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Original Paper

Statins and New-Onset Diabetes in Cardiovascular and Kidney Disease Cohorts: A Meta-Analysis

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Keywords
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Abstract
Background: Statins have long been prescribed for the primary and secondary prevention of cardiovascular disease (CVD) and kidney disease. Their benefits and efficacy are widely accepted in current clinical practice, but like any other therapeutic agents, they have adverse effects. One of the emerging concerns with statin therapy is the development of new-onset diabetes mellitus (NODM), a dreaded risk factor for CVD and kidney disease and widely viewed as CVD equivalent. Accumulating evidence indicates that NODM is a consequence of statin use. ***Methods:*** We conducted a meta-analysis of studies reporting on associations between NODM and statin use. Based on strict exclusion criteria, a total of 11 studies were selected. Their data were analyzed using Comprehensive Meta-Analysis® statistical software and reported as odds ratios (OR) with 95% confidence intervals (CI). ***Results:*** The cumulative fixed effect for use of statin therapy and incident NODM was an OR of 1.61 (95% CI 1.55–1.68, $p < 0.001$). Our results suggest that statin therapy is associated with NODM, such that there is a small but significant risk of NODM among patients receiving statin for CVD prevention therapy. However, this high-risk population also has other diabetes risk factors (such as obesity and hypertension) contributing to the development of NODM. ***Conclusions:*** It is imperative that patients on statin therapy be monitored carefully for NODM. However, it can be argued that the risk of statin therapy is offset by the multitude of cardiovascular and kidney-protective effects provided by such an important and highly effective therapeutic agent.

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Introduction

Statins are one of the most commonly prescribed medications [1, 2]. Over 25% of Americans over the age of 45 years are prescribed a statin according to a CDC study from 2010 [3]. The role of statins in reducing the number one cause of death worldwide – that is, cardiovascular disease (CVD) – has been well established, dating back to the 1980s [4]. Indications for statins continue to expand, likely due to their observed and evolving pleotropic effects above and beyond the lipid-lowering effects that have been observed in several randomized controlled trials [4–6]. Statins are effective and have shown to be responsible for a 60% risk reduction in ischemic heart disease [7]. In addition, being widely available in generic forms, statins are cost-effective means for reducing CVD risk in large populations, particularly among high-risk groups such as people with diabetes and kidney disease, thus reducing global mortality [4, 8, 9]. In addition to their benefits, adverse effects have also been established, most notably myopathy [10, 11] and perhaps liver disease, although emerging data indicate that statins induce a reduction in the extent of hepatic steatosis [12–15]. Nevertheless, despite the stated side effects, in most scenarios the benefits have outweighed the risks.

Statins were initially thought to reduce the risk of incident diabetes [4, 16], based on the retrospective analysis of the West of Scotland Coronary Prevention Study (WSCOPS), which examined the development of new diabetes mellitus in men aged 45–64 years [16]. In this study, a total of 5,974 of the 6,595 randomized subjects were included in the analysis, and the assignment to pravastatin therapy resulted in a 30% reduction ($p = 0.042$) in the hazard of developing diabetes [16]. The reduction in diabetes incidence was associated with a significant decrease in triglyceride levels. However, this decline in triglycerides did not account for the total effect of pravastatin on new-onset diabetes in the WSCOPS [16]. Several potential hypotheses were introduced at the time to explain the results of the WSCOPS, including the pleotropic effects of statin in reducing inflammation and affecting substrate delivery to insulin-sensitive tissue, combined with enhancing endothelial nitric oxide synthase activity as well as increasing endothelial nitric oxide synthase expression, which might have a beneficial effect in terms of increased capillary recruitment and glucose disposal [4, 17].

The recent literature, however, has suggested a relationship between statins and hyperglycemia to the extent of causing new-onset diabetes, thereby questioning the medication's safety. The mechanism is not yet fully understood, but effects of hyperglycemia and rising HbA_{1c} with statin use in both those with and those without diabetes have been recorded. It is unclear what these findings will mean for those currently on statins or considering initiating this medication, but with the prevalence of diabetes and its complications already at alarming levels, it is therefore imperative to further examine this relationship. Diabetes is a known risk factor for several disease states, with CVD being the most common cause of morbidity and mortality in this ever-growing population. Furthermore, diabetes poses a large burden on the healthcare system, with the CDC estimating it at USD 245 billion, accounting for 20% of the overall healthcare expenditure annually [18].

With this in mind, statins as a class should be reexamined in regard to their relationship to diabetes. Over the past decade, many studies have been performed examining this relationship. The aim of this study is to perform an updated meta-analysis of the available data from the past 10 years to assess the risk of new-onset diabetes mellitus (NODM) among people receiving statins.

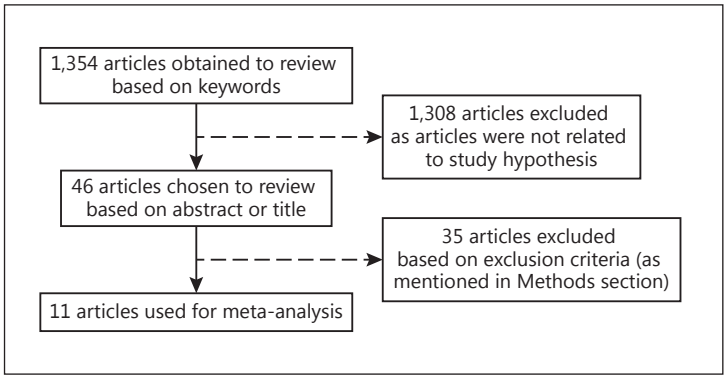

Fig. 1. Flow diagram of the literature search.

Table 1. Exclusion criteria

1. Subjects had a prior diagnosis of diabetes
2. Patient sample was unique (i.e., those after liver transplantation or with familial hypercholesterolemia)
3. Results or data presented in the written section of the published study did not match data presented in tabular or chart format
4. Study was a subanalysis of a previous study already examined
5. There was no control group
6. Authors only had access to the abstract and not the full article, such as in cases where the study was only in abstract form and no full manuscript was written
7. Study looked at changes in HbA_{1c} levels but not at new-onset diabetes.

Methods

PubMed was searched for studies related to incident diabetes and statin therapy. The search included studies published over a 10-year span, beginning July 1, 2006, and ending June 30, 2016. The search was performed using the following keywords: "statin" or "HMG-CoA reductase inhibitor" in addition to either "incident diabetes," "new onset diabetes," "insulin resistance," or "impaired insulin secretion." Studies were then excluded if they were found to be not related to the study hypothesis that statin use is associated with incident diabetes. Of the remaining manuscripts, studies were excluded for one of 7 reasons, as described in Figure 1 and Table 1: (1) the subjects had a prior diagnosis of diabetes; (2) the cohorts comprised a very specific set of patients (i.e., patients after liver transplantation or with familial hypercholesterolemia); (3) the data presented in the written section of the published results did not match the data included in the tables or charts of the study; (4) the study was a subanalysis of a previous study already examined; (5) there was no control group; (6) we only had access to the abstract and not the full article, or the study was only in abstract form, such as in cases where a full paper was not written; or (7) the study looked at changes in HbA_{1c} levels but not at NODM.

Overall, 11 studies met the inclusion criteria and were included in this meta-analysis. The data were analyzed using the Comprehensive Meta-Analysis® statistical software. The Mantel-Haenszel method [19] was used for calculating a weighted, pooled odds ratio (OR) and 95% confidence intervals (95% CI) using fixed-effects models. A heterogeneity statistic was incorporated to calculate the summary OR under the random-effects model (DerSimonian and Laird). Both fixed and random effects are reported. The results are reported as OR (95% CI), with two-tailed p values <0.05 indicating statistical significance.

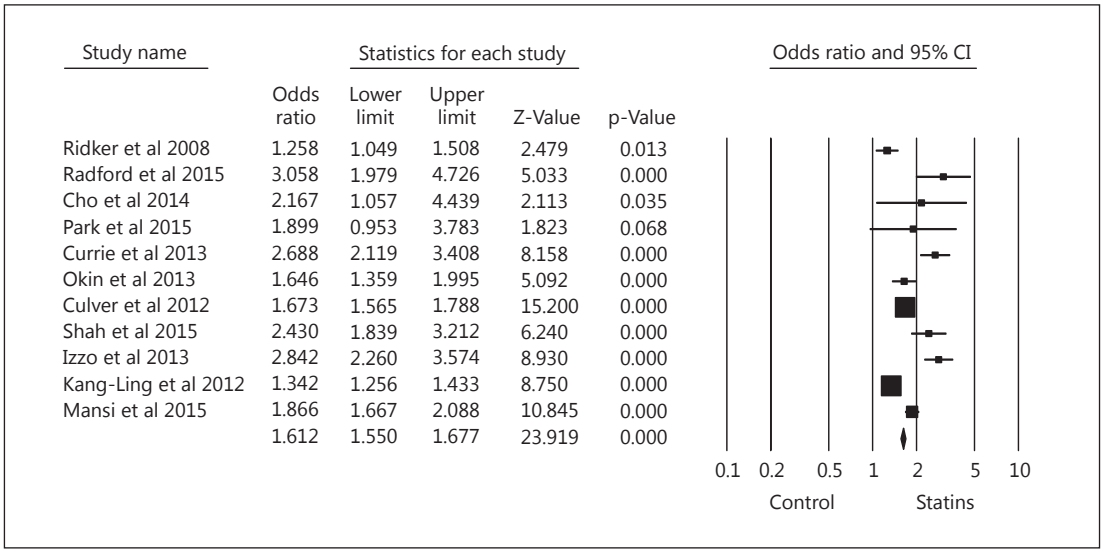

Fig. 2. Forest plot showing the association of statin use with new-onset diabetes mellitus. Also presented are the odds ratios, upper and lower limits of the 95% confidence interval, and *p* values.

Results

There are a total of 11 studies included in the meta-analysis. This resulted in a total of 236,864 subjects. Of these, 180,811 were in the control group and 56,053 were in the statin therapy group. Within the control group, 10,447 developed diabetes mellitus, while 4,732 of the statin group developed diabetes mellitus. Figure 2 summarizes the detailed results and depicts the forest plots of the studies included. The pooled OR (95% CI) for the fixed-effects model of statin use predicting NODM was 1.61 (1.55–1.68) and for the random-effects model 1.92 (1.64–2.25). These results suggest that overall there is a significant positive association between statin use and development of incident diabetes mellitus. The heterogeneity (Q statistic) observed for the studies included was 103.5 ($p < 0.001$).

Discussion

The results of this meta-analysis show that individuals on statins have an increased risk of developing NODM compared to individuals who did not receive statins, which is in agreement with findings from a previous meta-analysis [20]. The JUPITER trial was one of the first to note the increased incidence of physician-reported diabetes in individuals randomized to the rosuvastatin arm. However, diabetes was not an adjudicated end point in the JUPITER trial, and no further explanation for the finding was offered by the JUPITER investigators [21]. With burgeoning interest in the potential risk of statin-induced NODM, studies started to emerge that tried to elucidate the potential link between NODM and statins.

There are many strengths of our meta-analysis. First, we incorporated all data that were published within the past decade. Second, all published trials within the past decade were large and complete, thus providing good statistical samples and power. However, there were also limitations that were not under our control. First, there was heterogeneity in the diagnostic criteria used for NODM by trial, which is common. Second, there were different populations represented with varying incidences of NODM with statin included in this analysis.

However, the cumulative incidence was found to be statistically significant in our diverse set of studies and populations, suggesting common pathways that might in effect result in the development of statin-induced NODM. Third, we only considered clinical diagnoses of incident diabetes in clinical trials, and not self-reported diabetes or biomarker-based diagnoses. Finally, we were unable to consider the potentially modifying effects of blood lipid levels, physical exercise, genetic susceptibility, or polypharmacy.

This study does not intend to establish a molecular mechanism for statin-induced NODM. Nonetheless, there is increasing evidence from animal models that there are molecular mechanisms that impact the function and survival of beta cells with statin treatment. Statin-induced impairment of insulin secretion is related to multiple targets, including effects on ATP-sensitive potassium channels, voltage-gated calcium channels, and inhibited calcium release from the endoplasmic reticulum [22]. Furthermore, impaired endoplasmic reticulum function-induced islet dysfunction has been observed. This islet dysfunction was associated with a marked reduction of exocytosis as well as an increase in several oxidized phospholipids, tri- and diacylglycerols, and the apoptosis-inducing lipid molecule ceramide [23].

Liver function is an additional factor in determining insulin sensitivity and a target of statin therapy. The studies by Shah et al. [24] and Cho et al. [25] were included in our meta-analysis. Analysis of these studies shows that patients with a high liver fat content [24] and after liver transplantation [25] have a higher incidence of statin-induced NODM. The increase in liver fat content can be explained by recent population-level Mendelian randomization studies [26] suggesting a potential mechanistic basis for an association of statin-mediated HMG-CoA reductase inhibition with increased body weight and incidence of NODM. Other studies [27] have noted that weight gain in those treated with statins could be due to improved survival; however, the reported survival rates are similar among diabetics on and those off statins. Cho et al. [25] indicates that chronic statin treatment (>6 months) could contribute to the development of NODM in liver transplant recipients, especially if they have higher baseline fasting glucose levels. However, the sample size used in their study was small. These results might be due to confounding factors such as immunosuppressant medications commonly used in this patient population, including steroids, calcineurin inhibitors (cyclosporine and tacrolimus), and sirolimus.

Insulin effects on muscle are also of importance in developing diabetes. To our knowledge there is no study which shows that statins cause gradual loss of muscle mass, other than in extreme cases of statin-induced myositis. Radford et al. [28] showed attenuation of the risk of developing NODM in individuals with high baseline fitness, as measured by maximal time spent on the treadmill. Those with low fitness at baseline were at a 2-fold increased risk of developing NODM while on statins. There are several studies [29–31] showing that statins can lead to decreased expression of glucose transporter 4 in adipocytes, skeletal muscle, and liver tissue. This causes changes in glucose homeostasis and development of statin-induced NODM. This suggests that preexisting skeletal muscle function and efficiency might also modify the effects of statins on NODM.

This meta-analysis also highlights the importance of statin dosing in development of NODM. Park et al. [32] used low-dose atorvastatin in propensity-matched individuals and found that there was an increased risk of NODM in those receiving atorvastatin versus controls. However, these results were not statistically significant, underscoring the impact of dosing on development of statin-induced NODM.

Additionally, statin's effects on a patient's lipid profile could also have a role in development of NODM. The LIFE study demonstrated that a reduced in-treatment HDL fraction increased the risk of NODM [33]. This could be explained by the fact that HDL helps reduce levels of oxidized LDL, which inhibits insulin secretion. Therefore, a reduction in HDL increases oxidative stress and reduces insulin secretion. Though the study states that this finding was

not driven by statin's effects on HDL, concomitantly there needs to be additional consideration given to statin's effects on LDL and triglycerides. Since then, another study [34] employed data from genome-wide association studies to investigate the association between lipid fraction and the risk of diabetes using a Mendelian randomization approach that accounted for the pleiotropy of the genetic instruments. This study [34] found that increased LDL, HDL, and possibly triglyceride levels are associated with lowering the risk of diabetes. It should be noted that this study did not directly measure the effects of statins on lipid fractions and development of NODM. These findings, therefore, warrant further investigation of the effects of statins on the entire lipid fraction and subsequent development of NODM.

Our data suggest that there are multiple factors involved in accurately assessing the risk of developing NODM versus the well-known cardiovascular benefits of statins. The benefits of preventing major adverse cardiovascular outcomes in patients with and without diabetes in comparison to the small, yet significant, risk of NODM is favorably balanced by the cardiovascular benefits [35–38]. This suggests that clinical decision-making should not change, especially for those with a medium or high risk of cardiovascular events or existing cardiovascular disease. We posit that there is a susceptible subpopulation at risk of developing NODM while on statins, regardless of the cardiovascular risk, and these individuals deserve closer monitoring of blood glucose and HbA_{1c} levels. Individuals at risk of developing NODM should be identified based on both "on-target" as well as "off-target" effects of statins. These include impaired fasting glucose at baseline, body mass index, liver fat content (presence of NASH), use of additional diabetogenic medications such as steroids, physical exercise capacity, statin potency and dosage, and baseline lipid fractions. Currently, the small absolute risk of developing NODM does not outweigh the benefit of statins on cardiovascular outcomes. It is absolutely imperative that there be further investigation using adequately powered, randomized, controlled trials to assess each target of statin therapy. Another aspect that needs further investigation and consideration is the approach to management and potentially prevention of NODM in individuals requiring statin therapy.

Statement of Ethics

No ethics committee approval was sought for this study, since it only involves a meta-analysis of data from preexisting research studies. No direct patient contact was made in the study.

Disclosure Statement

The authors do not have any relevant disclosure, other than the below-mentioned funding source for Moro O. Salifu, which had no impact on any aspect of this publication.

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