio 1.27, 95% CI 1.14–1.41, $P \leq .001$). The hazard ratios varied depending on which statin the patients received, and they were all statistically significant except for lovastatin (and the risk was lower in lovastatin users than in those not receiving any statin at all). Hazard ratios were as follows:

- Lovastatin 0.87
- Atorvastatin 1.30
- Fluvastatin 1.38
- Rosuvastatin 1.42
- Pravastatin 1.71.[7]

Engeda et al[8] performed a meta-analysis of 8 randomized controlled trials and 15 observational studies. They found an association between statin use and new-onset diabetes mellitus and also showed that the risk was higher in observational studies (relative risk 1.55, 95% CI 1.39–1.74) than in randomized controlled trials (relative risk 1.11, 95% CI 1.00–1.22).[8]

In summary, the weight of the evidence suggests that statin use is associated with an increased risk of new-onset diabetes mellitus, but the magnitude of the effect varied across studies, including differences between randomized controlled trials and observational studies.

DO ALL STATINS DO IT? DOES RISK VARY BY STATIN INTENSITY?

Statin potency, now more commonly called statin intensity, is based on the amount by which each statin lowers LDL-C and at what dose. Statins are thus classified as high-, moderate-, or low-intensity (**Table 2**),[9] and this classification is widely used in guidelines for giving statins to prevent atherosclerotic cardiovascular disease based on the patient's baseline risk of cardiovascular events.[9]

TABLE 2
Categories of statin therapy

High intensity (lowers LDL-C at least 50%)
Atorvastatin 40–80 mg
Rosuvastatin 20–40 mg
Moderate intensity (lowers LDL-C 30%–49%)
Atorvastatin 10–20[a] mg
Fluvastatin 40 mg twice a day
Fluvastatin XL 80 mg[a]
Pitavastatin 1–4 mg[a]
Pravastatin 40–80 mg
Rosuvastatin 5[a]–10 mg
Simvastatin 20–40 mg
Low intensity (lowers LDL-C less than 30%)
Fluvastatin 20–40 mg[a]
Lovastatin 20 mg
Pravastatin 10–20 mg
Simvastatin 10 mg[a]

[a]Not evaluated in randomized controlled trials at dosage shown.

LDL-C = low-density lipoprotein cholesterol

Based on information in reference 9.

Dose-response relationships among statins and their effects on LDL-C levels have been well known since the first statins came on the market.[10] Since proprotein convertase subtilisin/kexin type 9 inhibitors, which lower LDL-C levels even more than statins do, have not been reported to increase the risks of dysglycemia or new-onset diabetes, any relationships between statins and diabetes risk is likely related to the statin itself and not to the LDL-C reduction.[11]

A number of studies have addressed whether statin dose and intensity are related to the risk of new-onset diabetes mellitus.

Preiss et al[12] reported on 5 large clinical trials comparing statins in higher vs lower doses and showed that each of them had an odds ratio point estimate greater than 1 for higher doses to increase incident diabetes. The odds ratio for the pooled estimate was 1.12 (95% CI 1.04–1.22).[12]

Downloaded from www.ccjm.org on April 20, 2024. For personal use only. All other uses require permission.

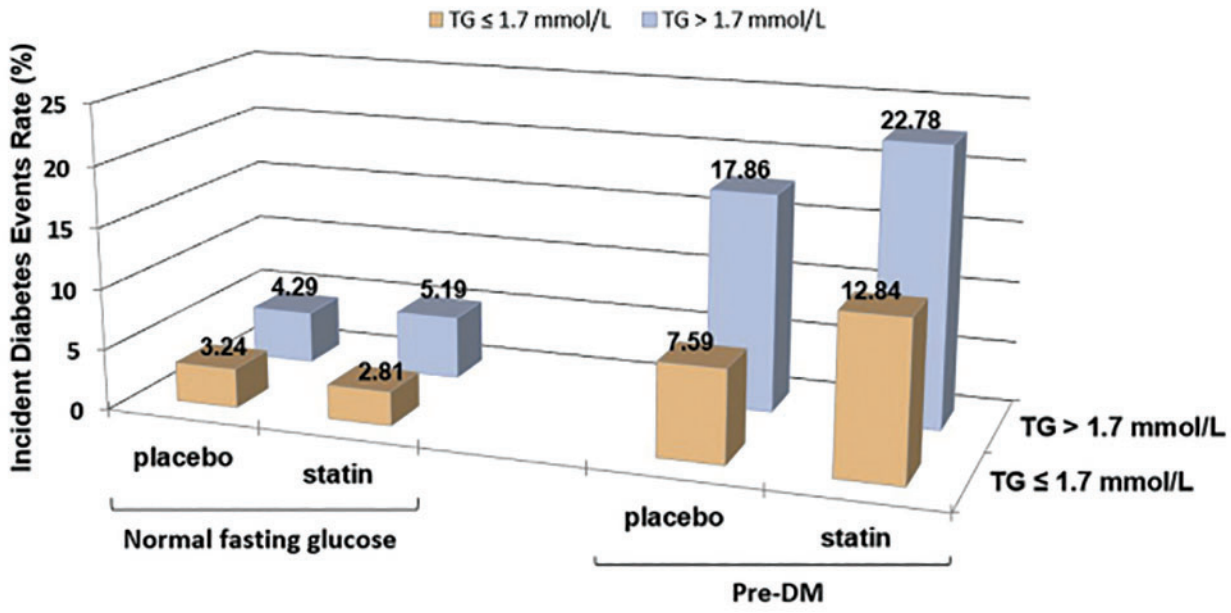

Figure 1. Risk of new-onset diabetes according to statin use, prediabetes, and elevated triglyceride (TG) level in the Treating to New Targets trial and the Stroke Prevention by Aggressive Reduction in Cholesterol Levels trial. For triglycerides, 1.7 mmol/L = 150 mg/dL.

Reprinted from Am J Cardiol, Vol 118(9), Kohli P, Knowles JW, Sarraju A, Waters DD, Reaven G. Metabolic markers to predict incident diabetes mellitus in statin-treated patients (from the Treating to New Targets and the Stroke Prevention by Aggressive Reduction in Cholesterol Levels Trials), pages 1275–1281; 2016, with permission from Elsevier.

Other investigators have analyzed higher- and lower-intensity statins, each compared with placebo.

Sattar et al,[5] in the meta-analysis described above, calculated that the overall odds ratios for incident diabetes were nominally higher with rosuvastatin (1.18), atorvastatin (1.14), and simvastatin (1.11) than with pravastatin (1.03) and lovastatin (0.98); recall that for all 13 studies combined it was 1.09 (**Table 1**).[5] The analysis could not adjust for all confounders such as age, new-onset diabetes mellitus being more common in older patients.[5]

Navarese et al[13] performed a network meta-analysis of 17 randomized controlled trials (14 placebo-controlled and 3 that compared 2 doses of statins) with a total of 113,394 participants. The data generally suggested a relationship between statin intensity as well as higher vs lower doses of some statins and risk of diabetes. The incidence of new diabetes was highest with rosuvastatin and lowest with pravastatin.

Carter et al[14] performed a population-based study using information from several databases in Ontario, Canada. Data from 471,250 patients who did not have diabetes at baseline and were treated with a statin supported the idea that the risk was greater with rosuvastatin, atorvastatin, and simvastatin than with lovastatin and fluvastatin in both primary and secondary cardiovascular disease prevention cohorts. The incidence of diabetes was also a function of duration of exposure.

In summary, the weight of the evidence from randomized controlled trials and observational studies suggests that higher-intensity statins and higher doses of statins are associated with higher risk of new-onset diabetes mellitus.

RISK FACTORS FOR DIABETES IN NON–STATIN-TREATED PATIENTS

Phenotypic and laboratory variables that may be associated with risk of new-onset diabetes mellitus in general include the following:

- Fasting blood glucose levels
- Postprandial glucose levels
- Triglyceride levels
- Hypertriglyceridemia, including elevated ratio of triglyceride to high-density lipoprotein cholesterol
- Hypertension

Downloaded from www.ccjm.org on April 20, 2024. For personal use only. All other uses require permission.

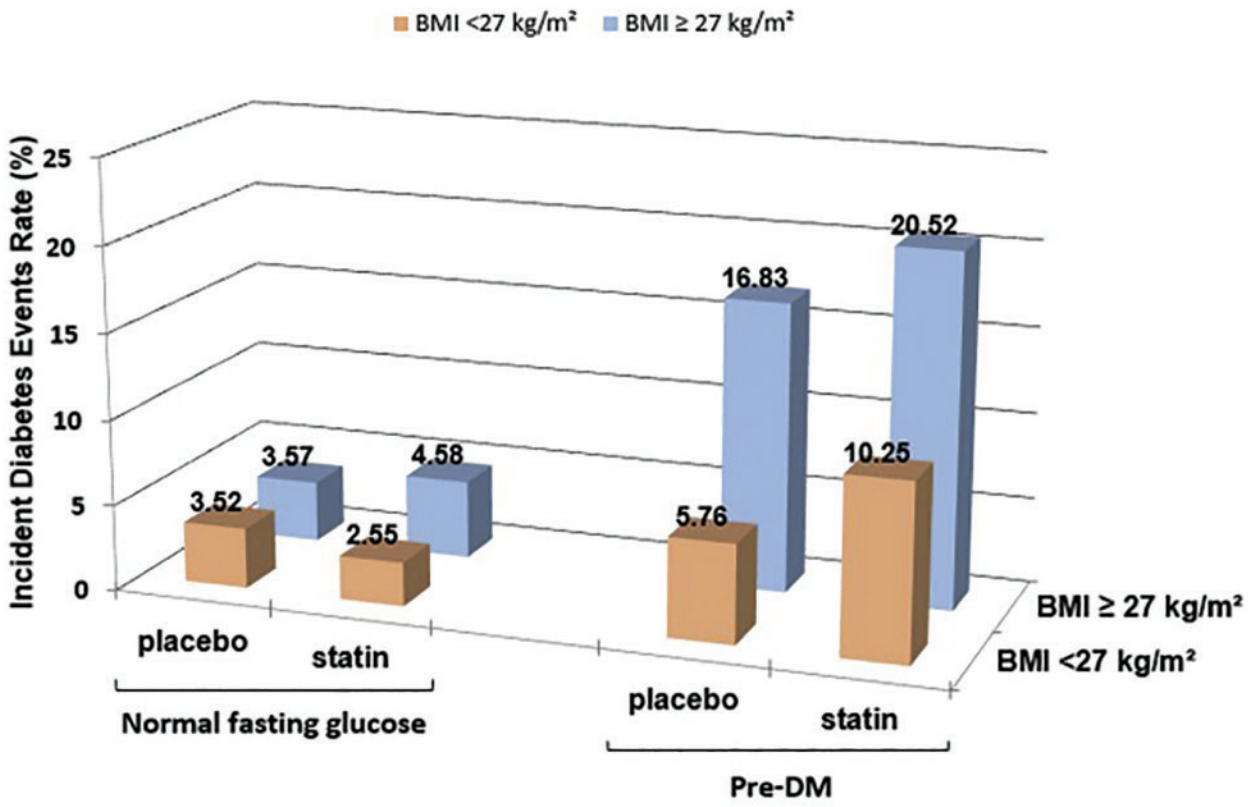

Figure 2. Risk of new-onset diabetes by statin use, prediabetes, and body mass index (BMI) in the Treating to New Targets trial and the Stroke Prevention by Aggressive Reduction in Cholesterol Levels trial.

Reprinted from Am J Cardiol, Vol 118(9), Kohli P, Knowles JW, Sarraju A, Waters DD, Reaven G. Metabolic markers to predict incident diabetes mellitus in statin-treated patients (from the Treating to New Targets and the Stroke Prevention by Aggressive Reduction in Cholesterol Levels Trials), pages 1275–1281; 2016, with permission from Elsevier.

- Elevated measures of obesity, including body mass index and waist-to-hip ratio
- Smoking
- Depression
- Hyperuricemia
- Sleep disturbances
- Gestational diabetes
- Polycystic ovary disease.
- Biomarkers of insulin resistance.[15,16]

RISK FACTORS FOR DIABETES IN STATIN-TREATED PATIENTS

Many of the same risk factors associated with the development of diabetes in the general population are also present in statin users who develop associated diabetes.[17–20]

Kohli et al,[21,22] in an analysis of 2 large trials of atorvastatin,[19,20] reported that the risk of new-onset diabetes in patients who had high triglyceride levels or high body mass index depended on whether they had prediabetes, ie, fasting blood glucose or hemoglobin A1c levels higher than normal but not high enough to be classified as diabetes. Statins had little effect on the incidence of diabetes in those who did not have prediabetes (**Figure 1, Figure 2**).[21] The risk continued to diverge over time between the group with prediabetes and the group without prediabetes, and was greatest in those with prediabetes receiving atorvastatin 80 mg daily (**Figure 3**).[21]

Among the 15,056 participants who did not have diabetes at baseline, 5,924 (39%) had a fasting glucose level between 100 mg and 126 mg (designated prediabetes) and 9,132 (61%) had normal fasting glucose levels.[22] Statin treatment was balanced between groups. As in other studies, the participants with prediabetes were older and more likely to have features of metabolic syndrome, hypertension, higher

Downloaded from www.ccjm.org on April 20, 2024. For personal use only. All other uses require permission.

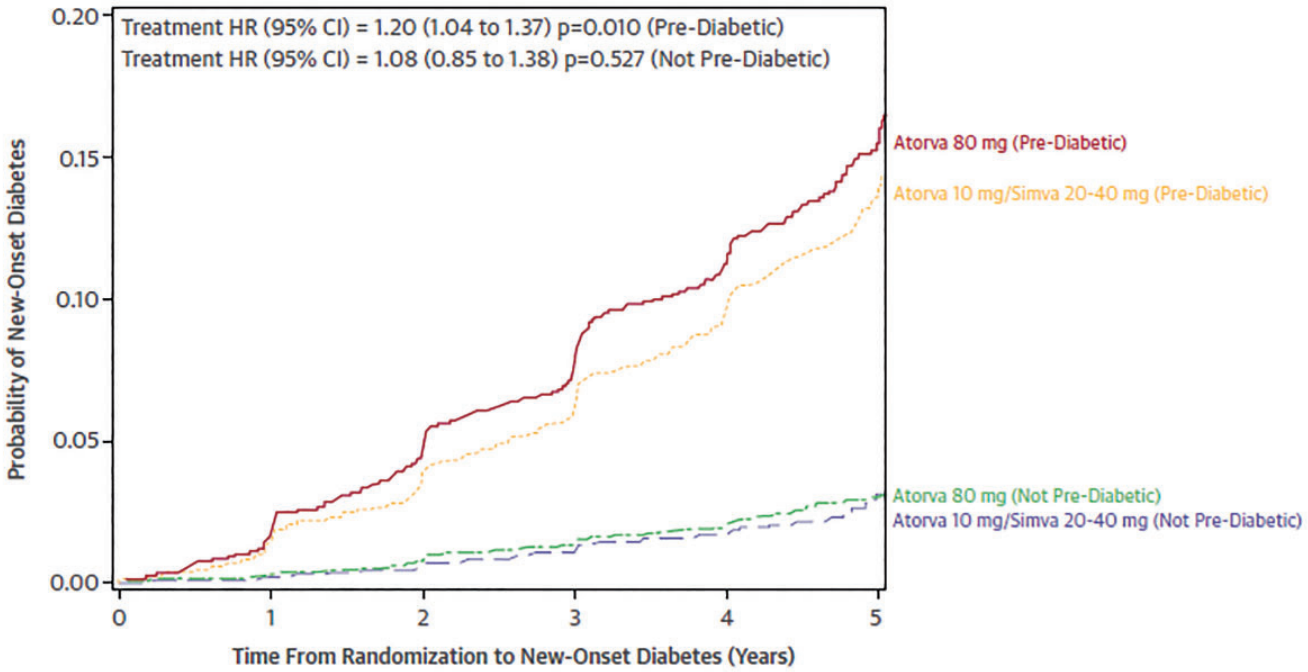

Figure 3. Risk of new-onset diabetes by statin use, prediabetes, and body mass index in the Treating to New Targets and the Stroke Prevention by Aggressive Reduction in Cholesterol Levels trials (Atorva = atorvastatin; CI = confidence interval; HR = hazard ratio).

Reprinted from Am J Cardiol, Vol 118(9), Kohli P, Knowles JW, Sarraju A, Waters DD, Reaven G. Metabolic markers to predict incident diabetes mellitus in statin-treated patients (from the Treating to New Targets and the Stroke Prevention by Aggressive Reduction in Cholesterol Levels Trials), pages 1275–1281; 2016, with permission from Elsevier.

triglyceride levels, and lower HDL-C levels. During a mean 5-year follow-up, 14.2% of participants with prediabetes developed new diabetes compared with 2.9% of those without prediabetes.[22]

High-intensity statin use in prediabetes was associated with a higher risk of new diabetes, but in patients with normal fasting glucose levels there was no difference in diabetes risk between those who received high-intensity vs low-intensity statins.[22]

Arsenault et al[23] assessed 18 biomarkers associated with the risk of cardiovascular disease in the Treat to New Targets trial and found that plasma lipids, adiponectin, and lipoprotein-associated phospholipase A2 might be also useful for predicting incident diabetes in statin-treated patients.

In summary, variables associated with increased risk of progression to diabetes in general cohorts are also associated with an increased risk of diabetes in statin-treated patients. The statin-associated risk of diabetes is most evident in patients with high fasting blood glucose levels and prediabetes. These observations suggest that statin use is an additional risk factor for new-onset diabetes.

DO STATINS WORSEN GLYCEMIC CONTROL?

Statin use was associated with increasing hemoglobin A1c and fasting blood glucose levels in patients with established type 2 diabetes in some studies.[24–31] Several small randomized controlled trials had designs that allowed analyses of statin effects on glycemic control.

Simsek et al[24] reported that hemoglobin A1c values increased by 0.3% with both atorvastatin 80 mg/day and rosuvastatin 40 mg/day over 18 weeks.

The AFORRD trial (Atorvastatin in Factorial With Omega-3 EE90 Risk Reduction in Diabetes),[25] in 800 patients with type 2 diabetes, reported that hemoglobin A1c increased by the same amount (0.3%) with atorvastatin 10 mg over 4 months.

Teramoto,[26] in contrast, found that hemoglobin A1c decreased with pitavastatin.

Three meta-analyses addressed the effects of statins on glycemic control in type 2 diabetes.

Zhou et al[27] analyzed 26 statin trials that included 3,232 participants and concluded that statin therapy "had no remarkable influence" on hemoglobin A1c. The mean change was 0.04%.[27]

Downloaded from www.ccjm.org on April 20, 2024. For personal use only. All other uses require permission.

Erqou et al[28] performed a meta-analysis of 9 placebo-controlled trials of atorvastatin, simvastatin, and pravastatin. Overall, the hemoglobin A1c levels were 0.12% higher in the statin groups than in the control groups after an average follow-up of 3.6 years, with most of the effect related to atorvastatin use. This analysis is confounded by inadequate information on any changes in use of glucose-lowering agents.

Cui et al[29] performed a network meta-analysis of 23 trials to assess the overall effects of statin and statin dosage on hemoglobin A1c. Overall, in statin users, hemoglobin A1c increased by 0.11%. The greatest effect was with high-intensity atorvastatin, which was associated with a mean increase of 0.63%. Pitavastatin was associated with a reduction in hemoglobin A1c compared with all other statins.

The Fremantle Diabetes Study,[30] an observational study in Australia, found that low-intensity statins (n = 119) were not associated with any change in hemoglobin A1c, moderate-intensity statins (n = 195) were associated with a mean increase of 0.22% (P = .022), and high-intensity statins (n = 11) were associated with a mean increase of 1.05% (P = .023).

Sukhija et al[31] reported changes in fasting blood glucose in a large database of US Veterans Affairs patients with type 2 diabetes mellitus. In unadjusted analyses, fasting blood glucose increased from 102 mg/dL to 141 mg/dL in statin users and from 100 mg/dL to 129 mg/dL in statin nonusers.

In summary, any conclusions about the effects of statins on glycemic control, especially hemoglobin A1c, in type 2 diabetes are confounded by the type of analyses, the limited data on any changes in glucose-lowering agents, and study durations and size. Overall, the data support the conclusion that there is a small aggregate effect of statins in increasing hemoglobin A1c. This effect may be greatest with high-dose atorvastatin and least with pitavastatin.

HOW MIGHT STATINS INCREASE DIABETES RISK?

Historically, type 2 diabetes has been largely characterized by 2 major metabolic abnormalities: insulin resistance and declining beta-cell function. However, many other abnormalities including inflammation, glucagon dysregulation, and altered renal thresholds for glycosuria are also associated with it.

Mechanistic studies in animals and humans have sought links between statin use and diabetes risk. One of the more likely possible explanations is statin-associated insulin resistance.[32–35] This hypothesis has not been tested in the large studies of new-onset diabetes mellitus or studies of changes in hemoglobin A1c in type 2 diabetes mellitus.

BENEFIT OUTWEIGHS RISK

Diabetes has been consistently shown to be associated with an increased risk for cardiovascular disease, and many clinical trials have shown that statin treatment is associated with a reduction in cardiovascular disease risk.[1] Most patients with type 2 diabetes mellitus are at high risk of atherosclerotic cardiovascular disease because they also have other risk factors such as obesity, hypertension, and the high triglyceride-to-low HDL-C ratio often associated with insulin resistance. Thus, the obvious concern revolves around whether the risk of developing diabetes with statin alters the benefit-risk considerations and whether statin use significantly attenuates the benefits of statins on atherosclerotic disease risk and events.

Conclusions about the effects of statins on glycemic control are confounded by the type of analysis, study duration and size, and other factors

Ridker et al[36] analyzed the JUPITER[3] data and concluded, "the cardiovascular and mortality benefits of statin therapy exceed the diabetes hazard, including in participants at high risk of developing diabetes."[36] The benefit-risk question has also been addressed in thoughtful reports by Navarese et al[37] and Collins et al.[38] Each of these groups concluded that the evidence supports the contention that in patients with a high risk for atherosclerotic disease, the benefits of statin use outweigh the risk of new-onset diabetes. Navarese et al noted that the benefit-risk considerations are less clear for patients without diabetes and 0 to 1 risk factors.[37] Collins et al stated that "the absolute benefits of statin therapy depend on the individual's absolute risk of occlusive vascular events and the absolute reduction in LDL cholesterol that is achieved."[38]

GUIDELINES SUGGEST SHARED DECISION-MAKING

The 2018 guidelines[9] suggest that in patients at low risk of atherosclerotic cardiovascular disease based on a low 10-year risk score and no diabetes, starting a statin is recommended only after discussing it with the patient. This approach aligns with the considerations raised by Navarese et al.[37]

Downloaded from www.ccjm.org on April 20, 2024. For personal use only. All other uses require permission.

TABLE 3
Starting statin therapy: Things to consider and discuss

For all patients when considering statin therapy:
Screen to determine baseline glycemic status
Consider nonstatin therapies to lower cholesterol (resins, ezetimibe, bempedoic acid)
Consider variables associated with an increased risk of diabetes, including potentially adverse antihypertensive drugs (thiazides and beta-blockers) and potentially beneficial antihypertensive drugs (angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers)
When starting statin therapy in patients without diabetes, discuss:
The possibility of developing diabetes mellitus
Types and doses of statins
Benefits of statins in reducing the risk of cardiovascular disease generally far outweigh risks on the development of new-onset diabetes
For patients with diabetes mellitus, discuss:
The possible adverse effects of statins on glycemic control, which are small
The benefits of statins in reducing the risk of atherosclerotic cardiovascular disease, which significantly outweigh a small increase in hemoglobin A1c
Adverse glycemic effects of statins can be mitigated by glucose-lowering therapies, especially those with favorable cardiovascular profiles

Based on recommendations from references 9, 40, and 41.

If patients have a calculated 10-year risk of 7.5% or higher but no other significant risk factors, besides elevated LDL-C, the guidelines suggest a discussion about starting a moderate-intensity statin, eg, pravastatin 40 mg, lovastatin 40 mg, fluvastatin 80 mg, or pitavastatin 1 to 4 mg daily. Each of these is associated with a lower risk of new-onset diabetes mellitus than the high-intensity statins.

Some data suggest that pitavastatin actually lowers the risk of diabetes, but this drug lacks the extensive cardiovascular disease outcomes data in patients with diabetes that exist for the other statins,[1] and this fact may be a point of discussion between the healthcare team and patient.

If patients have a calculated 10-year risk of 7.5% to 19.9%, especially when associated with additional risk factors, then the guidelines favor starting an intermediate-intensity statin. As noted above, the risk of new diabetes with statin use is higher in people who already have multiple atherosclerotic cardiovascular disease risk factors.[9,37]

In patients without type 2 diabetes and at low 10-year risk of atherosclerotic cardiovascular disease, if statin use is agreed on between the healthcare team and patient, a low-intensity statin is likely the best consideration.

In patients without type 2 diabetes but with multiple risk factors and a high risk for atherosclerotic cardiovascular disease over 10 years, the use of moderate- or high-intensity statins is justified, as the benefits of statins outweigh the risk of developing diabetes.

The guidelines do not discuss how statin therapy may change in a patient who develops new-onset diabetes mellitus related to statin use, but it has been addressed by Collins et al.[38] In cardiovascular disease risk calculators, diabetes is a yes-or-no question, and having diabetes approximately doubles one's risk. However, this may be overly simplistic, as the relationship between glucose and cardiovascular risk is continuous and graded.[39] In general, benefits of both moderate-intensity and high-intensity statins on reducing the risk for atherosclerotic cardiovascular disease events outweigh risks associated with hyperglycemia.

In patients with type 2 diabetes who are treated with moderate- or high-intensity statins, careful follow-up of hemoglobin A1c and appropriate glucose-lowering therapy should be implemented. Glucose-lowering therapies with established benefits on atherosclerotic cardiovascular disease are preferred.

Backes et al[40] have distilled these recommendations into a digestible format, which I have combined with those of the guidelines in **Table 3**.[9,40,41]

DISCLOSURES

Dr. Hoogwerf has disclosed ownership interest in Eli Lilly and consulting for Mannkind and Zealand Pharmaceuticals.

Downloaded from www.ccjm.org on April 20, 2024. For personal use only. All other uses require permission.

REFERENCES

1. **Cholesterol Treatment Trialists' (CTT) Collaborators, Kearney PM, Blackwell L, Collins R, et al.** Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. Lancet 2008; 371(9607):117–125. doi:10.1016/S0140-6736(08)60104-X
2. **Freeman DJ, Norrie J, Sattar N, et al.** Pravastatin and the development of diabetes mellitus: evidence for a protective treatment effect in the West of Scotland Coronary Prevention Study. Circulation 2001; 103(3):357–362. doi:10.1161/01.cir.103.3.357
3. **Ridker PM, Danielson E, Fonseca FA, et al.** Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med 2008; 359(21):2195–2207. doi:10.1056/NEJMoa0807646
4. **Rajpathak SN, Kumbhani DJ, Crandall J, Barzilai N, Alderman M, Ridker PM.** Statin therapy and risk of developing type 2 diabetes: a meta-analysis. Diabetes Care 2009; 32(10):1924–1929. doi:10.2337/dc09-0738
5. **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(9716):735–742. doi:10.1016/S0140-6736(09)61965-6
6. **Culver AL, Ockene IS, Balasubramanian R, et al.** Statin use and risk of diabetes mellitus in postmenopausal women in the Women's Health Initiative. Arch Intern Med 2012; 172(2):144–152. doi:10.1001/archinternmed.2011.625
7. **Lin ZF, Wang CY, Shen LJ, Hsiao FY, Lin Wu FL.** Statin use and the risk for incident diabetes mellitus in patients with acute coronary syndrome after percutaneous coronary intervention: a population-based retrospective cohort study in Taiwan. Can J Diabetes 2016; 40(3):264–269. doi:10.1016/j.jcjd.2015.12.006
8. **Engeda JC, Stackhouse A, White M, et al.** Evidence of heterogeneity in statin-associated type 2 diabetes mellitus risk: a meta-analysis of randomized controlled trials and observational studies. Diabetes Res Clin Pract 2019; 151:96–105. doi:10.1016/j.diabres.2019.04.005
9. **Grundy SM, Stone NJ, Bailey AL, et al.** 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2019; 73(24):3168–3209. doi:10.1016/j.jacc.2018.11.002
10. **Weng TC, Yang YH, Lin SJ, Tai SH.** A systematic review and meta-analysis on the therapeutic equivalence of statins. J Clin Pharm Ther 2010; 35(2):139–151. doi:10.1111/j.1365-2710.2009.01085.x
11. **Monami M, Sesti G, Mannucci E.** PCSK9 inhibitor therapy: a systematic review and meta-analysis of metabolic and cardiovascular outcomes in patients with diabetes. Diabetes Obes Metab 2019; 21(4):903–908. doi:10.1111/dom.13599
12. **Preiss D, Seshasai SR, Welsh P, et al.** Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis. JAMA 2011; 305(24):2556–2564. doi:10.1001/jama.2011.860
13. **Navarese EP, Buffon A, Andreotti F, et al.** Meta-analysis of impact of different types and doses of statins on new-onset diabetes mellitus. Am J Cardiol 2013; 111(8):1123–1130. doi:10.1016/j.amjcard.2012.12.037
14. **Carter AA, Gomes T, Camacho X, Juurlink DN, Shah BR, Mamdani MM.** Risk of incident diabetes among patients treated with statins: population based study. BMJ 2013; 346:f2610. doi:10.1136/bmj.f2610
15. **Ismail L, Materwala H, Al Kaabi J.** Association of risk factors with type 2 diabetes: a systematic review. Comput Struct Biotechnol J 2021; 19:1759–1785. doi:10.1016/j.csbj.2021.03.003
16. **Defronzo RA.** Banting lecture. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. Diabetes 2009; 58(4):773–795. doi:10.2337/db09-9028
17. **Waters DD, Ho JE, DeMicco DA, et al.** Predictors of new-onset diabetes in patients treated with atorvastatin: results from 3 large randomized clinical trials. J Am Coll Cardiol 2011; 57(14):1535–1545. doi:10.1016/j.jacc.2010.10.047
18. **Waters DD, Ho JE, Boekholdt SM, et al.** Cardiovascular event reduction versus new-onset diabetes during atorvastatin therapy: effect of baseline risk factors for diabetes. J Am Coll Cardiol 2013; 61(2):148–152. doi:10.1016/j.jacc.2012.09.042
19. **LaRosa JC, Grundy SM, Waters DD, et al.** Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med 2005; 352(14):1425–1435. doi:10.1056/NEJMoa050461
20. **Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Investigators, Karam JG, Loney-Hutchinson L, McFarlane SI.** High-dose atorvastatin after stroke or transient ischemic attack: the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Investigators. J Cardiometab Syndr 2008; 3(1):68–69. doi:10.1111/j.1559-4572.2008.07967.x
21. **Kohli P, Knowles JW, Sarraju A, Waters DD, Reaven G.** Metabolic markers to predict incident diabetes mellitus in statin-treated patients (from the Treating to New Targets and the Stroke Prevention by Aggressive Reduction in Cholesterol Levels Trials). Am J Cardiol 2016; 118(9):1275–1281. doi:10.1016/j.amjcard.2016.07.054
22. **Kohli P, Waters DD, Nemr R, et al.** Risk of new-onset diabetes and cardiovascular risk reduction from high-dose statin therapy in pre-diabetics and non-pre-diabetics: an analysis from TNT and IDEAL. J Am Coll Cardiol 2015; 65(4):402–404. doi:10.1016/j.jacc.2014.10.053
23. **Arsenault BJ, Kohli P, Lambert G, et al.** Emerging cardiovascular disease biomarkers and incident diabetes mellitus risk in statin-treated patients with coronary artery disease (from the Treating to New Targets [TNT] study). Am J Cardiol 2016; 118(4):494–498. doi:10.1016/j.amjcard.2016.05.044
24. **Simsek S, Schalkwijk CG, Wolffenbuttel BH.** Effects of rosuvastatin and atorvastatin on glycaemic control in type 2 diabetes—the CORALL study. Diabet Med 2012; 29(5):628–631. doi:10.1111/j.1464-5491.2011.03553.x
25. **Holman RR, Paul S, Farmer A, et al.** Atorvastatin in factorial with omega-3 EE90 risk reduction in diabetes (AFORRD): a randomised controlled trial. Diabetologia 2009; 52(1):50–59. doi:10.1007/s00125-008-1179-5
26. **Teramoto T.** Pitavastatin: clinical effects from the LIVES study. Atheroscler Suppl 2011; 12(3):285–288. doi:10.1016/S1567-5688(11)70888-1
27. **Zhou Y, Yuan Y, Cai RR, et al.** Statin therapy on glycaemic control in type 2 diabetes: a meta-analysis. Expert Opin Pharmacother 2013; 14(12):1575–1584. doi:10.1517/14656566.2013.810210
28. **Erqou S, Lee CC, Adler AI.** Statins and glycaemic control in individuals with diabetes: a systematic review and meta-analysis. Diabetologia 2014; 57(12):2444–2452. doi:0.1007/s00125-014-3374-x
29. **Cui JY, Zhou RR, Han S, Wang TS, Wang LQ, Xie XH.** Statin therapy on glycemic control in type 2 diabetic patients: a network meta-analysis. J Clin Pharm Ther 2018; 43(4):556–570. doi:10.1111/jcpt.12690
30. **Davis TM, Badshah I, Chubb SA, Davis WA.** Dose-response relationship between statin therapy and glycaemia in community-based patients with type 2 diabetes: the Fremantle Diabetes Study. Diabetes Obes Metab 2016; 18(11):1143–1146. doi:10.1111/dom.12710
31. **Sukhija R, Prayaga S, Marashdeh M, et al.** Effect of statins on fasting plasma glucose in diabetic and nondiabetic patients. J Investig Med 2009; 57(3):495–499. doi:10.2310/JIM.0b013e318197ec8b
32. **Abbasi F, Lamendola C, Harris CS, et al.** Statins are associated with increased insulin resistance and secretion. Arterioscler Thromb Vasc Biol 2021; 41(11):2786–2797. doi:10.1161/ATVBAHA.121.316159
33. **Suazo J, Rigotti A.** Risk of type 2 diabetes mellitus associated with statin therapy: evidence and possible mechanisms. Rev Med Chil 2014; 142(2):222–228. Spanish. doi:10.4067/S0034-98872014000200011
34. **Brinton EA.** Statin-related new-onset diabetes appears driven by increased insulin resistance: are there clinical implications? Arterioscler Thromb Vasc Biol 2021; 41(11):2798–2801. doi:10.1161/ATVBAHA.121.316893
35. **Duvnjak L, Blaslov K.** Statin treatment is associated with insulin sensitivity decrease in type 1 diabetes mellitus: a prospective, observational 56-month follow-up study. J Clin Lipidol 2016; 10(4):1004–1010. doi:10.1016/j.jacl.2016.04.012

Downloaded from www.ccjm.org on April 20, 2024. For personal use only. All other uses require permission.

36. **Ridker PM, Pradhan A, MacFadyen JG, Libby P, Glynn RJ.** Cardiovascular benefits and diabetes risks of statin therapy in primary prevention: an analysis from the JUPITER trial. Lancet 2012; 380(9841):565–571. doi:10.1016/S0140-6736(12)61190-8
37. **Navarese EP, Szczesniak A, Kolodziejczak M, Gorny B, Kubica J, Suryapranata H.** Statins and risk of new-onset diabetes mellitus: is there a rationale for individualized statin therapy? Am J Cardiovasc Drugs 2014; 14(2):79–87. doi:10.1007/s40256-013-0053-0
38. **Collins R, Reith C, Emberson J, et al.** Interpretation of the evidence for the efficacy and safety of statin therapy. Lancet 2016; 388(10059):2532–2561. doi:10.1016/S0140-6736(16)31357-5
39. **Gerstein HC.** Dysglycemia, not just diabetes, is a continuous risk factor for cardiovascular disease. Evid Based Cardiovasc Med 1997; 1(4):87–88. doi:10.1016/s1361-2611(97)80002-4
40. **Backes JM, Kostoff MD, Gibson CA, Ruisinger JF.** Statin-associated diabetes mellitus: review and clinical guide. South Med J 2016; 109(3):167–173. doi:10.14423/SMJ.0000000000000423
41. **American Diabetes Association Professional Practice Committee.** 10. Cardiovascular disease and risk management: standards of medical care in diabetes–2022. Diabetes Care 2022; 45(suppl 1): S144–S174. doi:10.2337/dc22-S010

Address: *Byron J. Hoogwerf, MD, FACP, FACE, 8972 Huntington Pointe Drive, Sarasota, FL 34238; byronhoogwerf@gmail.com*

Downloaded from www.ccjm.org on April 20, 2024. For personal use only. All other uses require permission.