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Statins and Incident Diabetes: Can Risk Outweigh Benefit?

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Abstract We review the most recent data regarding the association of incident diabetes and statin use, examine potential mechanisms to explain this association, and compare the potential risk of diabetes with the known cardiovascular benefits derived from statin use. We discuss new and interesting findings, as well as significant trends and developments. The risk of statin-induced dysglycemia and diabetes appears to be dose-dependent, but generally small in magnitude and confined to an unmasking of a strong predisposition to diabetes or accelerated diagnosis in individuals with diabetes risk factors. We focus on the concept of net benefit and find that although risk of diabetes could outweigh cardiovascular benefits in select individuals at low cardiovascular risk, the vast majority of people being managed for cardiovascular risk are most likely to derive net benefit. The need to weigh risks and benefits highlights the importance of shared decision-making in clinician-patient risk discussions.

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Introduction

Statin therapy is one of the cornerstone strategies in preventing atherosclerotic cardiovascular disease (ASCVD) events. It is currently estimated that over 200 million people worldwide take a statin [1]. Statins act through inhibition of HMG Co-A reductase to lower low-density lipoprotein cholesterol (LDL-C), ASCVD risk, and cardiovascular mortality [2, 3].

In 2013, the American College of Cardiology (ACC) and American Heart Association (AHA) jointly published new guidelines for cholesterol management incorporating a new risk assessment tool and identifying four patient groups likely to benefit from statins [4••]. Since the new guidelines were issued, much attention has focused on the potential increase in the number of patients eligible for statin use in primary prevention [5–7]. While these are important estimates, final eligibility depends on clinician-patient risk discussions, a key virtue of the new guidelines [8, 9]. Examining potential benefits and potential adverse effects of statins is a core component of such discussions.

As with every pharmacotherapy, statins are associated with a number of possible unintended effects [10]. Among these, statin-induced dysglycemia and diabetes mellitus have recently come to the forefront. With accumulating evidence, and potentially important clinical and public health implications, the U.S. Food and Drug Administration released a safety label change for statins in 2012. Diabetes risk in association with statins was subsequently taken into careful consideration in the 2013 ACC/AHA cholesterol treatment guideline [4••].

In this article, we review the most recent data regarding the association of incident diabetes and statin use, examine potential mechanisms to explain this association, and compare the potential risk of diabetes with the known cardiovascular benefits derived from statin use.

Statins and Diabetes

One of the first studies to investigate the association of statins and incident diabetes was a post hoc analysis of the West of Scotland Coronary Prevention Study (WOSCOPS) [11]. This landmark randomized controlled trial involved severely hypercholesterolemic men with a mean baseline LDL-C exceeding 190 mg/dL. Participants were enrolled at 45–64 years of age and followed for ~5 years on average in a primary prevention context. In 2001, the investigators reported a ~1 % absolute reduction and 30 % relative reduction in the risk of diabetes associated with pravastatin 40 mg/day versus placebo. The apparent protective effect was consistent with the authors' prediction based on previously described anti-inflammatory effects of statins.

A subsequent large placebo-controlled statin trial, "Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER)," published in 2008, found the opposite result. There were important differences in several aspects of WOSCOPS and JUPITER. For example, JUPITER used a different and higher-intensity statin, rosuvastatin 20 mg/day, and enrolled participants who had LDL-C <130 mg/dL, but elevated high-sensitivity C-reactive protein levels. The investigators reported a small but statistically significant absolute increase in the number of physician-reported diabetes cases [12]. The subject remained controversial, as it was unclear how to reconcile JUPITER with WOSCOPS, and prior reports from other placebo-controlled statin trials had reported inconsistent relationships between statin use and glycemic control [13–15].

Four meta-analyses inclusive of a large number of statin trials have suggested an association between statin use and incident diabetes [16, 17•, 18, 19•]. In 2008, Coleman et al. reported significant statistical heterogeneity such that pravastatin was associated with reduced diabetes risk whereas other statins showed increased risk [16]. In 2009, Rajpathak et al. reported a 13 % relative increase in diabetes risk, representing a 0.5 % absolute risk increase in patients taking a statin [18]. A subsequent meta-analysis of published and unpublished data on 13 placebo-controlled and standard-of-care-controlled trials reported similar results, showing a 9 % higher relative risk and 0.39 % absolute risk difference for development of diabetes with statin use [19•].

In 2013, a retrospective cohort study was performed using the Irish pharmacy dispensing database, with data from 1,235,671 individuals [20]. A 20 % relative increase in the risk of diabetes, corresponding to a 1.2 % absolute difference, was observed in association with the prescription of rosuvastatin, atorvastatin, and simvastatin, compared with those without a prescription for a statin. Another large observational study reported a 14 % increase in the relative risk of diabetes, a 2.6 % absolute difference, associated with statin therapy after analyzing data from electronic medical records from 500 UK practices [21].

Therefore, considerable evidence supports a modest increase in the incidence of diabetes with statin use. However, it may be fruitful to further examine the signal of heterogeneity between statins. It is unclear how extensively this heterogeneity is related to intrinsic chemical properties of different statins or to the patient populations in which they were studied. At present, it might be premature to view diabetes risk as a broadly relevant adverse class effect.

Moreover, research studies have yet to determine the long-term consequences of statin-related diabetes. It is unknown whether the risks associated with statin-related diabetes are similar to those associated with incident diabetes in non-statin users. Diabetes associated with thiazide diuretics, for example, had less of an adverse long-term cardiovascular impact than incident diabetes occurring in patients on other antihypertensive therapies [22]. Furthermore, when a diagnosis of diabetes is established, statin use would then be expected to protect against macrovascular complications. Regarding microvascular complications of diabetes, a recent analysis of the Danish registries did not find negative long-term consequences with statin use before diagnosis of incident diabetes [23], and instead raised the possibility of protective effects.

Dose-Response Effect

Data examining differential risk of incident diabetes in relation to statin dose has been mixed but overall suggestive of a dose-response association. Sattar et al. did not find a correlation between the risk of diabetes and the degree of LDL-C lowering in a meta-analysis [19•]. Notably, most trials only used lower doses of higher-intensity statins or a lower-intensity statin. The Women's Health Initiative study, which found an adjusted 48 % relative increase in the risk of new-onset diabetes, and absolute risk difference of 3.5 %, with statins compared with placebo, reported no differential risk among low- or high-intensity statins [24].

In 2011, Preiss et al. analyzed five large trials of high- versus moderate-dose statin therapy [17•]. Patients receiving high doses of atorvastatin or simvastatin had a 12 % higher likelihood of developing diabetes compared with those receiving moderate doses of atorvastatin. In absolute terms, this corresponded to a 0.8 % increase in the risk of incident diabetes. A recent large population-based study of 471,250

patients who had no history of diabetes showed that those taking atorvastatin, rosuvastatin, or simvastatin had a higher risk of developing diabetes, compared with those taking pravastatin [25]. The same was not true for the lower-potency statins, fluvastatin, and lovastatin.

A recent comprehensive network meta-analysis of randomized controlled trials evaluated the impact of different statins and doses on incident diabetes [26]. Among high-intensity statins, a 25 % relative increase in the odds of diabetes was observed with rosuvastatin 20 mg/day. Risk from simvastatin 40 mg/day was of a similar magnitude, while the impact of atorvastatin 80 mg/day was less evident. Therapy with pravastatin 40 mg/day had the best safety profile, showing a 16 % relative risk reduction of new-onset diabetes, compared with rosuvastatin 20 mg/day. At moderate doses, rosuvastatin led to 11 % higher relative risk of diabetes, whereas pravastatin lowered risk when compared with placebo, although this heterogeneity was not statistically significant. In absolute terms, those treated with a high-dose statin had a 0.23 % increase in the absolute risk of diabetes, compared with those treated with moderate doses. Overall, rosuvastatin carried the greatest risk of diabetes, and higher doses of more potent statins were associated with the highest risk.

Predisposing Patient Characteristics

Meta-regression of potential clinical predictors for new-onset diabetes showed that older patients were at higher risk of developing diabetes [19•]. Neither body mass index (BMI) nor change in LDL-C was associated with differential risk. Subsequent data from three randomized statin trials showed that baseline hypertension, higher fasting glucose, BMI, and triglycerides were strong predictors of new-onset diabetes [27]. Taking a beta blocker, a class of medications previously associated with higher incident diabetes [28, 29] was a predictor in univariate analyses, but not in multivariate analyses.

In an attempt to further clarify patient characteristics predisposing to statin-related diabetes, a JUPITER analysis stratified participants according to the presence or absence of one of four major risk factors for development of diabetes: BMI >30 kg/m^2, metabolic syndrome, impaired fasting glucose, and hemoglobin A1C >6 % [30•]. When compared with placebo, statins were linked to diabetes in patients with one or more diabetes risk factors, but not in those without any risk factors. In the setting of diabetes risk factors, statins accelerated the diagnosis of diabetes by an average of only 5.4 weeks. While JUPITER participants were free of ASCVD at baseline, in individuals with established ASCVD, similar risk factors predicted likelihood of a new diagnosis of diabetes on statin therapy [31].

Mechanisms

Different statins have been shown to affect insulin sensitivity in distinct ways and through multiple potential mechanisms. A meta-analysis of 16 statin trials with available insulin sensitivity data showed that pravastatin increased insulin secretion [32]. However, other statins lowered insulin secretion, including atorvastatin, rosuvastatin, and simvastatin. Insulin signal transduction may also become impaired and contribute to altered insulin sensitivity [33].

In addition, altered glucose uptake by decreased GLUT-4 expression and translocation has been described [34, 35]. Impaired glucose handling was observed in cells treated with atorvastatin but not pravastatin. This finding further supports differences associated with the various statins.

Inhibited pre-adipocyte differentiation into adipocytes could contribute to insulin resistance by decreased secretion of insulin-sensitizing hormone [34] and other adipokines. In particular, adiponectin and leptin have been considered as potential mediators of the diabetogenic effect of statins.

Adiponectin seems to alter insulin sensitivity by affecting insulin receptor phosphorylation, and low levels of adiponectin are associated with insulin resistance [36]. The effects of statins on adiponectin levels have yielded different results, and at this time, no definitive conclusion can be drawn [33].

Leptin is another adipocyte-secreted hormone that may be affected by statins. Decreased leptin levels or leptin resistance (a state of relative leptin deficiency) are thought to contribute to insulin resistance and diabetes through multiple complex mechanisms, including a negative impact on beta cell proliferation and insulin secretion [37–39].

Other mechanistic insights have emerged. For example, in rat islet beta-cells, simvastatin but not pravastatin inhibited glucose-induced cytosolic calcium signaling and insulin secretion through blockage of L-type calcium channels [40]. Others have proposed that insulin secretion is impaired through an indirect mechanism caused by chronic cholesterol depletion [41]. This potential mechanism may, thus, extend to cholesterol-lowering agents other than statins.

Whether the mechanism underlying the association of statins and diabetes is specifically related to HMG Co-A reductase inhibition, the same mechanism that results in LDL-C lowering, has been explored. A recent Mendelian randomization study examined two single nucleotide polymorphisms of the HMG Co-A reductase gene and found an association with increased measures of obesity and risk of type 2 diabetes [42]. An association between statin treatment and increased body weight was reported (0.24 kg increase in weight in statin-treated individuals), although this was a small absolute change and unlikely to fully explain the increased risk of diabetes. The authors concluded that the reported increased incidence of diabetes associated with statin use could, at least in part, be

explained by an "on-target" effect through inhibition of HMG Co-A reductase.

Benefits of Statins

The cardiovascular benefits of statins are well-established for a variety of patient groups, including those with diabetes. This has been best shown by a series of high-quality, participant-level, prospective meta-analyses from the Cholesterol Treatment Trialists' (CTT) Collaboration [2, 3, 43]. In patients with and without diabetes, statin therapy can safely reduce the 5-year relative risk of major ASCVD events by ~20 % and all-cause mortality by ~10 % for each millimole per liter (39 mg/dL) lowering of LDL-C. Major ASCVD events include major coronary events, coronary revascularization procedures, and strokes. The absolute benefit depends on an individual's absolute risk for ASCVD events (generally higher in those with diabetes) and the absolute reduction in LDL-C that is obtained.

Although there seems to be a dose-response association between statins and incident diabetes, ASCVD benefits are also dose-dependent. Treatment with high-intensity statins leads to lower LDL-C levels, which translates into further reduction of all-cause mortality and major ASCVD events [3]. Overall, there is an approximate 15 % additional relative reduction in the risk of major cardiovascular events with the use of a high-intensity statin, an absolute risk reduction of 3 % (19.3 vs. 22.3 %) or number needed to treat of 33. The proportional risk reduction for each millimole per liter of LDL-C lowering appears to be similar even at low baseline LDL-C. This is important to note because many patients with diabetes have relatively low baseline LDL-C levels, often in part because LDL particles are small and dense.

Can Risk Outweigh Benefit?

Although it is possible for risk to outweigh benefit, this appears to be the exception rather than the rule for the majority of people undergoing management of ASCVD risk. Overall, a net benefit is expected with statin use (Fig. 1). The magnitude of raised glucose levels and development of diabetes was characterized as "small" in the U.S. Food and Drug Administration safety label change [44]. It was also emphasized in the label change that the cardiovascular benefits of statins generally outweigh the small increased diabetes risk.

The 2013 ACC/AHA guidelines also quantified the risk as minimal [4••]. The 2013 ACC/AHA guidelines quoted as a "conservative estimate" approximately 0.1 and 0.3 excess cases of diabetes per 100 individuals treated for 1 year with moderate- and high-intensity statins, respectively. The guideline panel emphasized that "occurrence of a major ASCVD event represents a much greater harm to health status than does an increase in blood glucose leading to a diagnosis

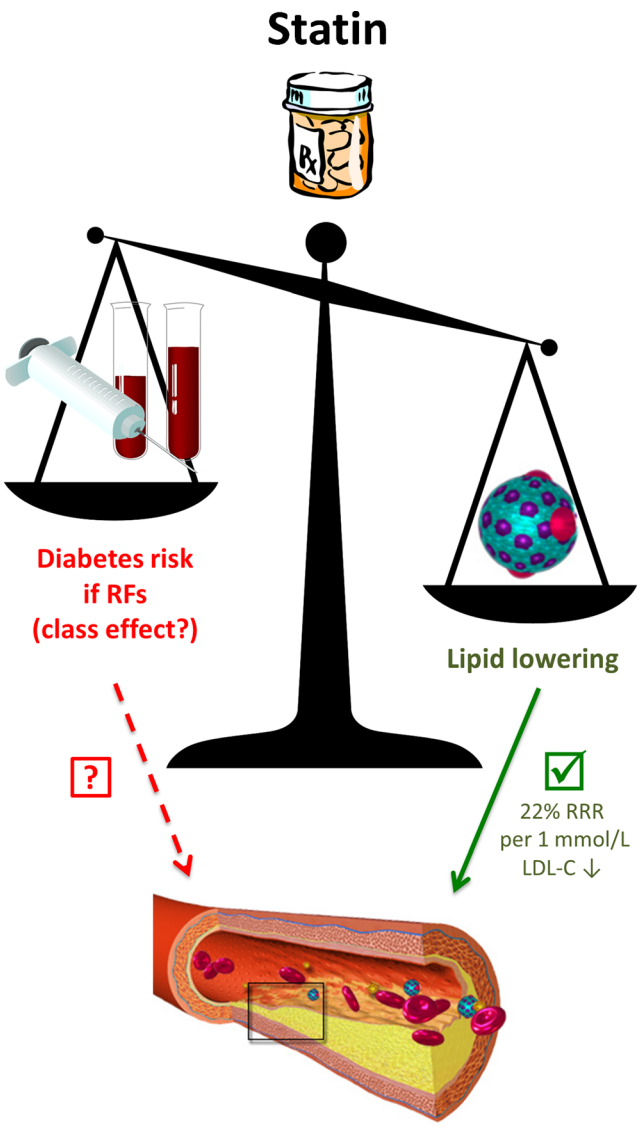

Fig. 1 The atheroprotective benefits of lipid lowering with statin therapy generally outweigh the potential risk of diabetes, thus providing a net benefit. Benefits are dose-dependent with each 1-mmol/L (39 mg/dL) lowering of low-density lipoprotein cholesterol (LDL-C) associated with a relative risk reduction (RRR) of ~22 % per meta-analyses by the Cholesterol Treatment Trialists. Risk of diabetes also appears to be dose-dependent, though the effect size is small and it is not entirely clear that it is a class effect. Moreover, statin-related diabetes risk appears to be confined to those with diabetes risk factors (RFs), including body mass index >30 kg/m^2, metabolic syndrome, impaired fasting glucose, or hemoglobin A1C >6 %. Unlike the well-established benefits of LDL-C lowering on atherosclerosis, the long-term macrovascular consequence of statin-related diabetes is unclear. Lipoprotein and atherosclerosis images reproduced in modified form with creative commons permission from "Blausen 0227 Cholesterol" by BruceBlaus—own work. Licensed under CC BY 3.0 via Wikimedia Commons—http://commons.wikimedia.org/wiki/File:Blausen_0227_Cholesterol.png#mediaviewer/File:Blausen_0227_Cholesterol.png

of diabetes." Overall, the guideline panel advised, "potential for an ASCVD risk-reduction benefit outweighs the excess risk of diabetes in all but the lowest-risk individuals." The lowest risk category defined in the guidelines was <5 % 10-year ASCVD risk. Finally, the guideline panel expressed the necessity of a healthy lifestyle and an evaluation for new-onset diabetes per current screening guidelines in individuals treated with a statin.

The potential risk of diabetes associated with the initiation of statins emphasizes the critical importance of balancing scientific evidence with clinical judgment and patient preferences. This is achieved through shared decision-making, a central aspect of the 2013 ACC/AHA cholesterol treatment guidelines. The guidelines recommend that when starting a statin in primary prevention, the clinician should have a dialogue with the patient that addresses the following six components: 1) potential for ASCVD risk-reduction benefits; 2) potential for adverse effects and drug-drug interactions; 3) heart-healthy lifestyle; 4) management of other risk factors; 5) patient preferences; and 6) if the decision is unclear, consider other factors that may modify the risk-benefit balance.

The dialogue depends on the concept of net benefit and allows for a case-specific assessment of whether therapeutic risks outweigh benefits. Given that the trade-off between protection from ASCVD and potential diabetes risk becomes less clear as the estimated baseline absolute ASCVD risk decreases, clinician-patient risk discussions are perhaps of even higher importance for these patients. In the "real-world" clinical setting, it should be considered that there might be different margins of safety in patients excluded from clinical trials (e.g., elderly, other serious comorbidities).

It is important to consider the impact a new diagnosis of diabetes would have on the patient, as well as the patient's personal opinions of this change. This will vary from patient to patient, and some may be highly concerned about the possibility of finger sticks and insulin treatment. Without this patient conversation, the personal significance of diabetes cannot be fully understood by the layperson or appreciated by the clinician. Patients need to be educated on the importance of weight gain prevention and improved exercise habits to most effectively avoid any possible dysglycemic effects of statin therapy.

Conclusions

Current best evidence shows a dose-dependent hyperglycemic effect of statins on individuals who have components of the metabolic syndrome. The magnitude of this effect generally appears to be small. Risk of diabetes, at least over a year or a few years, appears to be limited to unmasking of diabetes or acceleration of diagnosis in those with diabetes risk factors. The hyperglycemic effect does not appear to cause new-onset diabetes in healthy people.

The question of whether risk can outweigh benefit should be addressed on a case-by-case basis. This may be done in the context of a clinician-patient risk discussion that considers scientific evidence in conjunction with clinical judgment and patient preferences. For the vast majority of patients, it is unlikely that risks will offset the potential benefits of statins.

Finally, we caution that this topic may be oversimplified when addressed as a class effect. Differential effects between different statin regimens have been addressed but not fully clarified. Evidence for pravastatin is in the opposite direction of other statins. Future research would be beneficial if it can tease this out more clearly. To date, interesting mechanistic insights have emerged, but more is left to uncover, and there is a need for evaluation of the long-term risk implications of statin-related diabetes on both macrovascular and microvascular outcomes.

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Compliance with Ethics Guidelines

Conflict of Interest Roger Blumenthal and Roberta Florido have no disclosures. Seth Martin is listed as a co-inventor on a pending patent filed by Johns Hopkins University for a method of low-density lipoprotein cholesterol estimation.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

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