

A REVIEW OF STATIN-INDUCED NEW ONSET DIABETES

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ABSTRACT

Statins are the gold standard for the prevention of primary and secondary CVD events, which is a leading cause of mortality worldwide. Because of this, statins are the most widely prescribed drug. But as the use of statin-use increased, patients began to experience many difficulties. After conducting several studies based on this, we have come to know that it has side effects along with the long term and intensive use of statins. One of the main side effects is statin-induced new-onset diabetes. It is well established by several studies that statins may induce new-onset diabetes in patients. Intensive-dose statins are the most to induce diabetes as compared to moderate-dose statins. There are several mechanisms behind statin-induced diabetes. Mechanistically, statins inhibit the HMG CoA reductase enzyme in the cholesterol biosynthesis pathway. By this process, it will affect pancreatic β -cell leads to a decrease in insulin release. And also statin use enhance the resistance to insulin in adipocytes, muscles and liver because statin alters insulin sensitivity in these areas. This is how statin causes diabetes. However, statin is an indispensable drug for preventing CVD events. Therefore, statins are still recommended to continue for reducing cardiovascular disease event risk in appropriate patients with and without diabetes or risk factors for diabetes.

KEYWORDS: CVD events, diabetes, HMG CoA reductase.**INTRODUCTION**

Among the most commonly prescribed drugs worldwide, are cholesterol-lowering agents statins used to manage cardiovascular and other related heart diseases.^[1] Intensive-dose statin therapy has also been shown to further reduce cardiovascular events compared with moderate-dose statin therapy.² Statins competitively inhibit HMG-CoA reductase and upregulate LDL receptors, resulting in a reduction of plasma cholesterol levels.

Statin is not synthesized in the animal or human body. Specific statins such as mevastatin, lovastatin, and pravastatin are fungal origin natural statins and simvastatin is a semi-synthetic drug derived from lovastatin. Meanwhile, atorvastatin, cerivastatin, fluvastatin, pitavastatin, and rosuvastatin are fully synthesised statins.^[1]

Even though statins have been proven to significantly reduce the risk of cardiovascular disease (CVD) and its associated mortality, statins therapy may cause an increased risk of type II diabetes.^[1] Furthermore, in the recent recommendation for the treatment of hyperlipidemia, the 2013 American College of Cardiology/American Heart Association (ACC/AHA)

guideline extended the range of statin therapy in comparison to the previous 2002 National Cholesterol Education Program—Adult Treatment Panel III (NCEPATP III) guideline. Because of this change, statins are expected to be used more widely.^[3]

As statin use increases, the risks associated with statin use are important. Questions regarding the relationship between statin use and new-onset diabetes mellitus (NODM) have been consistently praised, and recently conducted studies have reported several results on the increased risk of NODM. The US Food and Drug Administration recently issued a warning on the possible increase in glucose and HbA1c levels, through changes in the labelling requirement for a statin. Moreover, the European Medicines Agency mentioned that statins could increase the risk of type 2 diabetes.^[3]

The general safety of statins is accepted widely, but adverse effects have been reported as a result of changes in renal, hepatic, and muscular function. The most common adverse effects of statins are on the skeletal muscle, which ranges from mild myopathy such as cramp, fatigability, and exercises intolerance to myotoxicity. In rare cases, severe rhabdomyolysis maybe develop. Rhabdomyolysis is a complex health condition

characterized by the swift dissolution of damaged muscle with increment in the release of toxic intracellular muscle components. Apoptosis in cardiac myocytes, human skeletal muscle cells, T-cells, B-cells, and myeloma tumour cells are induced by Simvastatin. Other toxicological effects of statin therapy include-hemorrhagic stroke, depression, and lower testosterone, decreased renal function, tendon rupture, elevated liver function tests, interstitial lung disease, among others.^[1]

Assessment and Diagnosis of Statin-Induced Diabetes

Statin use is moderate, but statistically significant, an overall increase in the odds for new-onset diabetes. Intensive-dose statin therapy is associated with an increase in risk for new-onset diabetes compared with standard-dose statin therapy. Given the well-established benefits of statin therapy in the primary and secondary prevention of cardiovascular events among those with indications for treatment, no changes to clinical practice are recommended other than the measurement of HbA1C or fasting glucose in those deemed to also be at elevated diabetes risk after initiating statin therapy, and potentially before initiation in selected patients considered to be at elevated risk of developing diabetes. Statins are still recommended to continue for reducing cardiovascular disease event risk in appropriate patients with and without diabetes or risk factors for diabetes. Lifestyle modification is recommended for all patients undergoing statin therapy, not only to reduce cardiovascular risk but also to moderately increase the risk of diabetes.^[4]

Ko et al published a study on “Time-and Dose-Dependent Association of Statin Use With Risk of Clinically Relevant New-Onset Diabetes Mellitus in Primary Prevention: A Nationwide Observational Cohort Study” in which they say, as compared with statin nonusers, being a statin user was significantly associated with an increased risk of new-onset diabetes mellitus. There was a time-and dose-dependent association of statin use with an increased risk of diabetes mellitus. Using healthcare data from the national health insurance examinees, this study comprised a cohort of adults aged ≥ 40 years with hypercholesterolemia who would be eligible for statin therapy for primary prevention from 2005 to 2012. The primary outcome was the occurrence of clinically relevant new-onset diabetes mellitus requiring medical therapy. Among 2 162 119 adults with hypercholesterolemia who might be eligible for statin therapy, 638 625 (29.5%) ever used statins and 1 523 494 (70.5%) never used statins. In the propensity-matched cohort of 518 491 pairs, during mean follow-up of 3.9 years, being an ever-user of statin was significantly associated with diabetes mellitus risk compared with being a never-user of statin. An excess risk of diabetes mellitus was also associated with a higher intensity and a cumulative dosing of statin.^[5]

From the study of “Diabetes Mellitus and Cardiovascular Events in Older Patients With Myocardial Infarction

Prescribed Intensive-Dose and Moderate-Dose Statins” by Dennis T Ko et al, a propensity score-matched cohort was created consisting of 17 080 patients with myocardial infarction aged >65 years old, hospitalized in Ontario, Canada, from 2004 to 2010. Clinical outcomes were compared in patients prescribed intensive-dose versus moderate-dose statins at hospital discharge. At 5 years, 13.6% of patients receiving intensive-dose statins and 13.0% of patients receiving moderate-dose statins had new-onset diabetes, which was not significantly different ($P=0.19$). By contrast, the 5-year rate of death or acute coronary syndrome was significantly lower at 44.8% in the intensive-dose statin group compared with 46.5% in the moderate-dose group ($P=0.044$). The reduction in combined clinical outcome was driven mainly by a significantly lower rate of acute coronary syndrome ($P=0.039$) associated with intensive-dose statins. No significant difference in mortality rates (34.8% in both groups) was observed between the treatment groups during the study period ($P=0.89$). They concluded as in older patients with myocardial infarction, we found intensive-dose statin therapy to be effective in reducing repeat hospitalization for acute coronary syndrome. The rate of new-onset diabetes mellitus at long term was not significantly different between intensive-dose and moderate-dose statins.^[6]

From the study of “Effect of statins on fasting glucose in non-diabetic individuals: nationwide population-based health examination in Korea” by Jinkwon Kim et al included 379,865 non-diabetic individuals who had ≥ 2 health screening examinations with fasting blood glucose levels measured in 2002–2013. Using the prescription records of statins in the database, they calculated the proportion of days covered (PDC) and the average number of defined daily doses per day (anDDD) by statins. They constructed multivariate linear mixed models to evaluate the effects of statins on the changes in fasting glucose (Δglu). High PDC by statins had a significant positive effect on Δglu (coefficient for PDC 0.093 mmol/L, standard error 0.007, $p < 0.001$). A DDD by statins was also positively associated with Δglu (coefficient for anDDD 0.119 mmol/L, standard error 0.009, $p < 0.001$). Unlike statins, the PDC by fibrate and ezetimibe were not significantly associated with Δglu . There was no significant interaction effect on Δglu between time interval and statin. Considering individual types of statins, the use of atorvastatin, rosuvastatin, pitavastatin and simvastatin were significantly associated with the increase of Δglu . Pravastatin, lovastatin, and fluvastatin were also positively associated with Δglu but were not statistically significant. More adherent and intensive use of statins was significantly associated with an increase in fasting glucose of non-diabetic individuals. In subgroup analysis of individual statins, use of atorvastatin, rosuvastatin, pitavastatin and simvastatin had significant association with increase in fasting glucose. Pravastatin, lovastatin, and fluvastatin had non-significant trend toward an increased fasting

glucose. Their findings suggest the medication class effect of statins inducing hyperglycemia.^[7]

Jill P Crandall et al published research on “Statin use and risk of developing diabetes: results from the Diabetes Prevention Program” and the DPP was a randomized clinical trial testing interventions to prevent or delay the development of diabetes mellitus (DM) among high-risk individuals. The 27 clinical centers in the USA recruited 3234 participants of both sexes. Eligible participants received standard advice on a healthy diet and physical activity and were randomly assigned to intensive lifestyle intervention, metformin or placebo. At the end of the main trial (mean follow-up 3.2 years), all participants were offered a group-administered version of the lifestyle intervention and were invited to enrol in the DPP Outcomes Study (DPPOS). During the DPPOS, all participants were offered quarterly lifestyle sessions, the former metformin group received open-label metformin and the former intensive lifestyle group was offered two additional lifestyle program per year. Incident diabetes was assessed by annual 75 g oral glucose tolerance testing and semiannual fasting glucose. Lipid profile was measured annually, with statin treatment determined by a participant’s own physician outside of the protocol. Statin use was assessed at baseline and semiannual visits, based on the question ‘Has the participant taken any prescription medications within the past 2 weeks?’ Participants were asked to bring all prescription pill bottles to each visit and drug name was recorded. Cumulative statin use was defined as the number of semiannual visits with reported use. At 10 years, the cumulative incidence of statin initiation prior to diabetes diagnosis was 33%–37% among the randomized treatment groups ($p=0.36$). Statin use was associated with greater diabetes risk irrespective of the treatment group, with pooled HR (95% CI) for incident diabetes of 1.36 (1.17 to 1.58). This risk was not materially altered by adjustment for baseline diabetes risk factors and potential confounders related to indications for statin therapy. In this population at high risk for diabetes, they observed significantly higher rates of diabetes with statin therapy in all three treatment groups. Confounding by indication for statin use does not appear to explain this relationship. The effect of statins to increase diabetes risk appears to extend to populations at high risk for diabetes.^[8]

A recent meta-analysis of “Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials” by Prof Naveed Sattar et al, 13 randomized placebo and standard care controlled trials involving 91140 participants, of whom 4278 (2226 assigned statins and 2052 assigned control treatment) developed diabetes during a mean of 4 years. Statin therapy was associated with a 9% increased risk for incident diabetes (odds ratio [OR] 1.09; 95% CI 1.02–1.17), with little heterogeneity ($I^2=11\%$) between trials. Meta-regression showed that the risk of development of diabetes with statins was highest in trials with older participants, but neither

baseline body-mass index nor change in LDL-cholesterol concentrations accounted for residual variation in risk. Treatment of 255 (95% CI 150–852) patients with statins for 4 years resulted in one extra case of diabetes. Statin therapy is associated with a slightly increased risk of development of diabetes, but the risk is low both in absolute terms and when compared with the reduction in coronary events. Clinical practice in patients with moderate or high cardiovascular risk or existing cardiovascular disease should not change.^[9]

Another meta-analysis of “Risk of Incident Diabetes With Intensive-Dose Compared With Moderate-Dose Statin Therapy” by David preiss et al, they included randomized controlled end-point trials that compared intensive-dose statin therapy with moderate-dose statin therapy and included 5 statin trials with 32752 participants without diabetes at baseline, 2749 developed diabetes (1449 assigned intensive-dose therapy, 1300 assigned moderate-dose therapy, representing 2.0 additional cases in the intensive-dose group per 1000 patient years) and 6684 experienced cardiovascular events (3134 and 3550, respectively, representing 6.5 fewer cases in the intensive-dose group per 1000 patient-years) over a weighted mean (SD) follow-up of 4.9 (1.9) years. Odds ratios were 1.12 (95% confidence interval [CI], 1.04-1.22; $I^2=0\%$) for new-onset diabetes and 0.84 (95%CI,0.75-0.94; $I^2=74\%$) for cardiovascular events for participants receiving intensive therapy compared with moderate-dose therapy. As compared with moderate-dose statin therapy, the number needed to harm per year for intensive-dose statin therapy was 498 for new-onset diabetes while the number needed to treat per year for intensive-dose statin therapy was 155 for cardiovascular events.^[2]

Type II diabetes is triggered by a mix of genetic factors associated with compromised insulin secretion, resistance, and environmental factors including; obesity, stress, overeating, lack of exercise, as well as ageing. The number of diabetic patients is rapidly increasing, reflecting lifestyle changes.^[1]

Possible Mechanisms

The drug statin regulates the enzyme HMG-CoA reductase in the metabolic pathway that produces cholesterol itself. Interactions between HMG-CoA reductase and statins inhibit the conversion of HMG-CoA to L-mevalonate, leading to the inhibition of downstream cholesterol biosynthesis and numerous metabolites such as farnesyl pyrophosphate (FPP) and geranylgeranyl pyrophosphate (GGPP1)(Figure 1).^[1]

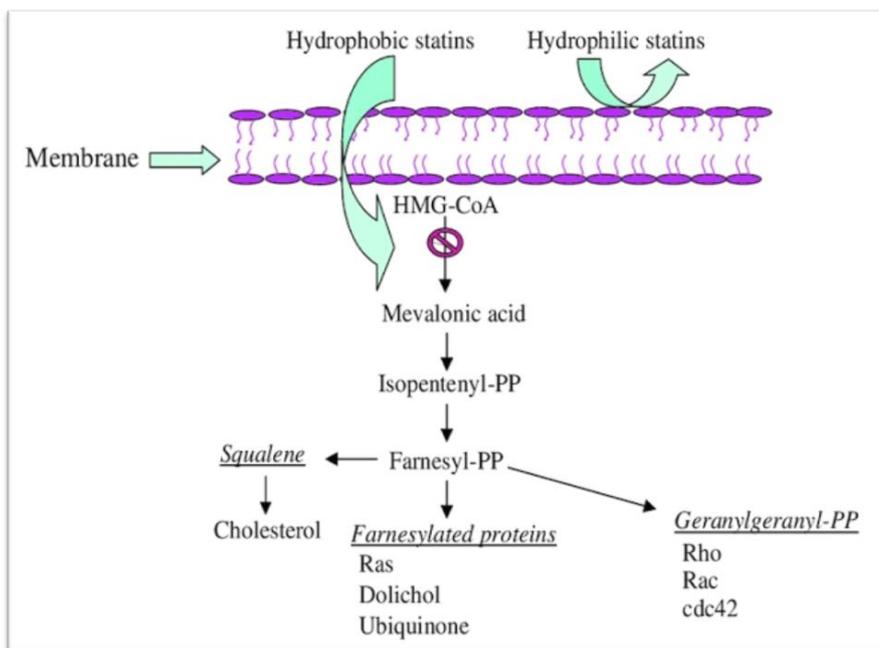


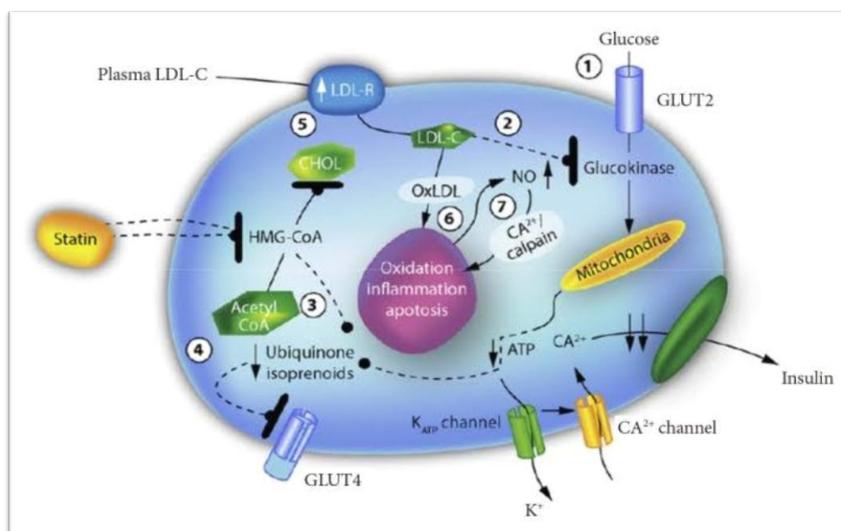
Figure 1: Inhibition of cholesterol biosynthesis pathway by statin.

The precise mechanism(s) for statin-induced diabetes remains unclear, although the majority of patients developing diabetes have pre-diabetes or features of metabolic syndrome indicating a high risk for diabetes at baseline. It has been controversial whether chemical differences and pharmacodynamic differences in statins or more intensive statin therapy are more likely to precipitate diabetes. In the analysis by Preiss et al., intensive statin therapy led to a greater increase in diabetes.^[10]

Several mechanisms have been postulated underlying the derangements in glucose metabolism by statins.^[10] The major mechanism associated with statin-induced diabetes is β -cell dysfunction, which included altered insulin secretion and sensitivity, changes in ion channel conductance, and oxidative stress and inflammation. Statins may also induce diabetes via the dysregulation of

insulin secretion endogenously. Glucose is the main impulse for pancreatic β -cells to release insulin. Pancreatic β -cells uptakes glucose through glucose transporter 2 (GLUT2), where it is phosphorylation takes place with the help of enzymes either glucokinase or hexokinase IV enzyme, to form glucose-6-phosphate. Thereafter, the glycolytic pathway is activated, which leads to an increase in the production of ATP and then closes the ATP-gated potassium ion channel. This resulting in membrane depolarization.^[1]

Depolarized membrane promotes the influx of Calcium ions via the L-type Calcium channel in β -cells causing exocytosis of insulin granules.^[1] It has been reported that lipophilic statins (e.g., simvastatin) can inhibit glucose-induced cytosolic Ca^{2+} signalling and insulin secretion by blocking L-type Ca^{2+} channels in beta-cells and their inhibitory potencies parallel their lipophilicities.^[11]

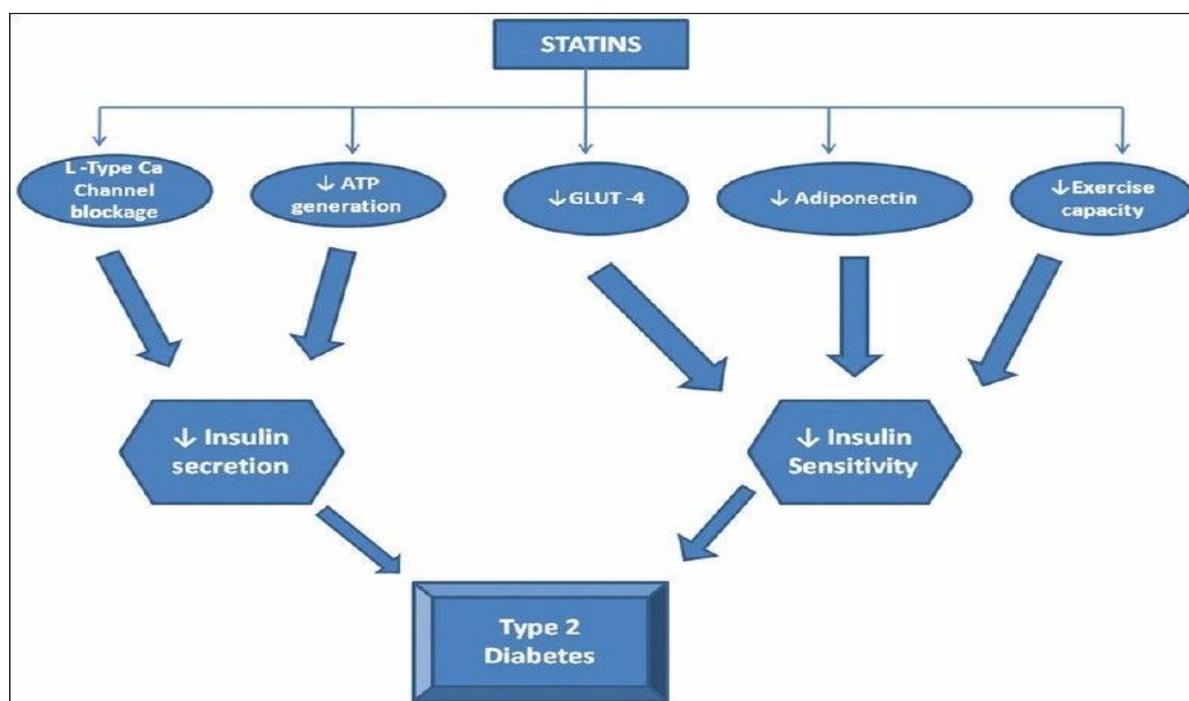


During the process of cholesterol synthesis from acetyl CoA, various metabolites such as isoprenoid, farnesyl pyrophosphate, geranylgeranyl pyrophosphate and ubiquinone (Coenzyme Q10 [CoQ10]) are normally produced. Statins can reduce these metabolites which may affect insulin secretion or action adversely. Statin may cause the reduction of CoQ10 level which is a constituent of the electron transport chain involved in the generation of ATP, results in a decrease in ATP production. This accounts for the diminution of insulin release.^[1]

Statin use also Leads to an alteration in insulin sensitivity. Therefore, it was assumed that diabetogenesis might be related to the consequence of statins on insulin sensitivity in the liver and muscle. Statin inhibits isoprenoid biosynthesis implicate down-regulation of glucose transporter 4 (GLUT4), which mediates for the glucose uptake into the adipocytes and skeletal muscles.

Down-regulation of GLUT4 may cause enhanced resistance to insulin in adipocytes, muscles and liver.¹ Atorvastatin and simvastatin have been shown to decrease the expression of GLUT4 in adipocytes which may result in impaired glucose tolerance.^[11] The metabolism of carbohydrates and fatty acids in liver and muscle influences insulin resistance by reducing hepatic gluconeogenesis and upregulating glucose uptake and beta-oxidation in the muscle, which is affected by the adiponectin released from the adipocytes. Therefore, insulin resistance has been shown to have a pathophysiological effect type II diabetes development.^[1]

Adiponectin is an insulin sensitizing and anti-inflammatory cytokine released from adipocytes. Rosuvastatin and simvastatin have been shown to decrease plasma adiponectin levels and insulin sensitivity while pravastatin increased both.^[11]



Mitochondrial dysfunction in beta cells, skeletal muscles and adipocytes has been linked with the pathogenesis of diabetes. Since statins are known to cause mitochondrial dysfunction in skeletal muscles, it is plausible that a similar mechanism is also responsible for their diabetogenic effect. In addition, statin-induced myalgia and fatigue may impair exercise capacity and aggravate sarcopenia, which is associated with glucose intolerance and type 2 diabetes. Therefore, multiple mechanisms may lead to impairment of glycemic control and risk of NOD with statins. Future studies are needed to confirm these Hypothesis.^[11]

Lipophilic statins (atorvastatin, simvastatin, lovastatin, fluvastatin and pitavastatin) may be more diabetogenic than hydrophilic statins (pravastatin and rosuvastatin) as

they can more readily penetrate extrahepatic cell membranes such as β -cells, adipocytes and skeletal muscle cells. Conversely, hydrophilic statins (e.g., pravastatin) are more hepatocyte specific and less likely to enter β -cells or adipocytes. While lipophilic statins have negative effects on pancreatic β -cell function, for hydrophilic statins such as pravastatin, neutral or improving effects have been observed and also the lipophilic ones have a strong affinity for the cell membrane, and therefore have easier access to the intracellular space. Atorvastatin (lipophilic) but not pravastatin (hydrophilic) affects insulin release and mitochondrial metabolism due to the suppression of the antioxidant defence system and induction of ROS production in pancreatic β -cell models. Hence,

hydrophilic and lipophilic statins show distinct diabetogenic effects.^[12]

CONCLUSION

Although statin has the benefit for the prevention of CVD events in both primary and secondary, but many studies have shown that statin treatment can cause diabetes in patients. Intensive dose statins are more likely to induce new-onset diabetes as compared to moderate dose statin therapy which is according to the meta analysis done by David priess et al. Another study, published by ko et al, found that diabetes was caused by higher intensity and cumulative dosing of statin. A research study by Jill P Crandall found that the effect of statin to induce diabetes was more common in high-risk diabetes patients. Furthermore, a study by Jinkwon Kim et al in which subgroup analysis of individual statin, use of atorvastatin, rosuvastatin, pitavastatin and simvastatin had significant association with increase in fasting glucose and pravastatin, lovastatin, and fluvastatin had non-significant trend toward an increased fasting glucose. So the recently available evidence supports that statin use induce new onset diabetes in patients. Even so, statins are still recommended to continue for reducing cardiovascular disease event risk in appropriate patients with and without diabetes or risk factors for diabetes.

REFERENCE

1. Olagunju AS et al, Effect of Statins Therapy in Diabetogenesis, Toxicology and Forensic Medicine open journal, 2020; 5(1): 1-4.
2. David Preiss et al, Risk of Incident Diabetes With Intensive-Dose Compared With Moderate-Dose Statin Therapy: A Meta-analysis, JAMA The Journal of the American Medical Association, 2011; 305(24): 2556-2564.
3. Dong-Won Kim et al, Association between statin treatment and new-onset diabetes mellitus: a population based case-control study, Diabetology & Metabolic Syndrome, 2019; 1-8.
4. Kevin C. Maki et al, An assessment by the Statin Diabetes Safety Task Force: 2014 update, Journal of Clinical Lipidology, 2014; 8(3): S17-S29.
5. Min Jung Ko et al, Time-and Dose-Dependent Association of Statin Use With Risk of Clinically Relevant New-Onset Diabetes Mellitus in Primary Prevention: A Nationwide Observational Cohort Study, Journal of the American Heart Association, 2019; 1-11.
6. Dennis T. Ko et al, Diabetes Mellitus and Cardiovascular Events in Older Patients With Myocardial Infarction Prescribed Intensive-Dose and Moderate-Dose Statins, Cardiovascular Quality and Outcomes, 2013; 6: 315-322.
7. Jinkwon Kim et al, Effect of statins on fasting glucose in non-diabetic individuals: nationwide population-based health examination in Korea, Cardiovascular Diabetology, 2018; 1-11.
8. Jill P Crandall et al, Statin use and risk of developing diabetes: results from the Diabetes Prevention Program, BMJ Open Diabetes Research and Care, 2017; 1-8.
9. Naveed Sattar et al, Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials, Lancet, 2010; 375(9716): 735-742.
10. Om P. Ganda et al, Statin-induced diabetes: incidence, mechanisms, and implications, F1000Research, 2016; 1-7.
11. Umme Aiman et al, Statin induced diabetes and its clinical implications, Journal of Pharmacology & Pharmacotherapeutics, 2014; 5(3): 181-185.
12. Unai Galicia-Garcia et al, Statin Treatment-Induced Development of Type 2 Diabetes: From Clinical Evidence to Mechanistic Insights, International Journal of Molecular Sciences, 2020; 21(4725): 1-25.