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A Systematic Review of Existing Data on Statin Use and New-Onset Type 2 Diabetes: The Need for Clear Answers

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Abstract

Background: *The relationship between statins use and the development of new-onset type 2 diabetes mellitus (NOT2DM) has been a subject of ongoing debate and investigation. In February 2012, the Food and Drug Administration (FDA) disclosed that statin use could lead to a modest rise in glycosylated hemoglobin (HbA1c) and fasting blood glucose (FBG), potentially contributing to the development of diabetes. We systematically reviewed the available evidence and summarized the impact of statin use on NOT2DM.*

Aim: *This systematic review aims to examine and provide a comprehensive overview of existing data relating to statin use and their association with the development of new-onset type 2 diabetes (NOT2DM). The primary objectives were to assess and explore: (1) the potential association between statin use and the development of new-onset diabetes; (2) the magnitude, extent, and incidence of new-onset diabetes due to statin use. The secondary objective was to explore the underlying mechanisms.*

Data Sources: *PubMed, Scopus, Science Direct, Wiley, and Google Scholar and databases between January 2012 and February 2021.*

Data Extraction: *The 2 reviewers Musa Basheer Mansour and Sara Elsheikh Ahmedana [MBM and SEA] independently assessed the qualities of the extracted studies and summarized data of the selected studies in tabulated forms for outcomes of interest and performed methodological and quality assessments based on review questions, citations, country of the study, aim, population characteristics, design, setting, sample size, sample technique, data source, measures, analysis, confounder variable and key observations for systematic review. We applied search keywords such as Statins, New-onset diabetes, Diabetes mellitus, Underlying mechanism, and incidents of diabetes.*

Results: *A total of 66 studies were identified through database searches in the initial search, and 7 studies were included in this review. Of the 2,567,888 adult patients, 861,925 were nondiabetic patients on statin use, and 1,705,963 were diabetic on statin or non-statin users. We considered Hazard Ratios (HR), Odds Ratios (OR), and Confidence Intervals (CI) of each study for further analysis. The mean OR for three studies showed that each statin therapy resulted in a 68% increased risk of NOT2DM (OR, 1.683; 95% CI: 1.273-2.237). The significant relationship between statin use and the rising risk of NOT2DM was also confirmed by an average HR of 1.53 (95% CI: 1.2-1.7) for the remaining four studies. Recent and short-term use of statins, as well as time- and dose-dependent connections, were linked to an increased risk of NOT2DM in statin users compared to non-users. These risks were more prominent among older adults, normotensive males, hypertensive females, and individuals with low physical activity. Although no proven mechanisms were found, the possible processes are discussed.*

Conclusion: *The systematic review found a significant level of risk of NOT2DM associated with statin use. The authors argued that the short-term diabetes risk caused by statin treatment was more prevalent among patients exposed to risk factors for diabetes. Although the precise mechanisms behind this association remain unclear, this research provides clinical practice with evidence-based guidelines. Additionally, conducting future research may be appropriate based on the gaps in knowledge identified from the results of this review.*

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Introduction

The relationship between statin use and the development of new-onset type 2 diabetes mellitus (NOT2DM) has been a subject of ongoing debate and investigation. Type 2 diabetes mellitus (T2DM) is a chronic metabolic disease with a rapidly growing incidence. The International Diabetes Federation Diabetes Atlas reported that in 2021, 537 million adults between 20 and 79 years had diabetes worldwide, with the number estimated to rise to 783 million by 2045 (International Diabetes Federation, 2021). The etiological factors include obesity, overweight, lack of physical activity, unhealthy diets, and genetic and epigenetic predispositions (Zheng, Ley, & Hu, 2018).

Statins, starting with Lovastatin, were first approved in the United States in 1987. Subsequent approvals included simvastatin and pravastatin in 1991, fluvastatin in 1994, atorvastatin in 1997, rosuvastatin in 2003, and pitavastatin in 2009. Many randomized clinical trials (RCTs) have reported the effectiveness of statins in lowering low-density lipoprotein cholesterol (LDL-C) levels (Kearney et al., 2008; Fulcher et al., 2015; Sattar et al., 2014). The American College of Cardiology / American Heart Association (ACC/AHA) classified statins into low, moderate, and high intensity (Stone et al., 2014). The adverse effects of statins may include myopathy, rhabdomyolysis, hepatotoxicity, nephrotoxicity (Horodinschi et al., 2014), and hyperglycemia (Chogtu et al., 2015).

Statin use has increased substantially over the last decade, particularly among adults aged 40 years and older (Salami et al., 2018), making them one of the most widely prescribed drugs for both primary and secondary prevention of cardiovascular disease (CVD), including Atherosclerotic CVD (ASCVD) (Hadjiphilippou & Ray, 2019; Collins et al., 2016; Jung, 2021). According to the 2019 American Heart Association (AHA)/American College of Cardiology (ACC) guidelines, statins are recommended for (1) Clinical ASCVD; (2) LDL-C $\geq$190 mg/dL, $\geq$21 years of age; (3) primary prevention—DM: 40–75 years of age, LDL-C 70–189 mg/dL; and (4) primary prevention—no DM (7.5% 10-year ASCVD risk, 40–75 years of age, LDL-C 70–189 mg/dL).

Despite numerous studies investigating this topic, the issue remains complex and unresolved. While some evidence suggests a potential association between statin use and an increased risk of T2DM, other studies have reported conflicting results or found no significant association. For instance, the JUPITER trial, Justification for the Use of Statins in Prevention: Intervention Trial Evaluating Rosuvastati, included 17,802 men and women, who were randomly assigned to rosuvastatin 20 mg daily (Ridker et al., 2008). Rosuvastatin lowered CVD events significantly by 44% and increased incident physician-reported T2DM by 26% compared to the placebo group. Specifically, the trial reported a 27% increase in physician-reported diabetes among participants receiving rosuvastatin compared to placebo (p=0.01). The absolute risk of developing diabetes was relatively low, with approximately 3% of participants in the rosuvastatin group and 2.4% in the placebo group (Ridker et al., 2012; Carter et al. 2013).

Sattar et al. (2010) published the first large meta-analysis of statin-induced incident T2DM, reporting a 9% increase from 13 trials involving 91,140 participants. The first study showing that statins were associated with the risk of T2DM was the WOSCOPS trial (West of Scotland Coronary Prevention Study), where Freeman et al. (2001) reported that among 5,974 participants without diabetes, 139 developed T2DM during the study. Pravastatin therapy led to a 30% reduction in the cases of T2DM in a post hoc analysis. Shepherd et al. (2002) found in the PROSPER trial (Pravastatin in elderly individuals at risk of vascular disease) that, among 5,804 participants, there was a 19% decrease in the risk of coronary artery disease (CAD), but no significant increases or decreases in incident T2DM. Sabatine et al. (2004) reported increases in glucose and HbA1c and incident T2DM for atorvastatin and simvastatin (de Lemos et al., 2004).

Wallemacq (2019) suggested that information might be deficient in changing the current practice worldview and that clinicians should screen for incident diabetes in patients on statins. Rajpathak et al. (2018) conducted a meta-analysis comparing statins with placebo, including 57,593 patients from 6 trials, and found an increased risk for incident T2DM (relative risk (RR) of 1.13). Carmena and Betteridge (2019) found in non-diabetic men a 46% higher risk of NOT2DM due to statin use, associated with a significant reduction in insulin secretion by 12% and increased insulin resistance by 24.3%.

In 2012, the FDA disclosed that statin use could lead to a modest increase in FBG and HbA1c, potentially contributing to the development of diabetes (Sampson et al., 2011). Studies demonstrated that atorvastatin did not worsen insulin sensitivity in patients with diabetes. Additionally, one study indicated that patients on atorvastatin could have a reduced risk of developing NOT2DM. (Angelidi et al., 2018). Research indicates that statin use in patients with concomitant risk factors for diabetes is associated with NOT2DM, although the precise mechanisms behind this association remain unclear (Had-

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jiphilippou & Ray, 2019). However, research on statin therapy has yielded conflicting findings regarding the association between statin use and the risk for incident NOT2DM. Questions regarding their adverse effects and benefits remain controversial and unresolved. Therefore, extensive studies are needed to elucidate both the association between NOT2DM, statin use, and the underlying mechanisms (Park et al., 2014).

These observations prompted this systematic review, which aims to examine and provide a comprehensive overview of existing data relating to statin use and its association with the development of NOT2DM. The primary objectives were to assess and explore: (1) the potential association between statin use and the development of new-onset diabetes; (2) the magnitude, extent, and incidence of new-onset diabetes due to statin use. The secondary objective was to explore the underlying mechanisms.

Materials and Methods

Study Design

This review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA) guidelines (Page et al., 2021). It was registered with the International Prospective Registry of Systematic Reviews (PROSPERO) under registration number CRD42021232559, dated 22/02/2021. This study did not require patient consent or Research Ethics Committee Approval.

Search Strategy

Two authors, Musa Basheer Mansour and Sara Elsheikh Ahmedana (MBM and SEA), independently conducted a comprehensive literature search for relevant studies on statin use and the incidence of NOT2DM, as well as the possible underlying mechanisms. The search employed Boolean operators "AND" and "OR," combined with various descriptors, across databases including PubMed, Science Direct, Wiley, Google Scholar, and Scopus, covering publications from January 28, 2012, to February 28, 2021. The search was limited to studies published in English and used a combination of Medical Subject Headings (MeSH) and free-text words in titles, abstracts, and index terms.

Inclusion and Exclusion Criteria (Eligibility Criteria)

The same two reviewers (MBM and SEA) independently assessed the titles, abstracts, keywords, and full texts of articles published after 2012, using inclusion and exclusion criteria derived from the research questions of this review. Included studies had to meet the following criteria: (1) nondiabetic adults (aged $\geq$18 years) using statins; (2) assessing and measuring the risk and/or incidence of NOT2DM; and (3) observational studies only. Excluded were studies involving pregnant populations, diabetic participants, nondiabetic participants (aged <18 years) using statins, as well as abstracts, conference proceedings, posters, presentations, commentaries, or editorials. Following the research questions, keywords, and literature search, we used the PICO/PECO frameworks (P: patient or problem; I: intervention or E: exposure being considered; C: comparator; O: outcome measurements). The PRISMA flow chart for the selection of studies is shown in Figure 1.

Data Extraction (Charting)

The two reviewers (MBM and SEA) independently assessed the quality of the extracted studies and summarized the data in tabulated forms for outcomes of interest. They performed methodological and quality assessments based on review questions, citations, country of the study, population characteristics, study aims and design, setting, sample size, sampling technique, data source, measures, analysis, confounder variables, and key observations. The reviewers compared their results, discussed, and resolved disagreements and discrepancies in data extraction. Relevant authors were contacted as needed for additional data, clarifications, or missing information.

Critical Appraisal (Quality Assessment and Risk of Bias)

Two researchers independently assessed the risk of bias for the observational studies using the Risk Of Bias In Non-randomized Studies - of Exposure (ROBINS-E) assessment tool (for follow-up studies) (Higgins et al., 2024). This tool shares many characteristics with the RoB 2 tool for RCTs and the ROBINS-I tool for non-randomized studies of interventions. The quality appraisal findings are presented in Figure 2.

Data Synthesis and Analysis (Summarizing and Presenting Findings)

The two reviewers (MBM and SEA) independently synthesized, summarized, compared, and presented the findings in Tables 1, 2, and 3, based on review questions, citations, country of the study, population characteristics, study aims and design, setting,

sample size, sampling technique, data source, measures, analysis, confounder variables, and key observations. The seven studies were grouped, and the extracted results compared the odds ratios, confidence intervals, and relative risk.

Results

Study Selection (Flow of the Studies)

As demonstrated in Figure 1, a total of 66 studies were identified in the initial search. We collected 53 studies from PubMed, Wiley, Google Scholar, and Science Direct, and generated 13 additional studies from other sources such as university sites, Academia, and ResearchGate. After removing duplicates, 61 studies remained. These were then screened, and 40 studies that only provided abstracts or were RCTs and non-RCTs were excluded. Twenty-one full texts remained, and 14 were excluded for including participants aged <18 years. Finally, 7 studies were included in the synthesis.

Characteristics of Included Studies

Seven studies met all the inclusion criteria and are summarized in the tables. Table 1 presents the citations and country of the study, study population characteristics, study design and aim, and outcomes. Table 2 identifies the research setting, the selected sample size, techniques applied during sampling, and the sources from which the researchers collected the data. Table 3 indicates the measures, methods of analysis, confounder variables, and key observations.

Further Results

After determining the effect of statins on NOT2DM, as indicated in the key observations of every study, this systematic review took further steps to determine the extent of the effect statins have on NOT2DM for this objective, confidence intervals and comparison percentages (for statins users and non-users) were collected. The intervals are presented in the table 4.

From Table 4, each statin therapy is associated with 68% increase in risk of T2DM incident (OR average 1.683; 95% CI average: 1.27-2.236). Data on confidence intervals collected and presented above were used to construct the histogram in Figure 3. The risk of NOT2DM with statin use ranges between 1.21 and 2.45. Median value was 1.21-2.44. The remaining 4 studies had Hazard ratios and confidence intervals presented in table 5 and figure 4. The findings above show that statins use increases chances of NOT2DM incident by 49% (HR average 1.5275; 95% CI average: 1.20-1.686).

Risk of Bias in The Studies

The assessed articles were rated to have either low, some concerns, high, or very high bias risk. According to the ROBINS-E, four observational studies [Lee et al. (2018), Ko et al. (2019), Corrao et al. (2017), and Ahmadizar et al. (2019)] were found to have a low risk of bias. Two studies [Kim et al. (2018) and Yoon et al. (2016)] were identified to have a high risk of bias, while one study by Li et al. (2018) was identified to have a very high risk of bias. In the first domain, four studies [Li et al. (2018), Ko et al. (2019), Corrao et al. (2017), and Yoon et al. (2016)] were found to have a high risk of bias, two studies [Lee et al. (2018) and Ahmadizar et al. (2019)] had a low risk of bias, and one study by Kim et al. (2018) had a very high risk of bias due to confounding.

Regarding the second domain, all studies had a low risk of bias arising from the measurement of exposure. In the third domain, all studies had a low risk of bias in the selection of participants into the study (or into the analysis) except one, conducted by Kim et al. (2018), which demonstrated a high risk of bias. Additionally, one study by Li et al. (2018) exhibited a very high risk of bias in this aspect. In the fourth domain, all studies had some concerns about bias due to post-exposure interventions. Regarding the fifth domain, all studies had a low risk of bias due to missing data except one, conducted by Lee et al. (2018), which demonstrated a high risk of bias. In addition, one study by Li et al. (2018) exhibited a very high risk of bias in this regard. In the sixth domain, all studies had a low risk of bias due to the measurement of the outcome. In the seventh domain, all studies had a low risk of bias in the selection of the reported result. Figure 2 summarizes the risk of bias assessment for observational studies in each domain based on the evaluation using the ROBINS-E tool.

The reviewed studies may interfere with the clarity and reliability of the conclusions derived in this systematic review. For instance, Lee et al. (2018) relied on observational data based on the South Korean population. Given that the study subjects came from East Asia, the recommended clinical practices require caution as the outcome may not be consistent in patients belonging to different ethnicities. The use of observational data also lacks control over confounder variables, increasing the chances of finding false links between the drug and results. Li et al. (2018) also employed observational data and argued that their definition of bias could promote further bias. Additionally, they utilized inpatient and outpatient

Citation and **Country of Study**	**Study Population Characteristics**	**Study Design and Aim**	**Outcomes**
1, Lee et al. (2018) South Korea	Study concentrated on the health-screening cohort all over the nation. Selected individuals had a minimum cholesterol level. Also, they had to be free from DM, cancer, and CVD. They must have undergone multiple health checkups and screenings as part of routine medical care or as participants in a health surveillance program.	Observational Cohort Study aims to investigate the relationship between statin use and NOT2DM risk, taking into account hypertension status and gender differences within a large, population-based health-screening cohort.	Incidence of NOT2DM among patients treated with statins. whether the association between statins and diabetes risk differs among hypertensive and non-hypertensive individuals. Comparison of diabetic risk. Identify any disparities in diabetes risk associated with statin use between male and female patients.
2, Li et al. (2018) China	Patients with or without T2DM. The selected age range was 30 to 90 years. Study population consists of hypertensive patients residing in the Yinzhou district of Ningbo city, China. These patients are identified through health records and databases available in the district.	Retrospective cohort study design aims to investigate the potential association between statin use and the risk of new-onset diabetes among hypertensive patients in the Yinzhou district of Ningbo city, China, using retrospective cohort data	The primary outcome is the incidence rate of new cases of DM among hypertensive patients who are prescribed statins compared to those who are not. RR or OR. Secondary outcomes may include assessing the impact of statin use on glycemic control among hypertensive patients with existing diabetes, evaluating changes in cardiovascular risk factors (e.g., lipid levels, blood pressure) associated with statin therapy, and examining the incidence of cardiovascular events (e.g., heart attack, stroke) among hypertensive patients with and without DM.
3.Kim et al. (2019) South Korea	Participants were among the 1 million individuals that subscribed to medical insurance in the country of study. Individuals without a diagnosis of DM, matched to cases based on relevant characteristics such as age, gender, and other potential confounders. Demographic characteristics, medical history, medication use, lifestyle factors, and other potential confounders would be collected from electronic health records, administrative DM, or patient interviews.	A population-based case–control aims to evaluate the association between statin treatment and NOT2DM in a population-based case–control framework, providing insights into the potential risk factors for diabetes associated with statin therapy.	The primary outcome would involve determining whether there is a statistically significant association between statin treatment and the risk of developing NOT2DM. This would be assessed by comparing the prevalence of statin treatment among individuals with NOT2DM (cases) to individuals without DM (controls). Secondary outcomes include investigating the association between specific statin types or doses and the risk NOT2DM. The duration of statin treatment influences the risk of developing DM.
4.Ko et al. (2019) Korea	Included adults with reported hypercholesterolemia in the period Jan 2005 to December 2012. Also included were adults in their 40s and older without atherosclerotic CVD, and overall cholesterol level exceeding 240mg/dL. Iindividuals from across the entire nation, representing a diverse range of demographics, geographic regions, and healthcare settings.	Observational Cohort study design aims to examine the time- and dose-dependent association of statin use with the risk of clinically relevant new-onset diabetes mellitus in individuals undergoing primary prevention, utilizing data from a nationwide observational cohort.	The incidence rate of clinically relevant new cases of DM among individuals exposed to statins. The clinical relevance. Dose-response relationship. The time- and dose-dependent.
5.Carrao et al. (2017) Italy	All the selected beneficiaries of National Health Service (NHS) belonged to Lombardy. The preferred age range was 40 to 80 years. To be included, an individual had to have a minimum of statins prescription in 2003 to 2005. A large cohort of individuals drawn from a population, such as patients enrolled in a national health insurance program or a healthcare database. Individuals with varying demographics, health conditions, and medication histories.	large cohort of individuals study design aims to assess the clinical significance of DM likely induced by statins in a real-world population setting, providing evidence on the relationship between statin use and DM risk in a large cohort of individuals.	The incidence rate or risk of developing DM among individuals exposed to statins compared to those not exposed. Implications for clinical practice.
6.Yoon et al. (2016) Korea	Study population comprised both statin and non-statin users aged 18 years and above. Iindividuals of varying demographics, health statuses, and medication use.	Population based cohort study design aims to investigate the relationship between statin use and the risk of new-onset DM in a real-world population setting using longitudinal data from a national health insurance claims database.	Primary outcome of interest is the incidence of NOT2DM among the study participants. Secondary outcomes may include assessing the impact of statin use on glycaemic control among individuals with existing DM, as well as exploring the association between statin use and cardiovascular outcomes in individuals with or without DM.
7.Ahmadizar et al. (2019) Netherlands	Were residents of Ommoord aged 45 years or older, Iindividuals are typically free of T2DM at the beginning of the study.	Study population involves a cohort of individuals drawn from a population, which may be a community, or a specific healthcare setting aims to investigate the relationship between statin use, glycemic traits, and the risk of incident T2DM in a longitudinal cohort setting, providing insights into the potential effects of statins on glucose metabolism and DM risk.	Glycaemic traits: This could involve various measures related to glucose metabolism, such as FBG, HbA1c), insulin sensitivity, and insulin resistance.

Table 1: *Location, population features, study design and aim, and outcomes.*

Citation	Study Setting	Sample Size	Sample Technique	Data Source
1, Lee et al. (2018) [South Korea]	A significant rise in prevalence of T2DM was noted in South Korea between 1970 and 2000. Also, the country was ranked among the countries with enormous numbers of adult diabetes (for persons aged 20 to 79 years). This made the South Korea one of the 30 members of Organization for Economic Cooperation and Development. The country is among those with highest population growth rates and is, thus, projected to record the largest numbers of T2DM come 2030. It was also noted that cardiovascular disease prevalence had more than doubled that of diabetes. The revelations indicate a need to plan national health interventions and identify the potential factors for T2DM incidence.	*n*= 40,164 patients (17,798 used statin and 22,366 did not use statin.)	Random sampling of people that began biennial NHIS health checkups around 2002 to 2003.	The National Health Insurance System (NHIS) database. Data reported in 2016 was used. It represented 10% of the overall target population.
2. Li et al. (2018) China	Yinzhou district in Ningbo city, China. The Health and Family Planning Commission of Yinzhou declared its intention to adopt primary care framework used in the United Kingdom, in 2005. Therefore, apart from being the largest district, Yinzhou has extensive data on diabetes, cancers, and hypertension follow-ups.	n= 67,993 (21,551 were nondiabetic on statin while 46,442 were non-users)	Random sampling of hospital, public health and community health data contained in the Health Information System within Yinzhou.	Yinzhou regional healthcare database. Data recorded between Jan 2010 and August 2016.
3. Kim et al. (2019) South Korea	The nationwide case control study conducted with approval of Korea University's review board.	6417 NOT2DM 32,085 Nondiabetic [29932 non statin users, 2153 statin users]	Stratified random sampling of data from the database.	South Korean National Health Insurance National Sample Cohort database. The database includes a randomized sample consisting of 2% of the overall country population.
4. Ko et al. (2019) Korea	Examined combined data from the national health insurance and datasets based on statements of the administration. The study targeted the Korean National Insurance Services because the organization had the obligation to collect and manage all the relevant information. As such, the possibility of data loss would be minimal. Researchers were, thus, certain that their study objectives would be obtained through the systematic linkage codes used in in- and out-patient points along with the records showing the dispensed drug prescriptions.	*n* = 2,162,119 (638,625 eligible for statin therapy and 1,523,494 never tried statin)	Purposive sampling of adults with hypercholesterolemia, and random sampling of participants that fit this group.	National Health Insurance Services for Korean population
5. Carrao et al. (2017) Italy	The study targeted Lombardy region, Italy. The region consists of 16% of Italy's population covered by NHS.	4,391 eligible diabetic division and 77,893 other group members on statin	Random selection of diabetics and others without diabetes symptoms.	NHS healthcare databases of Lombardy
6. Yoon et al. (2016) Korea	Ajou University Hospital, a tertiary teaching institution found in Korea.	156,360 patients (94,370 statin users and 61,990 non statin users)	Random sampling of patients whose demographic, diagnosis, drug subscription and laboratory test outcomes were recorded in the database.	Clinical research database belonging to Ajou University Hospital
7. Ahmadizar et al. (2019) Netherlands	Study targeted Ommoord district in the Netherlands.	9535 participants for analysis of statins and glycemic factors, and 8567 patients for statin and T2DM development	Random selection of samples from the dispensed data.	Rotterdam study reports on visits of 1997 to 1999, 2000-2001 and 2006 to 2008.

Table 2: *Setting, size of sample, sampling approaches, and sources of data.*

Citation	Measures	Analysis	Confounder Variables	Key Observation
1. Lee et al. (2018) South Korea	Fasting glucose, total cholesterol, systolic and diastolic blood pressure, BMI, height, body weight, and waist circumference.	Percentages, means, Chi-square tests, and standard deviations applied on normally distributed variables. Median for non-normally distributed. Cox regression for rate of NOT2DM development and Hazard raters to calculate influence of statin on DM development.	Female gender, hypertensive women, and normotensive men.	Statin use was a risk factor for normotensive patients as well as hypertensive women.
2. Li et al. (2018) China	Age, sex, BMI, comorbidities, features of lifestyles and baseline antihypertensive drugs in use.	Employed multivariate Cox model alongside propensity approaches to identify potential confounders. Cox proportional hazard framework to relate statin initiators with non-users. Propensity scoring of statin use were determined through logistic regression. The analysis also applied Cox regression. Mean, standard deviation and median for BMI and age. Also, student's t test for variations in BMI and age.	Use of antihypertensive drugs, older adults, overweight, and having dyslipidemia.	Found a significant relationship between use of statin and rising risk of NOT2DM.
3. Kim et al. (2019) South Korea	The inspection utilized self-questionnaire to measure drinking, smoking, and exercise status of participants.	*t* tests for continuous variables and Chi-square for categorical data. Also, conditional logistics model for regression aided the estimation of relative usefulness of statin therapy.	Gender, smoking, alcohol consumption, high total cholesterol, poor exercising routine, the first six months of statin therapy and hypertension.	Recent and short-term use of statin was linked to a rise in risk of NOT2DM. Cumulative duration in use of statin and non-recent application of statin therapy had no significant association with NOT2DM.
4. Ko et al. (2019) Korea	Impaired fasting glucose, BMI of 25kg/m^2 and above, effect of different types of statins (atorvastatin, rosuvastatin, simvastatin, pravastatin, etc.), clinical risk of DM development.	Propensity score applied to measure differences in baseline features of statins users and non-user groups. Student t test was applied on continuous variables. Study also employed Cox regression framework to compare outcomes of risks. For estimation and comparison of proper approaches, Kaplan-Meier method was used.	Older age, gender, type of statin.	Findings revealed time and dose-dependent connections in statin use and indicated that the association increased the risk of NOT2DM.
5. Carrao et al. (2017) Italy	Calculation of period of prescription, identification of statins type, determining existence of antihypertensive agents in the past, test for fibrates, test for chronic obstructive lung disease, and comorbidities.	Involved a two-stage data evaluation. First stage included search for replication of findings on factors that raise chances of diabetes development. Also used Cox proportional model to determine ratio of hazard. In the next step, the chances (greater/lesser) of diabetes development were derived. Two ancillary assessments to find out the cause of macro vascular complications.	High adherence to statins, male gender, older adults, combination of atorvastatin with antihypertensive, anti-inflammatory, respiratory and antithrombotic agents.	With very high level of previous statins adherence, T2DM could not be associated with macro vascular risk. This implied that T2 DM was induced by statins.
6. Yoon et al. (2016) Korea	Baseline glucose levels, gender, hypertension, age, comorbidities, concomitant drugs.	For continuous variables, study employed mean, standard deviation and percentages for categorical variables. Chi-square and t tests enabled comparison of exposure levels across groups. NODM risk was tested by Kaplan-Meier while Cox proportional hazard regression model tested effect of statin exposures.	Older age, male gender, greater level of baseline glucose, thiazide exposure, and hypertension.	An increased risk for new-onset DM for statin users. Patients exposed to atorvastatin showed a higher NOT2DM risk than those without statin use. However, no significantly different outcomes were found with statins type
7. Ahmadizar et al. (2019) Netherlands	Serum glucose, insulin concentrations, health status, BMI, hypertension, height, weight, total cholesterol, diastolic/systolic blood pressure, triglycerides, and lipoproteins-cholesterol.	Chi-square statistics for relating statin use and *t* tests for continuous variables with normal distribution. Also, univariate and multivariate linear models for regression analysis of statins and glycemic relations. Correlation coefficients helped with identification of level of connection between insulin concentrations and serum fasting glucose.	Cumulative exposure.	There is higher hyperglycemia risk among statin users. This could cause resistance to insulin and in the long run led to the development of T2DM.

Table 3: *Measures, methods of analysis, confounder variables, and key observations.*

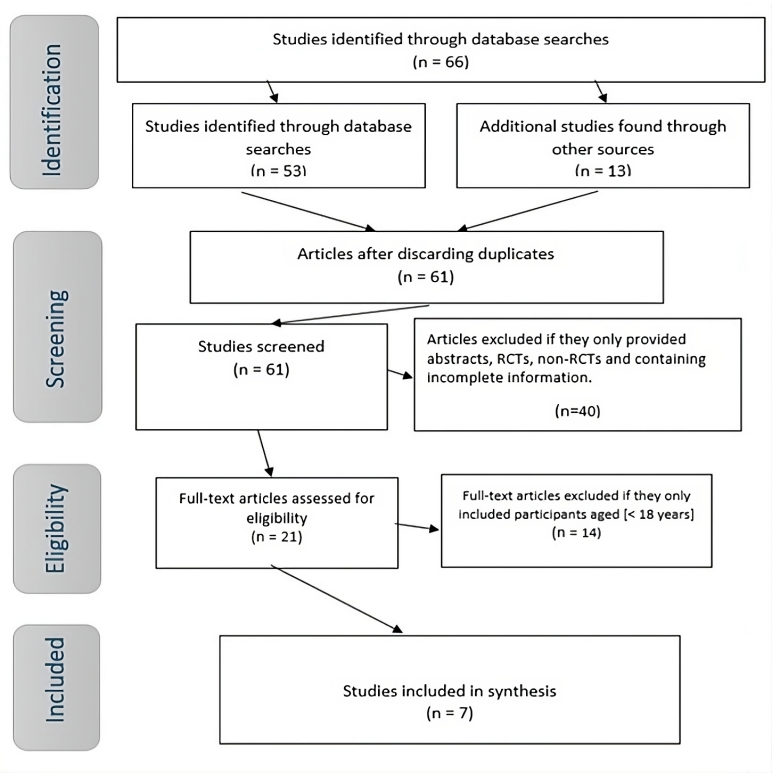

Figure 1: *PRISMA, flow chart of the study selection process [n= number of articles].*

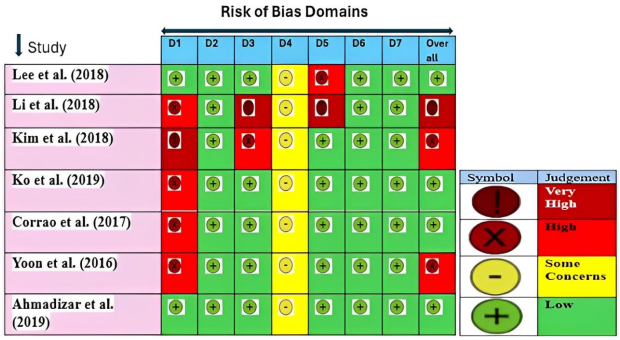

Figure 2: *Summarizes risk of bias assessment for observational studies in each domain based on the evaluation of the study using the ROBINS-E tool.*

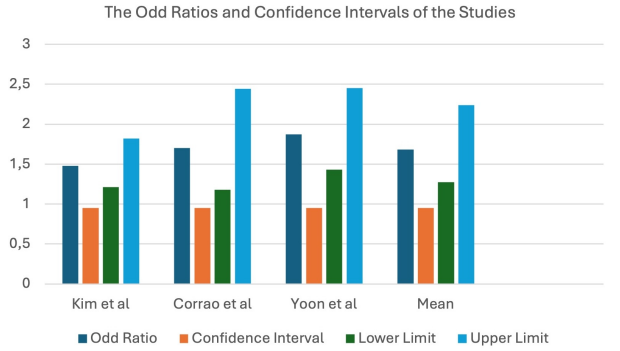

Figure 3: *The odd ratios and confidence intervals of the studies.*

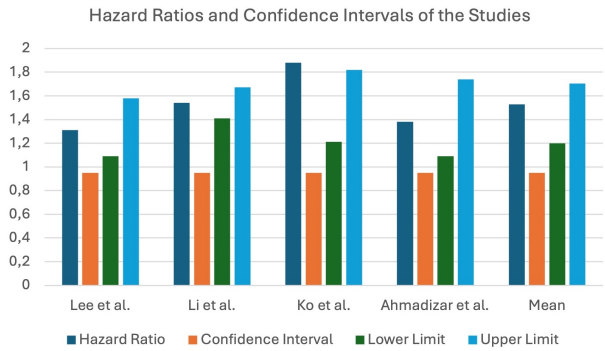

Figure 4: *The hazard ratios confidence intervals from included studies.*

diagnoses to select subjects suffering from diabetes, hypertension, and other comorbidities. The records may not have accurately captured the right diabetic patients, a problem common to observational studies relying on databases. Li et al. (2018) also reported encountering confounding factors beyond their control and failed to acquire adequate information on hypertension and dyslipidemia levels, crucial potential NOT2DM risk elements. The Yinzhou database used in their study did not include dietary systems, which influence NOT2DM incidents (Li et al., 2018). Furthermore, the reliance on database records made it impossible to verify if patients used the prescribed medications. The National Health Interview Survey database used by Kim et al. (2019)

also lacked data on Hb1c, making it difficult to apply definitive criteria for diagnosing diabetes. Ko et al. (2019) did not find any effects related to a specific type of statin but cautioned practitioners against selecting a drug strain for populations known to have a high risk of diabetes development. Despite substantial adherence to statins having impressive outcomes in Corrao et al. (2017), the researchers noted the involvement of other antidiabetic and antihypertensive agents. Additionally, the beneficial effects of statins on CVD and related drugs may not be factual as the hospitalization data used did not reveal values for fasting glucose, LDL-C, blood pressure, and lipids. The follow-up duration was also insufficient to evaluate the impact of novel statin treatment. Therefore, diabetes risk factors such as unhealthy diet and BMI should be considered, which were not found in the chosen database.

Key Findings in This Study

• Seven observational studies were included after full-text assessment: Two studies [Lee, Sung, Cho, Kim, and Chang (2018), and Kim, Kim, and Park et al. (2019)] were conducted in South Korea, two studies [Ko, Jo, Kim, Kang, Cho, Jo, Park, Yun, Lee, and Park (2019), and Yoon, Sheen, Lee, Choi, Park, Rae, and Lim (2016)] in Korea, one study [Li, Lin, Zhao, Xu, Cheng, Shen, and Zhan (2018)] in China, one study [Corrao, Compagnoni, Rea, Merlino, Catapano, and Mancia (2017)] in Italy, and one study [Ahmadizar, Ochoa-Rosales, Glisic, Franco, Muka, and Stricker (2019)] in the Netherlands.
• Statin therapy is associated with a 68% increase in the risk of NOT2DM incidence (OR average 1.683; 95% CI average: 1.27-2.237) for three studies (Kim et al., Ko et al., and Yoon et al.). These risks were more prominent among older adults, normotensive males, hypertensive females, and people with low physical activity.
• The significant relationship between statin use and the rising risk of NOT2DM was confirmed by five studies (Lee et al., Li et al., Ko et al., and Ahmadizar et al.) with an average HR of 1.494 (95% CI average: 1.19-1.686). No significantly different outcomes were found with statin types.
• Most studies assessed FBG, BMI, HbA1c, lipid panels, BP with OR, HR, and CIs.
• Recent and short-term use of statins minimized the chances of increasingly fatal incidents of CVD and were linked to a higher risk of NOT2DM in statin users compared to non-users.
• The cumulative duration of statin use showed no significant association with NOT2DM.
• Time and dose-dependent connections in statin use indicated an increased risk of NOT2DM.
• Hyperglycemia risk among statin users could cause insulin resistance and, in the long run, lead to the development of NOT2DM and reduced glycemic control in the short run.
• No proven mechanisms were found.

Discussion

We assessed seven observational studies to underscore the significance of the findings, summarize the best evidence across the three main areas addressed in this review, and offer insights into their implications for clinical practice as well as the limitations encountered. These areas include: (i) the possible association between statin use and incidents of NOT2DM; (ii) the magnitude and extent of this association; (iii) exploring the underlying mechanisms; and (iv) providing a concise summary and interpretation of the main findings.

Association between Statin Therapy and NOT2DM Development

Statin therapy is associated with a 68% increase in the risk of NOT2DM incidence (OR average 1.683; 95% CI average: 1.27-2.237) as demonstrated in three studies conducted by Kim et al., Ko et al., and Yoon et al. These risks were more prominent among older adults, normotensive males, hypertensive females, and people with low physical activity. Most studies assessed FBG, BMI, HbA1c, lipid panels, and BP with OR, HR, and CIs. They reported a significant association between statin and NOT2DM, though the conditions contributing to NOT2DM risk differed. For instance, Lee et al. (2018) found that statin therapy raised NOT2DM chances, but risk appeared more common among normotensive participants and hypertensive females. Lee et al. (2018) described NOT2DM as a sophisticated disease with several risk factors such as high levels of FBG and triglyceride, BMI, and hypertension. Leung Ong et al. (2014) found in a meta-analysis of large clinical trials that other drugs used for the prevention of CVD events, such as niacin, thiazide diuretics, and beta-blockers, increased the risk of T2D from 9% to 43%. Lee et al. (2018) demonstrated that these risk factors were proven in RCTs involving atorvastatin. However, they found no connection to NOT2DM among hypertensive men. These findings suggest that gender differences and other factors may influence how men and women use statins. The discovery necessitates the separation of treatment and monitoring approaches across gender, aligning with findings from Sattar et al. (2010), who conducted a large meta-analysis re-

Citation	Odd Ratio	Confidence Interval	Lower Limit	Upper Limit
Kim et al	1.48	95%	1.21	1.82
Corrao et al	1.7	95%	1.18	2.44
Yoon et al	1.87	95%	1.43	2.45
Mean	1.683	95%	1.273	2.236

Table 4: *Calculation of the odd ratios and confidence intervals of the studies.*

Citation	Hazard Ratio	Confidence Interval	Lower Limit	Upper Limit
Lee et al.	1.31	95%	1.09	1.58
Li et al.	1.54	95%	1.41	1.67
Ko et al.	1.88	95%	1.21	1.82
Ahmadizar et al.	1.38	95%	1.09	1.74
Mean	15.275	95%	1.20	17.025

Table 5: *Hazard ratios and confidence intervals calculation of the studies.*

vealing a 9% increase in incident T2DM with statin use. Preiss et al. (2011) also reported a significant rise in FBG and a 12% increase in the risk of T2DM from five statin trials.

Li et al. (2018) found evidence from a systematic review, RCTs, and observational studies that prompted the FDA to change statin labels in February 2012 to include information about diabetogenic effects, such as inducing diabetes and increasing HbA1c or FBG. Sabatine et al. (2004) reported an increase in glucose and HbA1c and incident T2DM for atorvastatin and simvastatin (de Lemos et al., 2004). Li et al. (2018) compared their findings to previous studies and concluded that the effect of statins in their study was moderate. They explained that higher levels of NOT2DM in their study could be due to targeting patients with hypertension, who might be at greater risk for diabetes than the general population. Li et al. (2018) found that the risk of NOT2DM was consistent for both genders across age groups, with a more significant relationship in those over 40 years old. Observational data lack control over confounding variables, increasing the likelihood of false associations between drugs and outcomes.

Li et al. (2018) also found that specific statins, such as atorvastatin and simvastatin, were associated with an increased risk of NOT2DM, particularly with higher intensity. Confounders and pre-existing risk factors such as blood pressure, age, obesity, high total cholesterol levels, gender, comorbidities, smoking, alcohol consumption, poor exercise habits, and ethnicity augmented the risk of T2DM (Sattar et al., 2014; Waters et al., 2011; Waters et al., 2013). Atorvastatin and Simvastatin showed an increased risk of NOT2DM based on multivariate Cox model analysis results, revealing that NOT2DM risk grew with the intensity of statin use. Most studies found that NOT2DM is an emerging issue associated with statin use, with evidence suggesting a dose-dependent relationship. Higher doses of statins, such as atorvastatin and rosuvastatin, are more frequently associated with the risk of developing NOT2DM (Hadjiphilippou & Ray, 2019; Collins et al., 2016; Jung, 2021). Kim et al. (2019) reported that the cumulative number of days and non-current statin use did not contribute to NOT2DM risk. NOT2DM risk grew with statin use within six months or less. Ko et al. (2019) found a time- and dose-based interrelation between statin use and the rising risk of diabetes incidence, with higher risks associated with longer statin use. Their findings contradicted Lee et al. (2018) in that gender did not play a role in raising diabetes incidence. Carter et al. (2013) and Sattar et al. (2014) demonstrated that high-intensity statin trials were associated with a higher association with incident T2DM compared to moderate-intensity. Thakker et al. (2016) found that 12% of 141,863 participants without diabetes from 29 trials developed T2DM in their meta-analysis.

The study by Ko et al. (2019) observed the complete reimbursement of statin interventions for individuals with hypercholesterolemia, noting observable changes and clinical relevance. Time- and dose-dependent associations with NOT2DM risk were evident in their study. Statins showed higher risks for clinically relevant NOT2DM with higher intensity and cumulative dosing. The progressive decline in NOT2DM risks with increased adherence to statins suggested a protective influence of the drug in diabetic patients using the therapy. Yoon et al. (2016) found higher HR values than previous studies, likely due to including patients with dyslipidemia and comorbid cardiovascular disease. The study highlighted that CVD patients require statin therapy. Anynwagu et al. (2017) found statin use was associated with less glycemic control compared to non-users, with significant short-term changes in HbA1c but not long-term.

Magnitude and Extent of Statin Use and NOT2DM Incidents

The significant relationship between statin use and the rising risk of NOT2DM was corroborated by five studies (Lee et al., Li et al., Ko et al., and Ahmadizar et al.) with an average HR of 1.494 (95% CI average: 1.19-1.686), showing no significantly different outcomes regarding statin types. Ahmadizar et al. (2019) highlighted glycemic feature elevation at baseline as a major observation of statin association. Adjustments for age, exercise routine, and educational attainment did not alter the association, indicating a robust link between statin use and glycemic changes. Freeman et al. (2001) reported a 30% reduction in T2DM cases with Pravastatin use in a post hoc analysis, similar to results in the PROSPER trial by Shepherd et al. (2002). Statin therapy's impact was more common in individuals with high BMI, HbA1c, and impaired FBG. Kim et al. (2019) found that the risk of NOT2DM did not increase with cumulative statin use days and remained unchanged in non-recent users. The risk increased only in recent users' groups who took statins within the last six months. Corrao et al. (2017) reported a 24% NOT2DM risk among low statin adherence patients, 72% for intermediate, and 95% for high adherence. Ahmadizar et al. (2019) found a 38% increase in NOT2DM emergence with cumulative statin use. Lee et al. (2018) found a higher NOT2DM occurrence rate among statin users (7.6%) compared to non-users (5.7%). Li et al. (2018) reported a 54% increase in NOT2DM risk for statin users. Ko et al. (2019) found a significant higher NOT2DM risk for statin users compared to non-users during a 3.9-year follow-up (HR 1.88, 95% CI 1.85–1.93). Yoon et al. (2016) found a higher effect rate for statin users (6.0 per 1000 person-years) compared to non-users (3.2 per 1000 person-years). Na et al. (2020) found that the diabetogenic effect of Pitavastatin was not statistically significant, but the risk was highest for atorvastatin. Long-term statin exposure ($\geq$5 years) significantly increased NOT2DM risk, with simvastatin having the highest magnitude (HR 1.916, 95% CI 1.647–2.228) followed by atorvastatin (HR 1.830, 95% CI 1.487–2.252).

Underlying Mechanisms in Statin Use and Development of NOT2DM

No proven mechanisms were found in the included studies. The mechanisms linking statin use to T2DM risk are not yet adequately characterized and remain incompletely understood. Lee et al. (2018) noted that while many studies found a significant association between statin therapy and NOT2DM incidence, the relevant mechanisms are not well characterized. Potential mechanisms include a direct impact on insulin synthesis or secretion, increased insulin resistance, and interactions between statin and cholesterol levels. Li et al. (2018) suggested that the expected age gradient could be moderated if younger individuals with NOT2DM risk were correctly selected for statin interventions. Kim et al. (2019) noted that genetic variants within HMG-CoA R and statin intervention might cause increased body weight and higher NOT2DM risk. Statins may impair insulin secretion by interfering with beta-cell function and reduce glucose transporter expression, leading to insulin resistance. Various mechanisms, including genetic polymorphisms, reduced HMG CoA reductase activity, and decreased glucose-induced insulin secretion, contribute to NOT2DM risk (Robinson, 2015; Baigent et al., 2010; Fernandes Silva et al., 2022). Ko et al. (2019) indicated that excessive diabetes risk is prevalent among patients with primary risk factors, suggesting a 10% proportional rise in reported diabetes with a standard statin dose. Ahmadizar et al. (2019) found that statins might reduce insulin-mediated cellular glucose uptake, leading to glucose intolerance. Statins might also lower isoprenoid synthesis, affecting glucose transporter 4 regulation and causing hyperinsulinemia and hyperglycemia. Yoon et al. (2016) noted that atorvastatin had a considerable effect on NOT2DM development due to its lack of glucose tolerance and penetration of cell membranes, affecting beta-cell exocytosis. Statins may also deplete coenzyme Q10, inhibit phosphorylation activities, and prevent adipocyte differentiation, increasing muscle resistance to insulin. The mechanisms remain complex and multifaceted, emphasizing the need for further research to understand the interplay between statin use and NOT2DM risk.

Summary and Interpretation of The Main Findings

Lee et al. (2018) argued that modifications in dyslipidemia management could encourage global statin therapy adoption. Women and normotensive males faced a higher diabetes risk, necessitating serious monitoring and follow-ups. Diabetes screening is essential for patients requiring statin treatment. Corrao et al. (2017) found that statins were crucial in CVD treatment and beneficial for diabetic patients and those with CVD. Physicians should not withhold statin treatment from diabetic patients and patients with CVD, as there are no associated risks. Yoon et al. (2016) highlighted the benefits of statins in

CVD treatment due to their therapeutic efficacy on hyperlipidemia and influence on pleiotropic elements, suggesting NOT2DM risks associated with statin use should be labeled on the drug package. Ahmadizar et al. (2019) recommended monitoring glycemic impairment in patients on statin therapy.

Limitations

Firstly, this review includes only articles published in English, potentially excluding relevant studies. Secondly, the number of articles is relatively small, and some published studies were not included due to access restrictions, which may introduce bias. Thirdly, there is a lack of studies primarily investigating the association between statin use and the incidence of NOT2DM. Many published trials assessed NOT2DM as a secondary outcome and were underpowered to detect this association. Fourthly, including studies with large sample sizes may bias the result, whereas a new systematic review might not face this issue. Lastly, we included studies published from 2012-2021, potentially missing reports published after this period, introducing the possibility of publication bias.

Strengths

We followed a predefined protocol to minimize bias in study selection, data extraction, and analysis. Additionally, we included studies based on a transparent and reproducible process, with rigorous search strategies to identify all relevant studies to minimize selection bias. Critical appraisal was addressed to help readers evaluate the reliability and validity of the evidence and consider the strength of the overall conclusions.

Conclusion

While some evidence suggests a potential association between statin use and an increased risk of incident T2DM, other studies found no significant association and reported conflicting results. This analysis presented the most current research and found a significant link between statin therapy and NOT2DM. Patient characteristics, statin type, dose, and duration may contribute to the observed heterogeneity across studies. The benefits of statins exceed the related risks, and their use should not be discouraged due to the risk of NOT2DM. The balance between continuity and intermission of statins should be considered, as discontinuity could be more harmful. This prompts a discussion on whether the benefits of treatment outweigh the risk of diabetes, emphasizing the need for rigorous monitoring, screening, periodic follow-up, and assessment. Various treatment plans can consider statin dose reduction, switching from one type of statin to another, or switching to non-statin hypolipidemic agents if tolerance occurs.

Impact on Clinical Practice

Clear answers regarding the impact of statin therapy on new-onset T2DM are crucial for informing clinical decision-making and optimizing patient care. This review may guide policymakers, physicians, and clinicians in designing future clinical guidelines or audit programs for non-diabetic people using statins.

Abbreviations

ASCVD: Atherosclerotic Cardiovascular disease
BMI: Body Mass Index
CVD: Cardiovascular Disease
CI: Confidence Interval
DM: Diabetes Mellitus
FBG: Fasting Blood Glucose
FDA: Food and Drug Administration
FBG: Fasting Blood Glucose
HbA1c: Glycosylated Hemoglobin A1c
HR: Hazard Ratio
LDL-C: Low-Density Lipoprotein Cholesterol
MA: Meta-analysis
NOT2DM: New-Onset Type 2 Diabetes
Non-RCT: Non- Non-Randomized Controlled Trials
OR: Odds Ratio
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols
RCT: Randomized Controlled Trials
HMG-CoA : Statins inhibit 3-Hydroxymethyl Glutaryl Coenzyme A (HMG-CoA)
T2DM: Type 2 Diabetes Mellitus

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Conflicts of Interest

The authors declare no conflict of interest.

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