Abstract: This review paper seeks to identify the possible mechanisms lovastatin either promotes or inhibits new-onset diabetes in patients. Diagnosis for new-onset diabetes in adults includes type 2 diabetes, type 1 diabetes, diseases of the exocrine pancreas, drug-induced diabetes, and much rarer causes, such as maturity-onset diabetes of the young (defined as diabetes diagnosed after hospital discharge for patients with no history of diabetes) in patients. Lovastatin is a lipophilic statin that works with the enzyme HMG-CoA reductase to competitively inhibit HMG-CoA conversion to mevalonate (the rate-limiting step in cholesterol synthesis). Several studies have shown that there might be a high chance of getting new-onset diabetes (NOD) with an increase in dose. The cholesterol derived from plasma is capable of promoting inflammation and induce oxidative stress. This also results in reduced insulin secretion. It had been established that Statins generally lead to cholesterol removal. Although statins have a weak but consistent association with NOD, studies analyzed so far do not give conclusive evidence. Moreover, the benefit of statins in dyslipidemia outweighs the risk of Because not all statins have been proven to have a greater hazard ratio for getting NOD, this is a possibility. Although Lovastatin has a minimal effect on developing NOD, further research and evidence is essential to ascertain a definite conclusion.

Keywords: Lovastatin, statins, diabetes, NOD, diabetes patients
statins class of drug is used commonly for the treatment of patients with hypercholesterolemia by decreasing builds up cholesterol levels (Hababheh & Alkhalaileh, 2020). Effectively, Lovastatin undergoes extensive first-pass metabolism. The medication is transformed into hydroxyl acid forms in the liver through a lactone pro-drug (Hu et al., 2020). According to past clinical studies, statins have shown a significant reduction in primary as well as secondary cardiovascular disease (CVD). Moreover, there have been recent reports of Statin-induced Type II diabetes, and this development is of grave concern. The US FDA in February 2012 cautioned the high used of cholesterol-lowering medications upon noticing elevated risk of new-onset diabetes associated with poor regulation of glucose in diabetic patients. The evidence of Statin-induced NOD was identified in clinical trials (Ahuja et al., 2012). While several meta-analyses have been presented in recent years analysing this adverse event from different viewpoints, the reports ultimately drive contradictory findings. According to (Stuijfzand et al., 2020). Many studies have indicated that statins may act as a barrier to the insulin signalling pathway. (Torlak et al., 2021) This barrier may decrease the sensitivity of insulin secretion and systemic insulin. Importantly, statins also have cholesterol-independent, pleiotropic effects that are blocked by blockage of the mevalonate pathway. (Alam et al., 2021). Statins are generally anti-inflammatory due to [3-hydroxy-3-methylglutaryl-CoA reductase] inhibitors’ inhibition. It also includes targeted reduction in prenylation of proteins (Ashtari et al., 2015). These mechanisms are not directly associated with cholesterol reduction. Understanding the reliance of statins on cholesterol and its pleiotropic effects is quite necessary thus guide therapeutic practises and provide relief to patients suffering from cardiovascular diseases. These interventions can minimise the incidence of diabetes and intend increase the effectiveness of statins (Haxhi & Thompson, 2021). Studies have reported that statins are eight times more likely to avoid coronary problems in patients with cardiovascular risk factors than they are likely to cause diabetes (Lee & Lee, 2020). This article examined the mechanism of action of Lovastatin, proposed theories on the statins induced NOD, and the different studies carried out to determine if statins promote or inhibit the onset of Type II diabetes in patients who are administered this medication.

II. MECHANISM OF ACTION OF LOVASTATIN IN TREATING CARDIOVASCULAR DISEASE

Lovastatin is a lipophilic statin that works with the enzyme HMG-CoA reductase to competitively inhibit the conversion of HMG-CoA to mevalonate (the rate-limiting step in cholesterol synthesis). The possible effect of statins on the mevalonate pathway is given in Fig1. Lovastatin is a well-known cholesterol synthesis inhibitor and is considered the first-line treatment for hypercholesterolemia, along with second-generation statins. (Driggin et al., 2020). The HMG-like portions of statins are similar in structure to HMG-CoA. There is also a consequent decline in cholesterol synthesis alongside the inhibition of the mevalonate pathway. (Jaarsma et al., 2021). The up regulation of low-density lipoprotein (LDL) receptor, low-density lipoprotein receptor (LDLR) (Wamamba et al., 2017) in the peripheral tissues and liver is the outcome of the statin mediated reduction in the intracellular cholesterol (Torlak et al., 2021). This up regulation of LDLR leads to a decrease in LDL Cholesterol (LDL-C) in the serum. The elimination of LDL-C from circulation is the responsibility of low-density lipoprotein receptor (LDLR). Statins decrease the cellular cholesterol concentration and thus stimulates the production of LDLR. This promotes the removal of LDL-C from the bloodstream, which finally reduces cardiovascular disease risk (Timm & Tyler, 2020).

III. HOW STATINS AND NEW-ONSET DIABETES ARE RELATED?

Epidemiological evidence of most statins class of drugs have shown association towards sudden spike or increase in New-Onset Diabetes. (Torlak et al., 2021). There is serious controversy on the significance and validity of statin-induced diabetes. Statins are mainly used for treating dyslipidemia and preventing cardiovascular diseases. The benefits provided by statins are not only due to their lipid-lowering ability but also due to their pleiotropic effects (Wamamba et al., 2017). Statin-mediated pleiotropic effects may be due to the induction of isoprenoid synthesis, which in turn inhibits the Rac, Rho, and Cdc42 intracellular signalling (Lin et al., 2021). It has been pointed out that the group that is at greater risk of developing new-onset diabetes is highlighted. Rho is involved in the development of stress fibers and focal adhesions, whereas Rac and Cdc42 are respectively involved in membrane ruffling and filopodium formation.
a. The population in which the risk factors for diabetes mellitus present in them before the start of statin therapy. The risk factors such as Body Mass Index (BMI) greater than 30, triglycerides concentration greater than 150 mg/dL, and fasting blood glucose more than 100 mg/dL.

b. Women, especially post-menopausal women.

c. Geriatric population (Old People).

d. The population of Asian ethnicity.

e. Population with long term use of Statin

f. Family history of diabetes mellitus

The inhibition of isoprenoid biosynthesis and down regulation in the Statin-induced insulin resistance is thought to be caused by the synthesis of CCAAT/enhancer-binding protein delta (CEBPD), adipocyte cells, decreased isoprenoid synthesis would lead to a decreased regulation of GLUT4 expression. CCAAT/enhancer-binding protein delta (CEBPD) may contribute to reduced insulin-mediated cellular glucose uptake and can manifest as glucose sensitivity or intolerance. (Timm & Tyler, 2020). Statins also inhibit insulin secretion by suppressing the synthesis of ubiquinone because of the reduced production of ATP-Adenosine Triphosphate (Joshi et al., 2021).

Statins decrease insulin secretion via different mechanisms that compromise the function of β-cells of the pancreas (Carcamo-Orive et al., 2020). A number of hypotheses have also been proposed in support of the statin mechanism to inhibit insulin secretion. These includes:

a. Statins inhibit HMG-CoA Reductase and, in return, suppress ubiquinone synthesis. This inhibits ATP and prevents the closure of K⁺ ATP channels. This helps in the prevention of calcium inflow, thus preventing the release of insulin from the pancreatic beta cells.

b. The uptake of glucose gets inhibited through glucose transporter 2 (GLUT2). GLUT2 is responsible for initiating signalling cascades for the secretion of insulin. When glucose uptake is inhibited, this prevents release of insulin.

c. Statins inhibit isoprenoid synthesis that, in return, inhibits glucose uptake. This also stops the release of insulin.

d. Statins increase uptake of LDL that inhibits Glucokinase (the enzyme that converts glucose to pyruvate). This also stops the release of insulin from the beta cell of pancreas.

e. The adaptive NO synthase leads to overproduction of nitric oxide persuaded by cytokines. This leads to the induction of Beta cell apoptosis (Nashawi et al., 2020).

![Fig 1. The possible effect of statins on mevalonate pathway (Source: Mukesh Mehra, IJCP January, 2019)](image-url)
Statin’s ability to impair the intracellular signal transduction pathways of insulin and the ability to suppress phosphorylation is also the hypothesized mechanisms for their association with new-onset diabetes. This reduces the action of the small GTPase as they inhibit adipocyte differentiation. This also decreases the activated gamma receptor peroxisome proliferator. They also suppress β-cell proliferation and insulin secretion via the inhibition of leptins (Bhuvana & Ashraf, 2020).

Rashid & Hersi, (2021) reported that by reducing exocytosis, Lovastatin reduces insulin secretion depending on the dose. Statins have been shown to indirectly decrease or actively limit the absorption of glucose and inhibit the maturation and expression of adipocyte. This reduces expression of the protein-beta (C/EBP-beta) binding major transcription factor called CCAAT/enhancer. After stimulation of insulin, it has been found that adipocyte maturation with lovastatin decreases the activation of phosphatidylinositol triphospho-kinase (PI-3K). This interferes with the PI-3K regulatory subunit p85's interaction with IRSs and undermines IRS/IR intracellular signalling. Lovastatin, thus prevents the insulin pathway or compromises glucose metabolism by

a. Autophosphorylation of tyrosine residues in the IR β-subunits
b. Upregulation of GLUT-1 and Downregulation of GLUT-4 in 3T3-L1 adipocytes. (Dong et al., 2020)

Statins should be used carefully in people having cardiovascular diseases and therefore patients who receive statins should have their fasting blood sugar tracked regularly. In adults with a high risk of cardiovascular disease and reduced glucose tolerance, statins and diuretics raise the risk of NOD. (Dong et al., 2020). Factors such as elevated blood sugar levels, weight and age of the subject have a high stake in predicting whether the subject will develop diabetes mellitus with statin therapy. Some investigators also suggest that the genetic tendency (family history) to Type II Diabetes Mellitus may also play a significant role in statin induced New Onset Diabetes. (Veluthakal & Thurmond, 2021). A meta-analysis by (Semb et al., 2020) showed that in subjects who were non-diabetic, statins have a different relation with insulin sensitivity. The analysis showed that insulin sensitivity was Simvastatin decreased it, Pravastatin raised it, while atorvastatin and rosuvastatin both increased it. had little to no effect (Semb et al., 2020).

IV. EXPERIMENTAL STUDIES ON THE RELATION OF STATINS WITH NEW ONSET DIABETES MELLITUS

Despite extensive clinical trials performed on both humans and animals, no substantial conclusion has been arrived on the association of statins with diabetes mellitus. However, the data derived from these studies point out a direct proportionate relation between statins and chance of new onset diabetes mellitus. Below are certain scientific studies carried out with statins considering a group of healthy subjects in the USA. (Veluthakal & Thurmond, 2021). With subjects being majorly categorized into two streams, statin and non-statin users, simvastatin, atorvastatin and pravastatin, were the major statins which were followed up for analysis. The study was further divided into two periodic timelines: the 1st periodic timeline (October 1, 2003 to September 30, 2005) and the 2nd periodic timeline (October 1, 2005 to March 1, 2012). Chi-square test and student’s T-Test were the two major visualizing principle used to describe the baseline characteristics of the data regulated under 1st periodic timeline, while the follow-up periodic timeline was considered to capture the outcome of the events. The exclusion criteria for the study were 1) Patients suffering from trauma and burn. 2) Patients who were prescribed statins after September 30, 2005. 3) Patients with less than 90 days exposure to statins. An extensive approach covering a total of 25,970 patients were included in the study, thereby increasing the likelihood of a more precise and definite conclusion. Out of 3982 statin users, the study was further diversified into high-intensity statin users (1155) and moderate/low-intensity statin users (2827). The study postulated that high exposure to statin directly impacted the chance of new-onset diabetes mellitus. (Veluthakal & Thurmond, 2021). In addition to this, it was also observed that about 14% of the patient’s acquired diabetes during the follow-up phase. Analogous findings were also observed on conducting the secondary and sensitivity analysis (Veluthakal & Thurmond, 2021).

The first report to prove an association between the use of statins and incident diabetes was the study of West of Scotland Coronary Prevention Study (WOSCOPS). The report was mainly a postdoc errors analysis report which meant that the statistical analysis and the inference were drawn after getting the data. The
WOSCOPS was a randomized placebo-controlled trial carried out with 5974 patients. The drug of choice for this study was a second-generation statin called Atorvastatin. In the study, the investigators had two more parameters to confirm a patient to be New-Onset Diabetic. The first parameter was to get two fasting blood sugar levels measuring ≥126 mg/dl. Secondly, patients with new-onset diabetes had to show an increase in fasting blood sugar from the reference or baseline measurement of around 36 mg/dl. The first parameter was done to monitor patients who may have eaten food and had not fasted before lab testing. The second parameter was done to identify those subjects who showed a decrease in glucose concentration. The risk ratio showed 0.7%, indirectly reflecting the small number of incident events and the low accuracy of the risk estimate. The study reported a 30% decline in the probability of contracting diabetes (Yelemkoure et al., 2018).

A retrospective study was carried out to investigate whether statin use is related to risk for New-Onset Diabetes Mellitus in Koreans. The database for this study was collected from electronic health records. The study design included 8,265 patients who used statins and 33,060 patients who did not use statins between January 1996 and August 2013. Based on gender, baseline glucose (mg/dL), age, and high blood pressure, the susceptibility score was 1:4. The comparative risks associated with the use of different statins for New-onset Diabetes Mellitus were estimated by comparing statin exposed versus non-statin exposed patients. The study result showed that the incidence of the endpoint, i.e., New-onset Diabetes (NOD) Mellitus in the statin-exposed population, was greater than that of the non-exposed population. The hazard ratio (HR) of New-onset Diabetes Mellitus after statin exposure was 1.872. The study results conveyed that for patients who suffer from any of these three complications 1) simple dyslipidemia (unhealthy levels of one or more kinds of lipids), 2) subclinical atherosclerosis 3) patients with high-risk factors for diabetes mellitus, then it is always better to analyze the risk and benefits of the statin including the type and dose of the statin before proceeding for treatment. In conclusion, based on evidence from real-world clinical experience, the study confirmed an elevated risk for new-onset diabetes following statin therapy. torvastatin was found to be more likely to increase the likelihood of developing NODM (Cruanes, 2021).

Cruanes, (2021) used the results of a study on Diabetes Prevention Program as evidence to draw the statin-diabetes relationship. The DPP analyzed a cohort of obese people who were at high risk for diabetes. The endpoint of the study was to know if the obese people who were high-risk individuals develop incident diabetes. The study design was a randomized clinical trial that was undertaken in the USA in 27 health centres, where 3,234 subjects were drawn from both sexes. About 20% of the participants were over 60 years of age. Excluded from the study were participants who did not have fasting blood sugar levels (ranging between 95 mg/dL & 125 mg/dL) and decreased tolerance for glucose. Also, subjects who had

- Recent history of heart attack
- Active symptoms of coronary heart/artery disease
- Any serious health conditions/illness
- Been diagnosed with diabetes mellitus and were taking glucose-lowering medication before participating in the study
- Been using medications that disrupts glucose tolerance
- Increased Triglyceride level of more than or equal to 600 mg/dL was excluded from the study.

The qualified patients received standard instructions on a healthy diet and physical fitness. They were assigned into three treatment groups 1) one group followed intensive lifestyle intervention 2) one was given metformin 3) one was given placebo. A group-administered variant of the lifestyle experiment (mean follow-up 3.2 years) was given to all participants at the end of the main trial. They were asked to participate in the DPP Outcomes Review. To assess the long-term follow-up to a randomized clinical trial with therapies to reduce T2DM and incidence diabetes, an annual 75 g oral glucose tolerance and semi-annual fasting glucose tests were used. Diagnosis of diabetes was the principal endpoint for DPP/DPPOS. Statin use and other concomitant drugs dependent on self-report was reported in the DPP and DPPOS. Along with the semi-annual visit and baseline characteristics, the data were collected. At each semi-annual follow-up visit, the volunteers were asked the question if they did take any prescribed drugs during the past 2 weeks.
Participants were asked to carry each visit with all prescription pill bottles and the name of the medication was registered. The study result showed that statins were associated with a higher risk of diabetes regardless of the type of care. The correction for baseline diabetes risk factors and possible confounders linked to statin therapy indications did not significantly alter this risk. The researchers observed higher incidence of diabetes with statin therapy in all three treatment groups (El Hadidi et al., 2020).

El Hadidi et al., (2020) carried out a meta-analysis from 13 major statin studies to assess the relation of statins and New-Onset Diabetes. The studies were:

a. Anglo Scandinavian Cardiac Outcomes Trial abbreviated as ASCOT
b. Air Force/Texas Coronary Atherosclerosis Prevention Study abbreviated as AFCAPS/TexCAPS
c. Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial-Lipid Lowering Trial abbreviated as ALLHATLLT
d. Controlled Rosuvastatin Multinational Trial in Heart Failure abbreviated as CORONA
e. Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza cardiaca-Heart Failure abbreviated as GISSI-HF
f. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico-Prevenzione abbreviated as GISSI-Prevenzione
g. Heart Protection Study abbreviated as HPS
h. Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin trial abbreviated as JUPITER
i. LIPID
j. Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese abbreviated as MEGA
k. Prospective Study of Pravastatin in the Elderly at Risk abbreviated as PROSPER
l. Scandinavian Simvastatin Survival Study abbreviated as 4S
m. The West of Scotland Coronary Prevention Study abbreviated as WOSCOPS

In statin therapy patients, they found a relative risk of 1.09 for the development of diabetes. This turned into one new case of diabetes as 255 statin therapy patients were treated for four years (El Hadidi et al., 2020). A team of Canadian scientists examined the risk of new-onset diabetes among patients treated with different statins. It was a population-based cohort study and involved the calculation of hazard ratios in determining the effect of dose and type of Statin on the risk of incident diabetes. The subjects included in the study were aged 66 or older, without diabetes and went under statin treatment from August 1, 1997, to March 31, 2010. The patients who had diabetes before statin treatment were excluded from the study. The drugs used in the research were Pravastatin, Atorvastatin, Rosuvastatin, Simvastatin, Fluvastatin, and Lovastatin, with Pravastatin being the guide agent in all studies. The results of the study found that Atorvastatin, Rosuvastatin, and Simvastatin raised the probability of developing diabetes. No major risk was, however, observed among subjects receiving Lovastatin or Fluvastatin. Atorvastatin showed the highest hazard ratio of 1.22, whereas Lovastatin showed a hazard ratio of 0.99 (Lee & Lee, 2020).

V. CONCLUSION
The experimental studies mentioned above show that the incidence of NOD (new-onset diabetes) is not similar in all randomized trials. Long term treatment with statins definitely shows the rise in new-onset diabetes. Also, the studies showed that there might be a high chance of getting NOD with an increase in dose. Since most of the studies did not target any one specific statin and involved all statins, it can be observed that lovastatin is associated with fewer chances of creating NOD with respect to other statins (Abou Assi et al., 2021). Suggested several approaches to prevent new development of Statin-induced diabetes: Starting statins with a lower dose and, most importantly, avoiding higher doses in women and geriatric patients. Screening for Type II Diabetes mellitus should be done before carrying out treatment with statins. Proper intake of food rich in Vitamin D, a healthy diet, and regular exercise should be done. Patients who are starting with statins should be educated about the risk of getting new-onset diabetes.
VI. ACKNOWLEDGMENT

We thank Sunday Victoria and the external reviewers for proofreading and editing the manuscript and making useful suggestions to improve its quality.

REFERENCES


Nashawi, M., Sheikh, O., Mir, M., Te, T., & Chilton, R. (2020). The systemic implication of novel non-statin therapies pg. 783
in cardiovascular diabetology: PCSK9 as a case model. Cardiovascular Endocrinology & Metabolism, 9 (4), 143.


