Review Article

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Risk of new-onset diabetes associated with statin use

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Abstract

Objective: To identify and assess studies investigating the association between statins and new-onset diabetes and determine the clinical significance of this risk.

Data sources: A MEDLINE (1977–April 2015), Google Scholar (1997–April 2015), and International Pharmaceutical Abstracts (1977–April 2015) search was performed using the search terms *hydroxymethylglutaryl-CoA reductase inhibitors, hydroxymethylglutaryl-CoA reductase inhibitors/adverse effects, statins, adverse effects, diabetes mellitus, diabetes mellitus/etiology*, and *drug-induced.* Citations of identified articles and clinical practice guidelines were also reviewed.

Study selection and data extraction: Articles describing results from original investigations or meta-analyses specifically designed to assess the association between statins and new-onset diabetes and published in English were included.

Data synthesis: A total of 13 cohort studies and seven meta-analyses were included. In all, 11 were retrospective cohort studies and reported some degree of increased risk of new-onset diabetes associated with statins. The two prospective cohort studies differed. One identified increased risk of new-onset diabetes, but the other did not. Increased risk was not identified when any statin was compared to placebo alone, individual statins were compared, or in the single meta-analysis that included observational studies. Overall, the meta-analyses suggest that statin therapy is associated with an increased risk of new-onset diabetes when compared to placebo or active control, and when intensive therapy is compared to moderate therapy.

Conclusion: Statins have been associated with a small, but statistically significant risk of new-onset diabetes. Patients with risk factors for developing diabetes mellitus may be at higher risk. This risk is likely outweighed by the benefits of reducing cardiovascular risk.

Keywords
HMG-CoA reductase inhibitors, new-onset diabetes, drug-induced diseases

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Introduction

3-Hydroxy-3-methyl-glutaryl coenzyme-A (HMG-CoA) reductase inhibitors, also known as statins, are one of the most commonly prescribed classes of medications in the United States.[1] They are used for primary and secondary prevention of cardiovascular and cerebrovascular events and to reduce mortality.[1–6] Statins are well tolerated with common adverse effects including myalgia, elevations in creatine kinase, and impaired cognition.[7,8] Recently, there has been concern regarding the increased risk of developing new-onset diabetes attributed to statins.

The American College of Cardiology and the American Heart Association published updated recommendations in 2013, potentially increasing the number of prescribed statins. With the new recommendations, there are no target lipid goals, and lipid management is solely focused around the use of moderate-intensity and high-intensity statin therapy to reduce the risk of atherosclerotic cardiovascular disease (ASCVD) events. Important changes that could increase the use of statins include lowering the threshold from 10% to 7.5% for 10-year risk of ASCVD events, now calculated from Pooled Cohort Equations, drug initiation at low-density

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lipoprotein (LDL) cholesterol levels of 70 mg/dL or greater versus 100 mg/dL or greater, and the addition of stroke to the definition of ASCVD.[6]

In 2012, the Food and Drug Administration (FDA) updated labeling for all statins to include a warning for increases in blood glucose, glycosylated hemoglobin (HbA1c), and fasting serum glucose levels based on results of the Justification for the Use of Statins in Primary Prevention (JUPITER) trial.[4,8] In this trial, the risk of new-onset diabetes increased when a patient had one or more major risk factors for diabetes mellitus, which included metabolic syndrome, impaired fasting glucose, body mass index (BMI) greater than or equal to 30 kg/m^2, and glycosylated hemoglobin (HbA1c) of 6% or greater.[4] Additionally, in a study that looked at patients with zero to one risk factors versus two to four risk factors taking either atorvastatin 10 mg or simvastatin 40 mg versus atorvastatin 80 mg, the risk of new-onset diabetes increased with the atorvastatin 80 mg group in patients with two to four risk factors.[5] The four risk factors described were fasting blood glucose greater than 100 mg/dL, fasting triglycerides greater than 150 mg/dL, BMI greater than 30 kg/m^2, and history of hypertension.[5] In 2014, the Statin Diabetes Task Force similarly concluded that the risk of developing type 2 diabetes mellitus with statin use may be limited to patients with pre-existing risk factors for diabetes mellitus.[9] In addition, the American Diabetes Association recognizes the increased risk of developing type 2 diabetes mellitus with statin use and suggests those with diabetes risk factors may benefit from diabetes screening when taking statins.[10]

There are numerous potential mechanisms for developing new-onset diabetes with statin use.[1,7,9] One potential mechanism is via disruption of voltage-gated calcium channels in pancreatic beta cells. Statins may directly block L-type calcium channels, therefore inhibiting glucose-induced calcium signaling in beta cells and decreasing insulin secretion. Another mechanism involves decreased translocation of the glucose transporter, GLUT4, on the intracellular membrane of cells. GLUT4 is responsible for glucose uptake in both fat and muscle cells in the presence of insulin. In the presence of a statin, GLUT4 translocation can be altered resulting in decreased glucose uptake in cells ultimately leading to hyperglycemia. Other proposed mechanisms include peripheral insulin resistance as a result of mitochondrial dysfunction in cells (including fat cells and pancreatic beta cells) and chronic depletion of cellular cholesterol resulting in impaired insulin secretion.

Whether a statin is hydrophilic or lipophilic may account for alteration of glucose control.[7] Hydrophilic statins (i.e. pravastatin and rosuvastatin) require carrier-mediated uptake into cells, thus increasing selectivity for hepatic cells. Lipophilic statins are able to passively diffuse through membranes of the hepatic cells, but can also diffuse into extrahepatic tissues and disrupt cellular processes, including decreased insulin secretion in response to glucose.

The strength of association between statin therapy and development of new-onset diabetes is controversial. The objective of this review is to identify and assess studies investigating the association between statins and new-onset diabetes and to determine the clinical significance of this risk.

Methods

A search of MEDLINE (1977–April 2015), Google Scholar (1997–April 2015), and International Pharmaceutical Abstracts (IPA) (1977–April 2015) was conducted using the search terms hydroxymethylglutaryl-CoA reductase inhibitors, hydroxymethylglutaryl-CoA reductase inhibitors/adverse effects, statins, adverse effects, diabetes mellitus, diabetes mellitus/etiology, and drug-induced. Citations of identified articles and clinical practice guidelines for dyslipidemia and type 2 diabetes mellitus were also reviewed.[10–14] All fully published articles describing results from original investigations or meta-analyses specifically designed to assess the association between statins, for primary or secondary prevention, and new-onset diabetes, compared to a reference or control, and published in English were included in the review. After applying inclusion criteria to search results, 11 retrospective cohort studies, two prospective cohort studies, and seven meta-analyses were included. No interventional studies designed specifically to assess risk of new-onset diabetes due to statin therapy were identified.

Results

Observational studies

In all, 11 retrospective cohort studies evaluated the association of statins with new-onset diabetes. All reported some degree of increased risk of new-onset diabetes associated with statin use (range of absolute incidence reported: 3.1%–22.7%; number needed to harm (NNH) compared to no treatment: 53–67).[11–21] Some studies compared statins to no exposure, while others evaluated statins as a class, both in terms of individual agents and groups based on statin intensity. The results from observational studies are included in Table 1.

Several studies were designed to determine whether certain formulations or intensities of statins were associated with increased risk of new-onset diabetes when compared to others. Conflicting results were obtained from several studies designed to ascertain whether individual statins or different intensities of therapy were associated with an increased risk of new-onset diabetes. Ma et al.[12] concluded that pravastatin was associated with an increased risk (hazard ratio (HR) = 1.3, p = 0.0011), while fluvastatin and lovastatin were associated with decreased risk, and the remaining statins did not increase or decrease risk. In contrast, lovastatin and simvastatin, but not pravastatin, were associated with an increased risk of

Table 1. Results from observational studies assessing risk of new-onset diabetes.

Reference	Patient population	Demographics	Exposure groups	Endpoint	Results: new-onset diabetes	Results: cardiovascular	Key limitations
Retrospective cohort studies							
Wang et al.[11]	N = 42,060	Men ⩾ 45 years Women ⩾ 55 years Mean age 63 ± 9 years Comorbid conditions: Hypertension 74% Coronary heart disease 43.5% Stroke 6.5% Statins used for secondary prevention 47%	Statins: A, F, L, Pr, R, or S received continuously for ⩾30 days Reference: patients naive to statins	New-onset diabetes	Cumulative incidence of new-onset diabetes: Statin: 22.7% Control: 20.8% HR = 1.15, 95% CI = 1.08–1.22, p < 0.001	HR (95% CI) MI: 0.82 (0.68–0.98, p = 0.028) Ischemic strokes: 0.94 (0.68–0.98, p = 0.028) MACE: 0.91 (0.84–0.99, p = 0.031) In-hospital deaths: 0.61 (0.55–0.67, p < 0.001)	Patients with established coronary events excluded Mean daily dose of statins lower than doses in clinical trials Lack of individual information such as family history of diabetes
Ma et al.[12]	N = 16,027	Mean age 59.9 years Hypertension and hyperlipidemia at baseline	Statins: A, F, L, Pr, R, or S prescribed within 3.5 years before diagnosis of new-onset diabetes Reference: no treatment	New-onset diabetes	1360/16,027 (8.5%) developed new-onset diabetes HR for new-onset diabetes (95% CI) A: 1.15 (0.96–1.35, p = 0.5465) F: 0.46 (0.33–0.61, p < 0.0001) L: 0.70 (0.59–0.83, p < 0.0001) Pr: 1.3 (1.13–1.56, p = 0.0011) R: 0.54 (0.36–0.76, p = 0.0006) S: 1.11 (0.92–1.32, p = 0.3028)		Excluded patients with irregular follow-up Patient data based on claim datasets and possible miscoding of diagnosis Risk factors for diabetes and CVD not available from database
Ma et al.[13]	N = 15,637	Age 65–80 years with hypertension and dyslipidemia at baseline	Statins: A, F, L, Pr, R, or S Reference: no treatment	New-onset diabetes	2735/15,637 (17.5%) developed new-onset diabetes HR for new-onset diabetes (95% CI) A: 0.77 (0.72–0.83, p < 0.0001) F: 1.00 (0.87–1.16, p = 0.951) L: 1.36 (1.24–1.48, p < 0.0001) Pr: 1.07 (0.94–1.23, p = 0.3092) R: 0.66 (0.52–0.83, p = 0.0006) S: 1.30 (1.14–1.47, p = 0.0001)		Establishing cause and effect not possible based on retrospective analysis Data based on claims data—data lacking on risk factors of diabetes

(Continued)

Table 1. (Continued)

Reference	Patient population	Demographics	Exposure groups	Endpoint	Results: new-onset diabetes	Results: cardiovascular	Key limitations
Ko et al.[14]	N = 23,710	Age > 65 years (mean 77.97 ± 7.19 years) Cardiovascular comorbidities: Prior MI 5.2% Dysrhythmias 15.1% Hypertension 80.5% Peripheral vascular disease 2.5% Charlson comorbidity score 0.63 ± 1.04	Intensive-dose statins: A ⩾ 40 mg, R ⩾ 20 mg, S ⩾ 60 mg Moderate-dose statins: all other formulations	New development of diabetes after hospital discharge in patients receiving statins for secondary prevention	Cumulative incidence of new-onset diabetes at 5 years: Intensive dose: 13.6% Moderate dose: 13% p = 0.19	Rate of death or ACS at 5 years: Intensive dose: 44.8% Moderate dose: 46.5% p = 0.044 Rate of ACS at 5 years: Intensive dose: 22.2% Moderate dose: 23.5% p = 0.039	Statin intensity based on dose rather than LDL lowering Lack of information on risk factors, including obesity, diet, and physical activity
Carter et al.[15]	N = 471,250	Age ⩾ 66 years History of cardiac disease 39.3%–57.4% Previous ACS 19.1%–35.4% Chronic CVD 32%–50.2% Stroke/transient ischemic attack: 12%–16.1%	Statins: A, F, L, R, or S Reference: Pr	Incident diabetes	HR for new-onset diabetes (95% CI): A: 1.22 (1.15–1.29) F: 0.95 (0.81–1.11) L: 0.99 (0.86–1.14) R: 1.18 (1.10–1.26) S: 1.10 (1.04–1.17)		Lack of information on diabetes risk factors, such as weight, ethnicity, and family history Lack of information pertinent to diagnosis (e.g. A1C)
Cho et al.[16]	N = 3680	Age ⩾ 20 years (mean age 61 years) Mean BMI 24.41 kg/m^2 Mean FBG 91.10 mg/dL	Statins: A, Pi, Pr, R Reference: S	New-onset diabetes	HR for new-onset diabetes (95% CI): A: 1.52 (0.72–3.21) Pi: 2.68 (1.26–5.71) Pr: 1.59 (0.60–4.24) R: 1.94 (0.93–4.05)		Adherence could not be assessed Selection bias could not be excluded Dose of statin was not controlled
Dormuth et al.[17]	N = 136,936	Age ⩾ 40 years (mean 68 years); after hospitalization for major CV event[a]	High-potency statins: A ⩾ 20 mg, R ⩾ 10 mg, S ⩾ 40 mg Reference: low-potency statins (all others)	New-onset diabetes	HR for new-onset diabetes (95% CI) at up to 2 years of treatment: High-potency statins 1.15 (1.05–1.26)		Did not capture some patients diagnosed in ambulatory setting Captured patients with more severe disease due to being hospitalized
Corrao et al.[18]	N = 115,709	Age 40–80 years (mean age 62.4 years) History of CVD: 36.0%	Statins: high (>75%), intermediate (51%–75%), or low (26%–50%) adherence Reference: very low adherence (<26%)	New cases of diabetes	HR for new-onset diabetes (95% CI): High 1.32 (1.26–1.39) Intermediate 1.22 (1.14–1.27) Low 1.12 (1.06–1.18)		Evaluation of adherence based on pharmacy dispensing information Risk of detection bias
Zaharan et al.[19]	N = 197,138	Age ⩾ 65 years: 32.2%	Statins: A, F, Pr, R, or S Reference: no treatment	New-onset diabetes	Cumulative incidence of new-onset diabetes: Statins: 5.9% Reference: 2.5% HR = 1.20, 95% CI = 1.17–1.23		

Table 1. (Continued)

Reference	Patient population	Demographics	Exposure groups	Endpoint	Results: new-onset diabetes	Results: cardiovascular	Key limitations
Currie et al.[20]	N = 32,086	Age 40–60 years Male: 52.98% European: 69.46%	Antihypertensives thought to increase diabetes risk: TB Antihypertensives less likely to increase diabetes risk: AAC Any statin Reference: diclofenac	Proportion of patients receiving first prescription of metformin	Risk of new-onset diabetes at 5 years: TB: 1.5% AAC: 2.3% Statins: 3.1% Diclofenac: 1.2%		Lack of information affecting cardiovascular and diabetes risk (e.g. BMI, family history) Risk of misclassification using metformin prescription as endpoint Did not distinguish between statin type and dose
Van de Woestijne et al.[21]	N = 4645	History or recent diagnosis of arterial disease: coronary artery disease, cerebrovascular disease, peripheral artery disease, or aneurysm of the abdominal aorta	Moderate versus intensive statin therapy. Intensive statin therapy defined as LDL-c lowering ⩾40% theoretically Reference: no statin therapy	New-onset diabetes	Adjusted risk: HR for new-onset diabetes (95% CI): 1.71 (1.22–2.41) Intensive versus moderate statin: 1.18 (0.90–1.57)		Statin use not continuously monitored during follow-up Adherence to therapy not measured Registration and type of dose occurred only at baseline
Prospective cohort studies							
Culver et al.[22]	N = 153,840	Postmenopausal women aged 50–79 years	Statins: Any, A, F, L, Pr, or S Reference: non-user	New-onset diabetes	Overall incidence of new-onset diabetes: 1076/10,834 (9.9%) versus 9166/143,006 (6.4%), adjusted HR = 1.48 (95% CI = 1.38–1.59) HR for new-onset diabetes with specific statins: A: 1.61 (1.35–1.92) F: 1.61 (1.35–1.92) L: 1.35 (1.19–1.55) Pr: 1.63 (1.43–1.87) S: 1.41 (1.25–1.61)		Observational design limits ability to control all confounding factors Lack of data on lipids, C-reactive protein, or hemoglobin A1C Inability to track compliance
Izzo et al.[23]	N = 4750	Mean age 60.2 years Hypertensive adults Primary prevention Family history of diabetes: 29.2%	Statins: any Reference: non-user	New-onset diabetes	Overall incidence new-onset diabetes: 10.2% versus 8.7%, adjusted HR = 1.03 (95% CI = 0.79–1.35)		Diagnosis of diabetes based on fasting blood glucose only

A: atorvastatin; AAC: ACEi, ARB, CCB; ACEi: angiotensin-converting-enzyme inhibitor; ACS: acute coronary syndrome; ARB: angiotensin II receptor blockers; BB: beta blockers; BMI: body mass index; CCB: calcium channel blockers; CI: confidence interval; CVD: cardiovascular disease; F: fluvastatin; HR: hazard ratio; L: lovastatin; LDL: low-density lipoprotein; MACE: major adverse cardiovascular events—composite of MI and ischemic stroke; MI: myocardial infarction; Pi: pitavastatin; Pr: pravastatin; R: rosuvastatin; S: simvastatin; TB: thiazides and BB.

[a]Major CV event—myocardial infarction, stroke, coronary artery bypass graft, or percutaneous coronary intervention.

new-onset diabetes (lovastatin HR = 1.36, p < 0.0001; simvastatin HR = 1.30, p = 0.0001; pravastatin HR = 1.07, p = 0.3092) in a different study by Ma et al.[13] While the methods were similar in these two studies, differences that may contribute to the contrasting results include an older patient population and higher doses of lovastatin and simvastatin in the second study. Other baseline characteristics that influence the risk of new-onset diabetes were not available to assess differences between studies. Carter et al.[15] postulated that pravastatin would be beneficial to use in patients at increased risk of developing diabetes mellitus based on hydrophilicity and accordingly found increased risk with atorvastatin (HR = 1.22, 95% confidence interval (CI) = 1.15–1.29), rosuvastatin (HR = 1.18, 95% CI = 1.10–1.26), and simvastatin (HR = 1.10, 95% CI = 1.04–1.17) when compared to pravastatin. This increased risk may also be related to the higher intensity of the latter statins, including the other hydrophilic statin rosuvastatin, when compared to pravastatin. Cho et al.[16] concluded that pitavastatin was associated with an increased risk of new-onset diabetes when compared to simvastatin (HR = 2.68, 95% CI = 1.26–5.71, p = 0.011); however, this was the only study that included pitavastatin, so these results should be compared with the results from other studies with caution.

The relationship between statin intensity and new-onset diabetes has been explored. Ko et al.[14] concluded that intensive-dose statins had no higher risk of new-onset diabetes than moderate-dose statins at 5 years (13.6% versus 13.0%, p = 0.19); however, Dormuth et al.[17] found a 15% higher rate of new-onset diabetes in the high-potency statin group when compared to the other statins. A subgroup analysis in the study by Ma et al.[12] found a dose–response relationship with atorvastatin, but not with other statins. Corrao et al.[18] classified statins according to intensity, but compared results in groups based on adherence and determined that the rate of new-onset diabetes increased with increasing adherence (high-potency statins, high adherence HR = 1.43, 95% CI = 1.19–1.73; low-potency statins, high adherence HR = 1.24, 95% CI = 1.08–1.43). Zaharan et al.[19] found a significant association between new-onset diabetes and statin use, dose, and duration of therapy (HR = 1.02, p < 0.0001).

Difference in risk of patients receiving statins for primary or secondary prevention was also addressed in several studies. Wang et al.[11] noted that while the risk–benefit profile was similar in patients receiving statins versus control in the primary prevention population, patients receiving statins for secondary prevention showed a benefit in preventing in-hospital fatalities, which outweighed the risk of developing new-onset diabetes when compared to a control population. Carter et al.[15] found consistent results in the primary endpoint of new-onset diabetes in both the primary (HR atorvastatin = 1.20, rosuvastatin = 1.12, simvastatin = 1.12) and secondary prevention populations (HR atorvastatin = 1.25, rosuvastatin = 1.24, simvastatin = 1.14).

Only two of the studies simultaneously evaluated the effect of statins for prevention of cardiovascular outcomes in order to assess risk–benefit. Ko et al.[14] found that higher intensity statins were associated with a small increase in the number of cases of new-onset diabetes, but were also associated with a larger reduction in acute coronary syndromes (22.2% versus 23.5%, p = 0.039). Wang et al.[11] concluded that while statins are associated with an increased risk of new-onset diabetes (HR = 1.15, p < 0.001), the cardiovascular benefits seen in high-risk and secondary prevention populations outweigh this risk.

Inclusion and exclusion criteria varied among studies; however, in general, most studies included patients who were receiving statin monotherapy and excluded those who were already diagnosed with diabetes mellitus, as determined by prescription history or hospital admission data. These retrospective studies were limited by the fact that some diagnoses may have been missed based on retrospectively gathering secondary information from healthcare databases. Additionally, the definition of diabetes mellitus varied between the studies. Definitions of new-onset diabetes included International Classification of Diseases (ICD)-9 codes for diabetes mellitus, dispensing of oral antidiabetic medications or insulin, or diagnosis of diabetes mellitus listed in a validated healthcare database; however, the definition was not consistent among all studies and may have unintentionally excluded patients who had developed diabetes mellitus but did not meet the specified parameters. The populations included in the studies also differed, mostly by age. Adherence and compliance were not assessed in most of the studies, and the studies could not control for all potential confounders, as some confounders could not be found in the databases which were utilized, such as family history of diabetes mellitus and tobacco abuse.[11–21]

In addition to retrospective cohort studies, two prospective cohort studies were identified.[22,23] The results from these studies are available in Table 1. Unlike the retrospective studies, the prospective studies were mixed in that Izzo et al. did not identify increased risk of new-onset diabetes with statins (adjusted HR = 1.03, 95% CI = 0.79–1.35), but Culver et al. did (adjusted HR = 1.48, 95% CI = 1.38–1.59). Both studies were consistent in that approximately 10% of statin users experienced new-onset diabetes; however, Culver et al. observed a lower risk of new-onset diabetes in non-statin users (6.4%) compared to Izzo et al. (8.7%). Investigators accounted for different confounding variables in their multivariate analyses: Culver et al. adjusted for age, race, education, cigarette smoking, BMI, physical activity, alcohol intake, energy intake, family history, hormonal therapy, and baseline cardiovascular risk; however, the model used in Izzo et al. only accounted for age, gender, duration of hypertension, and undescribed "baseline parameters."

In addition to varying greatly in covariates assessed in their analyses, the two prospective cohort studies differed greatly in terms of patient population. Culver et al., as part of the Women's Health Initiative, included post-menopausal women, while Izzo et al. assessed a cohort of hypertensive patients treated at a sample of clinics in Italy. The results

from each study may be limited by inclusion of very specific populations of patients. Additionally, the results from Izzo et al. may be at increased risk of Type II statistical error giving relatively low enrollment compared to other observational studies and failure to account for the wide range of potential covariates assessed by Culver et al. The large size (n = 153,840) and prospective design lend additional credence to the results obtained by Culver et al. compared to other cohort studies; however, the large study design also increases power of the study to detect minor, clinically irrelevant differences between groups.

Meta-analyses

Seven meta-analyses assessing the risk of new-onset diabetes in patients on statins were identified.[24–30] Six of seven included only interventional studies. The results were varied with a small, statistically significant increased risk identified in patients on statins when compared to placebo or active control in aggregate (relative risk (RR) = 1.09–1.18)[25,28] and patients on intensive statin therapy compared to moderate statin therapy (odds ratio (OR) = 1.12, RR = 1.18).[26,28] However, increased risk was not identified when any statin use was compared to placebo alone,[23,30] individual statins were compared,[27] and in the single identified meta-analysis that included observational studies.[29] The meta-analysis conducted by Navarese et al.[27] is noteworthy for having the largest patient population while still not identifying a statistically significant increased risk of any individual statins; however, application of this finding is limited by the lack of heterogeneity data.

The NNH for new-onset diabetes varied from 125 to 250 in the meta-analyses which found statistically significant increases.[15–17] Similarly, the absolute differences in rates of new-onset diabetes were low (i.e. 0.4%–0.8%). Preiss et al.[26] published the only meta-analysis that directly compared risk of new-onset diabetes to risk of cardiovascular events. Investigators found that although there was increased risk of new-onset diabetes with high-intensity statin therapy compared to moderate-intensity statin therapy (8.8% versus 8.0%, OR = 1.12 (95% CI = 1.04–1.22), NNH = 125), the increased risk was offset by a composite reduction in cardiovascular events (19.1% versus 21.7%, RR = 0.84 (95% CI = 0.75–0.94), number needed to treat (NNT) = 39). The heterogeneity in the latter meta-analysis was substantial, likely due to the variety of events included in the composite cardiovascular outcome.

Heterogeneity results are reported in Table 2, when available. Overall, heterogeneity was low in most studies (i.e. 0%–11%) increasing confidence in findings;[24–26,28] however, there were several exceptions. Heterogeneity was moderate in the study conducted by Coleman et al.[30] (likely due to the inclusion of clinical studies describing both primary and secondary cardiovascular prevention) and substantial in the study conducted by Macedo et al.[29] The latter was the only identified meta-analysis that included observational studies; however, only two studies (one cohort and one case–control) of varying size (153,840 and 4682 patients) were included. Despite the large number of patients assessed in this study, the results are greatly limited by the large number of cohort studies, discussed in this review, that were not included. Few relevant studies were identified due to investigator requirement that only prospective, observational studies be included in the analysis. The higher heterogeneity in both Coleman et al. and Macedo et al. suggests that their common finding of a lack of association between statins and new-onset diabetes should be interpreted with caution.

The most common comparison was all statin therapy compared to control.[24,25,29] Only one meta-analysis assessed differences in risk of new-onset diabetes based on individual agents and doses,[27] rather than by pooling results for high-intensity and moderate-intensity therapy.[26,28] The study assessing individual agents did not find increased risk of new-onset diabetes with any one agent or dose,[27] possibly due to lack of power to identify such small incremental risk. Despite this finding, the possibility for a small risk of new-onset diabetes on higher intensity or higher dose statins is underscored by findings from a direct comparison where high-intensity therapy resulted in higher odds for new-onset diabetes than moderate-intensity therapy (8.8% versus 8.0%, OR = 1.12, 95% CI = 1.04–1.22).[26] The NNH for new-onset diabetes was 250 in the moderate-intensity and 125 in the high-intensity group.

Discussion

This review focused on observational studies and meta-analyses specifically designed to evaluate risk of statin-induced new-onset diabetes. Our findings, similar to those of the Statin Diabetes Task Force,[9] suggest that statins have been consistently associated with a small increased risk of new-onset diabetes, relative to placebo or no treatment, especially in studies of stronger study design (e.g. prospective, larger sample size observational studies, lower heterogeneity meta-analyses). It should be noted that while results were generally statistically significant in favor of a statin effect, the absolute risk of new-onset diabetes was generally small. While the Statin Diabetes Task Force states that any statin use is associated with a 10% increased risk of new-onset diabetes and a 12% increased risk of high-intensity statins, our findings suggest that these are relative numbers based on much smaller increases in absolute risk in observational studies (0%–5%) and meta-analyses (0%–2%).[9] Additionally, each study that assessed incidence of major cardiovascular endpoints found a corresponding reduction in these events (NNT = 39–77) that likely would outweigh the possible risk of new-onset diabetes (NNH = 125–250).[14,25,26] There was a lack of literature that simultaneously assessed both new-onset diabetes and major cardiovascular events, making it difficult to draw firm conclusions in this area. It should be

Table 2. Results from meta-analyses assessing risk of new-onset diabetes.

Reference	Types of studies included	Number of studies included	Patient population	Endpoint, intervention, control	Heterogeneity	Results	NNH/NNT	Key limitations
Rajpathak et al.[24]	Randomized, controlled trials	6	57,593 Mix of primary and secondary cardiovascular preventions	New-onset diabetes for patients on statins compared to placebo	Low: $I^2 = 1.6\%$	3.8% versus 3.5%, RR = 1.06 (95% CI = 0.93–1.22)	N/A	Only included placebo-controlled trials and pooled statin data; no funnel plot provided
Sattar et al.[25]	Randomized, controlled trials	13	91,140 Mix of primary and secondary cardiovascular preventions	New-onset diabetes for patients on statins compared to placebo or active control	Low: $I^2 = 11.2\%$	4.9% versus 4.5%, RR = 1.09 (95% CI = 1.02–1.17)	250	Excluded studies comparing two statins or doses; funnel plot not provided
Preiss et al.[26]	Randomized, controlled trials	5	32,752 Secondary cardiovascular prevention	New-onset diabetes for patients on intensive therapy compared to moderate therapy	Low: $I^2 = 0\%$	8.8% versus 8.0%, OR = 1.12 (95% CI = 1.04–1.22)	125	Patients could be categorized as having developed diabetes-based medications or laboratory values without a clinical diagnosis; funnel plot not provided
				Incident CVD for patients on intensive therapy compared to moderate therapy	Substantial: $I^2 = 74\%$	19.1% versus 21.7%, RR = 0.84 (95% CI = 0.75–0.94)	39	
Navarese et al.[27]	Randomized, controlled trials	17	113,394 Mix of primary and secondary cardiovascular preventions	New-onset diabetes for patients on high-intensity statin compared to placebo	Not provided	No difference for any agents[a]	N/A	Clinical trial registries not reviewed; patients could be categorized as having developed diabetes-based medications or laboratory values without a clinical diagnosis
				New-onset diabetes for patients on moderate-intensity statin compared to placebo	Not provided	No difference for any agents[a]	N/A	
				New-onset diabetes for patients on high-intensity statin compared to moderate-intensity statin	Not provided	No difference between any agents[a]	N/A	

Table 2. (Continued)

Reference	Types of studies included	Number of studies included	Patient population	Endpoint, intervention, control	Heterogeneity	Results	NNH/NNT	Key limitations
Cai et al.[28]	Randomized, controlled trials	14	95,102 Mix of primary and secondary cardiovascular preventions	New-onset diabetes for patients on high-intensity statin compared to placebo or active control	Low: $I^2 = 0\%$	5.4% versus 4.6%, OR = 1.18 (95% CI = 1.10–1.28)	125	Funnel plot not provided
				New-onset diabetes for patients on moderate-intensity statin compared to placebo or active control	Moderate: $I^2 = 34\%$	5.0% versus 4.6%, OR = 1.11 (95% CI = 1.03–1.20)	250	
Macedo et al.[29]	Observational studies	2	158,522 Mix of primary and secondary cardiovascular prevention	New-onset diabetes for patients on statins compared to patients not on statins	Substantial: $I^2 = 72\%$	OR = 1.31 (95% CI = 0.99–1.73)	N/A	Only included 2 studies that assessed new-onset diabetes; high heterogeneity; wide confidence intervals suggest imprecise results
Coleman et al.[30]	Randomized, controlled trials	5	39,791 Mix of primary and secondary cardiovascular prevention	New-onset diabetes for patients on statins compared to placebo	Moderate: $I^2 = 51.5\%$	RR = 1.03 (95% CI = 0.89–1.19)	N/A	Moderate heterogeneity; only included placebo-controlled studies; funnel plot not provided

NNH: number needed to harm; NNT: number needed to treat; RR: relative risk; CI: confidence interval; N/A: not available; OR: odds ratio; CVD: cardiovascular disease.
[a]Assessed as individual agents, data were not pooled.

Table 3. Studies included in meta-analyses of clinical trials.

Control	Rajpathak et al.[24]	Sattar et al.[25]	Preiss et al.[26]	Navarese et al.[27]	Cai et al.[28]	Coleman et al.[30]
	Placebo	Active or placebo	Active	Active or placebo	Active or placebo	Placebo
Included clinical trials						
4S		X		X	X	
A to Z			X			
AFCAPS/TexCAPS		X		X	X	
ALLHAT-LLT		X		X	X	
ASCOT	X	X		X	X	X
CORONA	X	X		X	X	X
GISSI		X		X	X	
GISSI-HF		X		X	X	
HPS	X	X		X	X	X
IDEAL			X	X		
JUPITER	X	X		X	X	
LIPID	X	X		X	X	X
MEGA		X		X	X	
PROSPER		X		X	X	
PROVE-IT-TIMI-22			X	X		
SEARCH			X			
SPARCL				X	X	
TNT			X	X		
WOSCOPS	X	X		X	X	X

4S: Scandinavian Simvastatin Survival Study; A to Z: early intensive versus a delayed conservative simvastatin strategy in patients with acute coronary syndromes; AFCAPS/TexCAPS: Air Force/Texas Coronary Atherosclerosis Prevention Study; ALLHAT-LLT: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial–Lipid-Lowering Trial; ASCOT: Anglo-Scandinavian Cardiac Outcomes Trial–Lipid-Lowering Arm; CORONA: Controlled Rosuvastatin Multinational Trial in Heart Failure; GISSI: Gruppo Italiano per lo Studio Della Sopravvivenza Nell'Infarto Miocardico; GISSI-HF: Gruppo Italiano per lo Studio Della Sopravvivenza Nell'Infarto Miocardio–Heart Failure; HPS: Heart Protection Study; IDEAL: Incremental Decrease in End Points through Aggressive Lipid Lowering; JUPITER: Justification for the Use of Statins in Primary Prevention; LIPID: Long-Term Intervention with Pravastatin in Ischemic Disease; MEGA: Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese; PROSPER: Prospective Study of Pravastatin in the Elderly at Risk; PROVE-IT-TIMI-22: Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22; SEARCH: Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine; SPARCL: Stroke Prevention by Aggressive Reduction in Cholesterol Levels; TNT: Treating to New Targets; WOSCOPS: West of Scotland Coronary Prevention Study.

cautioned that although observational studies are preferred for evaluating safety issues, inherent limitations such as use of retrospective data, potential for recall bias, and lack of randomization to reduce impact of confounding variables limit the ability to draw definite conclusions. The small difference in new-onset diabetes observed in some studies could also be attributed to survival bias, particularly in observational studies. This phenomenon could lead to small increases in diabetes diagnosis in the statin groups due to extended patient survival.

While the conclusion can be made that statins, as a class, are associated with an increased risk of new-onset diabetes, the question of whether a certain dose or agent carries a higher risk is not as clear. Several of the observational studies indicated that the risk of new-onset diabetes may be higher with higher intensity statins, but this finding was not consistent among all the studies that compared statin intensity. The definition of high-intensity statin also varied between studies, decreasing the ability to compare results across studies. Also, some observational studies found increased risk associated with certain statins. Other studies found decreased risk based on hydrophilic statins; however, the results from other studies contradicted those results. When the results from all studies are considered, no one dose or agent is clearly associated with increased risk of new-onset diabetes.

Differences in risk–benefit ratio based on indication of statin for primary or secondary prevention has also been explored. While the risk–benefit profile seems to be similar in patients receiving statins versus controls for primary prevention, patients receiving statins for secondary prevention experienced less in-hospital fatalities over 10 years than controls, which outweighed the risk of developing new-onset diabetes when compared to a control population in one study conducted in Taiwanese patients.[11] While the clear cardiovascular benefits of statins make randomized, controlled trials of high-intensity statins versus placebo or low-intensity statins inappropriate, further research is needed to determine individual patients who might be at highest risk of new-onset diabetes. The factors considered in the Pooled Cohort Equations estimating 10-year ASCVD risk have not been

consistently accounted for in prior studies and should be when weighing risk versus benefit of statin therapy for individual patients. Additionally, further research is needed to quantify statin impact on new-onset diabetes accounting for other confounding variables, such as lifestyle factors, metabolic syndrome, pre-diabetes, and comorbid conditions that increase new-onset diabetes risk. Covariates assessed in published studies were highly variable and often lacking or unreported, making it difficult to draw firm conclusions regarding whether statins themselves or incidental patient factors are more responsible for the small increased risk of new-onset diabetes.

The results from this review were similar to those found in three others, indicating that statins are associated with an increased risk of diabetes and that this is a class-related effect. Additional conclusions were that it would be prudent to closely monitor patients receiving statins who are at higher risk of developing diabetes, such as elevated triglycerides, high fasting glucose level, higher BMI, and advanced age.[31–33] This review provides findings from a wider scope of published studies compared to recent reviews, including that of the Statin Diabetes Taskforce and American Diabetes Association.[9,10,31–33]

The identified meta-analyses were generally limited in scope to randomized, controlled trials and excluded observational studies. While this approach decreased heterogeneity, it sets aside data from several large, impactful studies that were specifically designed to evaluate statin-induced diabetes. An overview of the studies included in meta-analyses of clinical trials is provided in Table 3. The identified meta-analyses were generally consistent in that the same studies were included; however, there were several minor differences that could have impacted results. A core group of 13 trials were included in all three meta-analyses that assessed both active- and placebo-controlled trials; however, additional studies were included in Navarese et al., possibly explaining the lack of statistically significant findings. The two meta-analyses that included placebo-controlled trials both included a common core group of five trials, but one included JUPITER,[24] and the other included post hoc analyses of West of Scotland Coronary Prevention Study (WOSCOPS) and Heart Protection Study (HPS),[30] which could be a factor in the different results observed between studies. Cai et al., possibly the most impactful meta-analysis in terms of number of included studies combined with low heterogeneity, detected that although high- and moderate-intensity statins were associated with statistically significant risk of new-onset diabetes, the results would not be considered clinically worrisome due to the low absolute event rates and high NNH values. One notable gap in the available literature was the lack of a meta-analysis that evaluated the large number of published observational studies on this topic, although the risk of heterogeneity due to differences in intervention, control, duration, patient population, and endpoints could limit impact of such a study.

There were several limitations to this review. First, the literature search was limited to use of PubMed, Google Scholar, and IPA. It is possible that additional databases (e.g. EMBASE) could yield further studies meeting our criteria; however, we believe the scope of our search was successful in identifying the most important studies focused on this topic. Additionally, it is possible that further data could be identified from major randomized, controlled trials assessing statin efficacy, as well as post hoc safety analyses of these studies. We chose to focus on studies designed to specifically answer research questions related to risk of statin-induced new-onset diabetes in order to focus on the most robust safety data available. Anecdotally, we observed that most of the major statin trials that incidentally observed increased risk of new-onset diabetes were included in the meta-analyses that were evaluated as part of this review.

Conclusion

In a review focusing on literature specifically designed to investigate this association between statins and new-onset diabetes, statins have been associated with a small, but statistically significant risk. This risk is not considered to be clinically significant (due to small increases in absolute risk, particularly in meta-analyses of multiple studies), was inconsistent across published evidence, and is likely outweighed by statins' benefits on cardiovascular risk reduction. Future research should focus on directly comparing risk of new-onset diabetes versus risk of cardiovascular events and accounting for all potential factors that could increase risk of new-onset diabetes.

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