"Latest Update on Statins for Diabetes".

Module 4

Statins and Cardiovascular Outcomes in Indian Diabetic Patients

CONTENT

Introduction

Diabetes is an epidemic in India.1 It is also associated with a greater prevalence of macrovascular and microvascular disease and these patients have a higher long-term mortality as compared with patients in developed countries.2 3 Multiple factors are responsible for greater morbidity and mortality from diabetes in India and include low awareness, treatment, and control of glycemia in patients with diabetes.4 5 Greater prevalence and low awareness, treatment, and control of cardiovascular risk factors (smoking, hypertension, dyslipidemia, and unhealthy lifestyles), especially in lower socioeconomic status patients, is also important.6 Control of cardiovascular risk factors such as hypertension and hypercholesterolemia in patients with diabetes can prevent complications. It has been reported that appropriate use of statins can prevent symptomatic coronary heart disease as well as acute coronary events in patients with type 2 diabetes in all populations including South Asians.7 8 Patients with type 2 diabetes have a longterm risk of cardiovascular mortality similar to patients without diabetes and overt cardiovascular disease.8–12 Based on these epidemiological observations and primary prevention trials, many international guidelines recommend routine use of statins in patients with type 2 diabetes.8 13–15 The American College of Cardiology/American Heart Association (ACC/AHA) 2013 statement classified diabetes as a coronary risk equivalent and recommended high-dose statin therapy in all patients with diabetes.8 Diabetes registries in developed countries, for example, the Swedish National Diabetes Register, have reported a high use of statins.

in patients with type 2 diabetes.16 No similar data are available from developing countries, including India. Previous studies that reported treatment patterns in type 2 diabetes in India were published before the recent recommendations17–20 and a review reported suboptimal quality of diabetes management in India.21 Therefore, to document the extent of prescriptions of statins and their types in patients with type 2 diabetes and to correlate this with vascular risk status of these patients, we performed a multisite registry-based study.

Evaluation of statin prescriptions in type 2 diabetes: India Heart Watch-2

Methods

We performed a multisite (n=9) registry-based study in eight cities across India to determine the prescription pattern of statins in patients with type 2 diabetes. The Institutional Ethics Committee at the central coordinating center at Jaipur, India, approved the study. Requirement of informed consent from each patient was waived by the Ethics Committee because anonymized data were used for analyses. We obtained data on successive patients attending the outpatient department at respective centers until the target of 500 patients was reached at each site. A larger sample size was available at the primary site where the pro forma was piloted.20 Demographic and clinical details were obtained that were similar to the previous India Heart Watch study.4 An abbreviated version useful for a disease registry was used in the present study.20 Sociodemographic factors were education, occupation, and socioeconomic status and lifestyle factors included details of smoking and tobacco use, physical activity patterns and diet. Details of concomitant risk factors—overweight or obesity (body mass index ≥25 kg/m2), hypertension, hypercholesterolemia (total cholesterol ≥200 mg/dL), hypertriglyceridemia (triglycerides ≥150 mg/dL), and low high-density lipoprotein (HDL) cholesterol (2 years and a third for >5 years. Risk factor details were available for most patients (table 1). Smoking and/or tobacco use was one-fifth while moderate-to-high physical activity in less than half. Hypertension was present in 51.5%, with total cholesterol ≥200 mg/dL in 34.9%, lowdensity lipoprotein cholesterol ≥100 mg/dL in 50.0%, triglycerides ≥150 mg/dL in 35.2%, and low HDL cholesterol in 48.9%. Hypothyroidism was present in 9.2% and was more in women (13.0%). Coronary heart disease was present in 15.4% and others (stroke, large vessel peripheral arterial disease in 5.2% while microvascular complications such as retinopathy diabetic foot or advanced chronic renal disease (creatinine ≥2.0 mg/dL) was in 6.1%, 13.9%, and 6.8%, respectively. Use of lipid-lowering drugs and others is shown in table 2. Statins were prescribed in 4802 (55.2%) patients, significantly more in men (57.2%) compared with women (52.1%; p20 mg/day or rosuvastatin >10 mg/day)8 were in 610 (12.7%), moderate dose (atorvastatin 10–20 mg/day or rosuvastatin 5–10 mg/day)8 in 4100 (85.4%) and low-dose (atorvastatin <10mg/day, simvastatin <20mg/day, or rosuvastatin < 5mg/day, moderate dose atorvastatin 10–20 mg/day, simvastatin 20–40 mg/day, or rosuvastatin 5–10 mg/day; and high dose as atorvastatin 40–80 mg/day or rosuvastatin 20–40 mg/day according to the ACC/AHA guidelines.

Statistical analyses: All the data were computerized and quality checks were performed to reduce duplicate and redundant data. Statistical analyses were performed using SPSS for Windows (SPSS, V.13.0). Descriptive statistics are presented with unadjusted data and proportions. Intergroup comparisons were performed using $\chi 2$ test. p Values <0.05 were considered significant.

Results

We obtained detailed prescriptions for 8699 patients with type 2 diabetes (men 5292, women 3407). Recruitment at different sites was Jaipur (3 sites, n=3714, 42.7%), Nagpur (n=1536, 17.7%), Madurai (n=971, 11.2%), Dibrugarh (n=796, 9.2%), Lucknow (n=792, 9.1%), Udaipur (n=548, 6.3%), and Jodhpur (n=342, 3.9%). Patients were subdivided according to level of care into the internists' group (n=2301, 26.5%), diabetologists' group (n=3299, 37.9%), and endocrinologists' group (n=3099, 35.6%). Demographic and clinical details of the study participants are shown in table 1. Twelve per cent of the study participants were 2 years and a third for >5 years. Risk factor details were available for most patients (table 1). Smoking and/or tobacco use was one-fifth while moderate-to-high physical activity in less than half. Hypertension was present in 51.5%, with total cholesterol ≥200 mg/dL in 34.9%, lowdensity lipoprotein cholesterol ≥100 mg/dL in 50.0%, triglycerides ≥150 mg/dL in 35.2%, and low HDL cholesterol in 48.9%. Hypothyroidism was present in 9.2% and was more in women (13.0%). Coronary heart disease was present in 15.4% and others (stroke, large vessel peripheral arterial disease in 5.2% while microvascular complications such as retinopathy, diabetic foot or advanced chronic renal disease (creatinine ≥2.0 mg/dL) was in 6.1%, 13.9%, and 6.8%, respectively. Use of lipid-lowering drugs and others is shown in table 2. Statins were prescribed in 4802 (55.2%) patients, significantly more in men (57.2%) compared with women (52.1%; p< 0.001). Use of fibrates was low (9.2%). Insulins were used in 15.8%, more in men (16.8%) as compared with women (14.2; p=0.016). Use of antihypertensive drugs is also shown in table 2. The most frequently used drugs were renin angiotensin system blockers, ACE inhibitors, or angiotensin receptor blockers in 36.4% of patients, while diuretics (31.8%), β-blockers (27.6%), and calcium channel blockers (23.7%) were prescribed in lesser proportions. Statin prescription was significantly greater by diabetologists (n=2126/3299, 64.4%) compared with internists (n=1227/2301, 53.3%) and endocrinologists (n=1449/ 3099, 46.8%; p<0.001; table 2). It was also lower in patients < 40 years of age (34.3%), compared with those aged 40–49 years (49.7%), 50–59 years (60.1%), or ≥60 years (62.2%; p<0.001figure 1) Statin prescription were significantly greater in high-risk patients (58.0%) compared with medium-risk (53.8%) and low-risk (56.8%) patients (p <0.001; table 2).

Atorvastatin was the most prescribed statin (n=3560, 74.1% of statin prescriptions), as compared with rosuvastatin (n=1098, 22.9%) or others (simvastatin or pitavastatin; n=144, 3.0%). Of the patients prescribed statins (n=4802), high-dose statins (atorvastatin >20 mg/day or rosuvastatin >10 mg/day)8 were in 610 (12.7%), moderate dose (atorvastatin 10–20 mg/day or rosuvastatin 5–10 mg/day)8 in 4100 (85.4%) and low-dose (atorvastatin<10mg/day, rosuvastatin <5mg/day) in 92 (1.9%; table 2). Use of high-dose statins was not significantly different in low-risk (13.5%), medium-risk (11.8%), or high-risk (14.5%) patient groups (figure 2).

Discussion

This multisite prescription audit and clinical study shows that statins are prescribed in <60% of clinic-based patients with type 2 diabetes in India. High-dose statins, which are recommended in all the patients with diabetes,8 are prescribed in less than one-sixth of patients prescribed statins. Although the prescriptions of statins are significantly greater in high-risk patients with diabetes, the overall prescriptions of statins as well as high-dose statins are suboptimal and much lower than the guidelines.8 Diabetes has long been considered a cardiovascular risk equivalent.22 A Finnish study initially reported that patients with diabetes without manifest coronary heart disease had long-term (7-year) risk of events and mortality similar to patients without diabetes with manifest coronary heart disease.10 Subsequently, a number of observational studies in Australia and Europe reported similar associations.11 12 Based on these studies, as well as randomized controlled trials that demonstrated lowering of coronary risk with statins in patients with diabetes,23 the 2013 AHA/ACC guidelines on lipid management recommended that all patients with diabetes should receive high-dose statins irrespective of cholesterol levels.8 Registry-based studies in developed countries have reported increasing statin prescriptions in patients with type 2 diabetes since the guidelines endorsed their use. Prescriptions of statins in patients with diabetes have been reported in a few countries and examples include the Swedish National Diabetes Register,24 US National Health and Nutrition Evaluation Surveys (NHANES),25 British National Health Service (NHS),26 and Australian general practice,27 and the proportion of patients with diabetes prescribed statins varied from 25% to 65%. Studies have also reported that the prescriptions are significantly greater in diabetologists' practices (75%).26 27 Targets are more than 90%.14 In our study, statins were prescribed in 55% of patients and, although, are lower than the Swedish and Australian registries and NHANES where these drugs are prescribed in 70–90% of patients,24 25 27 but, are higher than the British NHS-Check programme.26 However, in our study, the high-dose statins are prescribed in less than a sixth of patients prescribed statins (12.7%) and this is clearly suboptimal. Moreover, our study shows that statin prescriptions are much lower than optimal in patients with type 2 diabetes with known cardiovascular disease (highrisk group, figure 2). It has been recommended that all patients with coronary heart disease should be on a statin.8 28 We did not inquire regarding the intake of these drugs by the patients and this is a study limitation. It is well known that even after prescriptions, many patients do not take the statins and other medications for chronic diseases,29 especially in India.30 31 The study has multiple strengths as well as limitations. This is one of the largest contemporary registries on diabetes management from India and is especially relevant because it was performed after the publication of AHA/ACC Lipid Guidelines.8 Moreover, we have performed the study at clinics of qualified endocrinologists, as well as of diabetologists and internists who manage the majority of patients with diabetes in India.32 Limitations of the study include lower proportions of patients from the southern and eastern regions of the country and greater proportions from the northern and western regions, non-representation of secondary and primary care physicians who treat the majority of patients with diabetes in India, lack of systematic collection data on microvascular complications (especially renal disease), pragmatic risk classification of the patients which is different from the suggested criteria,33 and lack of patient-level consumption and adherence data. Other limitations include absence of baseline cholesterol levels of these patients to justify high-dose therapies and lack of data on the side effect profile of statins. Moreover, we did not perform a qualitative study to determine causes of low prescriptions of statins by physicians.

In conclusion, this study shows that prescriptions of statins in clinic-based patients with type 2 diabetes in India are suboptimal. Efforts to increase use of these drugs to all patients with diabetes to prevent cardiovascular complications are urgently required. These results are all the more important after the publication of the HOPE-3 study where statin use has been associated with a significant decrease in cardiovascular mortality and acute events in intermediate-risk patients including those with diabetes.34 Strategies to optimize prescriptions are better clinician awareness of guidelines and continuing medical education as well as periodic prescription audits and dissemination of results to improve quality of preventive care among patients with type 2 diabetes.

Key message

There are no contemporary data on statin prescriptions among patients with type 2 diabetes in India.

- In a multisite study in India, we observed suboptimal prescription of statins in patients with diabetes. A prescription of high-dose statins was low in all patients with diabetes, including those at high risk.

- Statin prescriptions were significantly less by endocrinologists and physicians compared with diabetologists.

Figures

Table 1 Demographic and clinical characteristics of the study cohort

Variable	Numbers with data Total, men/women	Total (N=8699)	Men (N=5292)	Women (N=3407)	X2 test p value (male/female differences)
Age groups					
<40	8699, 5292/3407	1016 (11.7)	625 (11.8)	391 (11.5)	0.635
40–49		2288 (26.3)	1385 (26.2)	903 (26.5)	0.731
50–59		2815 (32.3)	1728 (32.6)	1087 (31.9)	0.466
60+		2580 (29.7)	1554 (29.3)	1026 (30.1)	0.558
Socioeconomic status					
Low	6346, 3766/2580	2239 (35.3)	1345 (35.7)	894 (34.6)	0.384
Middle		2516 (39.6)	1499 (39.8)	1017 (39.4)	0.758
High		1591 (25.1)	922 (24.5)	669 (25.9)	0.191
Diabetes duration (year)					
<2	5081, 3027/2054	948 (18.6)	554 (18.3)	394 (19.2)	0.429
2–5		2263 (44.5)	1340 (44.2)	923 (44.9)	0.638
>5		1870 (36.8)	1133 (37.4)	737 (35.9)	0.261
Smoking/tobacco use	7695, 4678/3017	1633 (21.2)	1201 (25.6)	432 (14.3)	<0.001
Physical activity	7029, 4372/2657	3150 (44.8)	2122 (48.5)	1028 (38.7)	<0.001
Obesity, BMI≥25 kg/m^2	8699, 5292/3407	3070 (35.3)	1773 (33.5)	1293 (37.9)	<0.001
Hypertension	8673, 5275/3398	4464 (51.5)	2583 (48.9)	1881 (55.3)	<0.001
Cholesterol ≥200 mg/dL	3979, 2469/1510	1390 (34.9)	824 (33.4)	566 (37.5)	0.008
LDL cholesterol ≥100 mg/dL	3979, 2469/1510	1989 (50.0)	1193 (48.3)	796 (52.7)	0.007
Triglycerides ≥150 mg/dL	3979, 2469/1510	1403 (35.2)	866 (35.0)	537 (35.5)	0.754
HDL<40/50 mg/dL	3979, 2469/1510	1945 (48.9)	1025 (41.5)	920 (60.9)	0.001
Macrovascular complications					
Coronary heart disease	7131, 4391/2740	1099 (15.4)	720 (16.4)	379 (13.8)	0.003
Others (stroke, PAD)		372 (5.2)	232 (8.5)	140 (5.1)	0.743
Microvascular diseases					
Retinopathy	4851, 2992/1859	298 (6.1)	183 (6.1)	115 (6.1)	0.994
Others		670 (13.9)	424 (14.2)	246 (13.2)	0.357
Hypothyroidism	5423, 3289/2134	500 (9.2)	222 (6.7)	278 (13.0)	<0.001
Chronic renal disease (serum creatinine ≥2.0 mg/dL)	6381, 3915/2466	356 (5.6)	267 (6.8)	89 (3.6)	<0.001

Numbers in parentheses are percent.
BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PAD, peripheral arterial disease.

Table 2 Prescription audit of drug therapies in the study cohort

Variable	Numbers with data Total, men/women	Total (N=8699)	Men (N=5292)	Women (N=3407)	χ^2 test p value (male/female differences)
Antidiabetes drugs					
Insulin	5023, 3053/1970	794 (15.8)	513 (16.8)	281 (14.2)	0.016
Oral antidiabetics	8699, 5292/3407	4229 (84.2)	2772 (90.8)	1457 (73.9)	<0.001
Antihypertensive and other drugs					
Renin angiotensin system blockers	8699, 5292/3407	3169 (36.4)	1897 (35.8)	1272 (37.3)	0.159
β-blockers	6258, 3898/2360	1726 (27.6)	1060 (27.2)	666 (28.2)	<0.001
Calcium channel blockers	4636, 2820/1816	1100 (23.7)	601 (21.3)	499 (27.5)	<0.001
Diuretics	4515, 2733/1782	1438 (31.8)	815 (29.8)	623 (34.9)	<0.001
Antiplatelets	6229, 4515/2733	2073 (33.3)	1332 (29.5)	741 (27.1)	0.029
Lipid-lowering drugs					
Statins	8699, 5292/3407	4802 (55.2)	3026 (57.2)	1776 (52.1)	<0.001
Fibrates	3546, 2132/1414	325 (9.2)	209 (9.8)	116 (8.2)	0.106
Lipid-lowering drugs at level of care	8699, 5292/3407				
Internists	2301, 1261/1040	1227 (53.3)	714 (56.6)	513 (49.3)	<0.001
Diabetologists	3299, 2215/1084	2126 (64.4)	1424 (64.3)	702 (64.3)	0.791
Endocrinologists	3099, 1816/1283	1449 (46.8)	888 (48.8)	561 (43.7)	0.004
Statins in various risk groups	8699, 5292/3407				
Low risk	1506, 940/566	855 (56.8)	539 (57.3)	316 (55.8)	0.567
Medium risk	5424, 3208/2216	2920 (53.8)	1806 (56.3)	1114 (50.3)	<0.001
High risk	1769, 1144/625	1027 (58.0)	681 (59.5)	346 (55.3)	0.089
Statin types as percent of statin use	4802, 3026/1776				
Atorvastatin		3560 (74.1)	2252 (74.4)	1308 (73.6)	0.554
Rosuvastatin		1098 (22.9)	687 (22.7)	411 (23.1)	0.726
Other statins		144 (3.0)	87 (2.9)	57 (3.2)	0.511
Statins dosage as percent of statin use	4802, 3026/1776				
Low dose		92 (1.9)	54 (1.8)	38 (2.1)	0.386
Moderate dose		4100 (85.4)	2580 (86.2)	1520 (85.6)	0.758
High dose		610 (12.7)	392 (13.0)	218 (12.3)	0.497

Numbers in parentheses are percent; renin angiotensin system blockers include ACE inhibitors and angiotensin receptor blockers.

Figure 1 Statins in men and women with diabetes at different age groups show lower prescriptions at younger age groups.

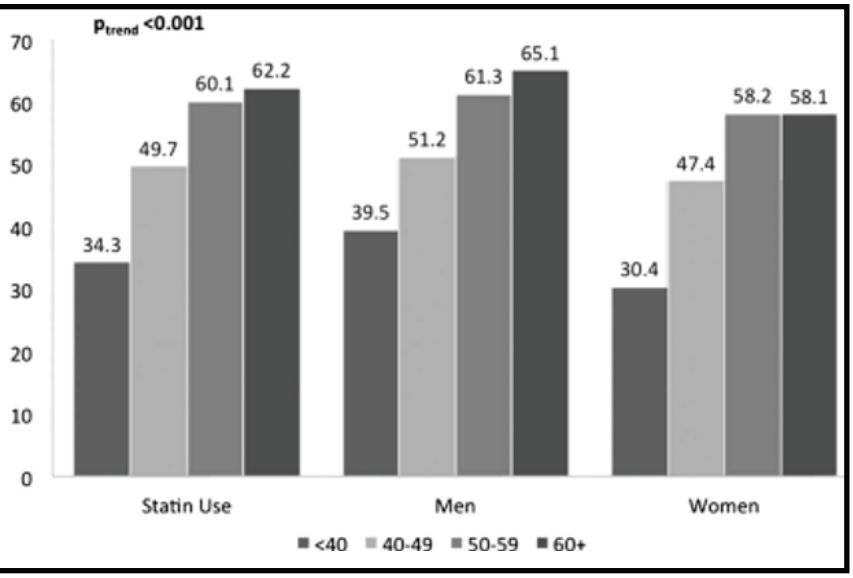
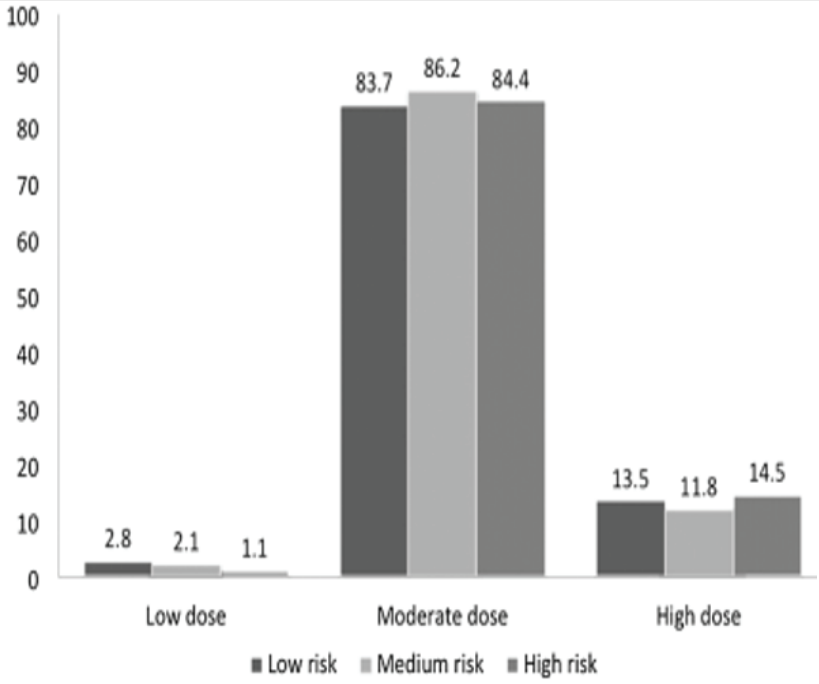


Figure 2 No significant differences in prescriptions of low-dose, moderate-dose, and high-dose statins in low-risk, medium-risk, and high-risk patients with diabetes. Low-risk patients had no cardiovascular risk factors—smoking/tobacco, hypertension; medium-risk patients had diabetes with any one of the above risk factors; and high-risk patients had diabetes with clinical evidence of microvascular or macrovascular disease.



The Impact of Statin Therapy on Cardiovascular Outcomes in Patients With Diabetes: Systematic Review

Introduction And Background

Cardiovascular disease (CVD) and diabetes mellitus (DM) are both related to each other. Most diabetic patients will develop CVD in the future if there is no prevention taken to lower the risk of it happening. CVD is the leading cause of death globally. Worldwide, around 17.9 million people die from this disease [1]. Around 2.6 million deaths are estimated to be caused by elevated cholesterol, and another 29.7 million people experience disability yearly. The prevalence of coronary heart disease is 1.5% and increases with age [2]. In diabetic patients, there is insulin resistance, which causes hyperglycemia that eventually causes metabolic abnormalities such as dyslipidemia, where there is a high cholesterol level, and other causes that favor the formation of atherosclerosis in the coronary artery [3,4]. The prevalence of CVD increases in the presence of DM. Atherosclerosis can cause myocardial ischemia due to partial or completely blocked blood vessels, which circulate and supply blood to the cardiac muscle, and thus disturb the cardiovascular (CV) function, in which blood is pumped all over the body [3,5]. These blocked blood vessels will cause a heart attack with chest pain due to myocardial ischemia. The complete blockage of the coronary artery will result in ST-segment elevation myocardial infarction (STEMI). Patients with non-ST-segment elevation myocardial infarction (NSTEMI) have a partial blockage with no visible ST elevation on ECG. STEMI patients have a greater mortality risk than NSTEMI patients [6]. It is crucial to curb the number of CVD mortality by controlling cholesterol levels, measured by low-density lipoprotein cholesterol (LDL-C) level of <100mg this lipid profile is considered a reversible risk factor. Elevated cholesterol levels can accumulate, narrowing the blood vessels, and plaque them, increasing the risk of CVD. To reduce LDL-C levels, we use statin as a gold standard treatment. Statin is a 3-hydroxy-3- methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor [7]. In the population of people aged more than 40 years old with DM, the usage of statin has been shown to decrease cardiovascular events and likely reduce mortality. Aggressive reduction in low-density lipoprotein cholesterol (LDL-C) reduces cardiovascular event rates, with each 1 mmol/L reduction in LDL-C reducing the annual rate of such major vascular events by approximately a fifth [8]. Although statin use can lower the risk of CVD in patients with DM, cardiovascular morbidity and mortality remain high in most patients with diabetes [9]. Diabetes increases the risk for vascular events regardless of age, and this increase is even more pronounced in people who have had diabetes in the long term or when multiple cardiovascular risk factors coexist, as is common among older people; this vascular dysfunction will promote the process of atherosclerosis in CVD. Other cardiovascular risk factors are hypertension, hypercholesterolemia, tobacco use, and obesity; the earlier onset age of DM and a more extended period of DM diagnosis are also associated with a higher chance of CVD [10,11]. Our objective in this systematic review is to evaluate the available evidence of the effectiveness of statin on cardiovascular outcomes in diabetic patients by answering the following question: can statin help reduce the risk of CVD in patients with DM?

Review Methods This review highlights clinical studies regarding the prescription of statin on CVD outcomes in patients with DM. We excluded animal studies and publications that only discussed the methodology of statins without presenting clinical data. The review follows the guidelines for Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 (Figure 1) while only taking data collected from published papers, eliminating the need for ethical approval [12].

A thorough search has been conducted to find relevant articles and publications using PubMed, as well as Medical Literature Analysis and Retrieval System Online (MEDLINE) and Google Scholar. We searched for studies mentioned in review papers, editorials, and commentaries on PubMed. Nevertheless, we continued searching for additional studies that fulfilled our inclusion criteria. We independently reviewed a list of abstracts for inclusion using specific criteria. The criteria included statin therapy, focusing on CVD outcomes of DM patients in the study. We excluded review papers and animal studies.

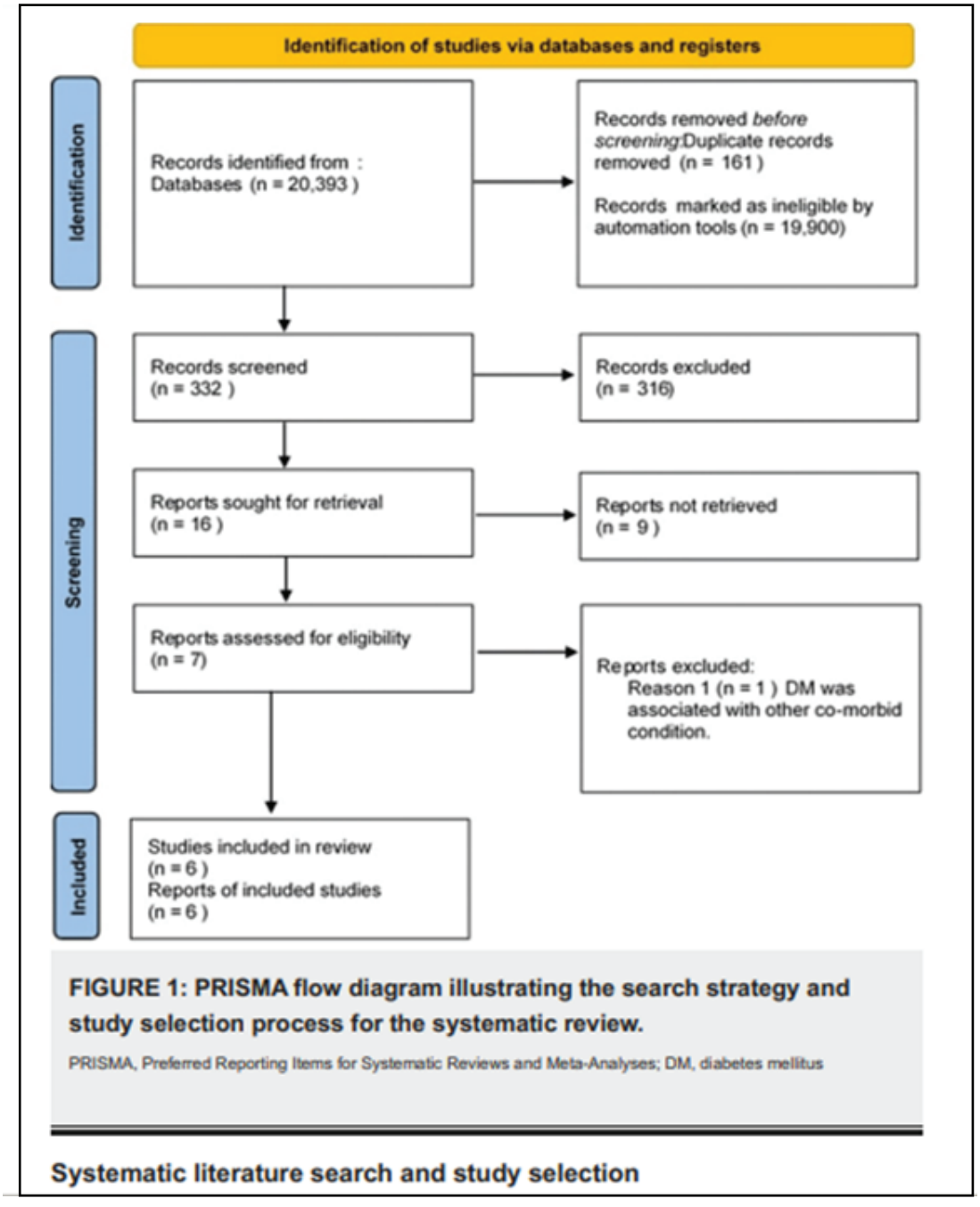


FIGURE 1: PRISMA flow diagram illustrating the search strategy and study selection process for the systematic review.

PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; DM, diabetes mellitus

Systematic literature search and study selection

Inclusion Criteria	Exclusion Criteria
Human studies	Animal studies
2013-2023	Only methodological studies explaining programming details
English text	Non-English texts
Gender: all	Age: <40 years
Age: >40 years of age	Studies involving clinical data other than cardiovascular health on patients with diabetes mellitus
Free papers	Papers that need to be purchased

TABLE 1: The criteria adopted during the literature search process.

Search strategy

Table 2 shows the search strategy, search engines used, and the number of results displayed.

Database	Search Strategy	Results
PubMed	((Statin therapy[Title/Abstract]) OR (Statin on cardiovascular[MeSH Terms]) OR (Cardiovascular on Diabetes patients[MeSH Terms]) AND ("2013/01/01"[Date - Publication] : "3000"[Date - Publication]))	7,467
PubMed (with filters)	((Statin therapy[Title/Abstract]) OR (Statin on cardiovascular[MeSH Terms]) OR (Cardiovascular on Diabetes patients[MeSH Terms]) AND ("2013/01/01"[Date - Publication] : "3000"[Date - Publication]) AND (y_10[Filter]) AND (fft[Filter]) AND (clinical trial[Filter] OR meta-analysis[Filter] OR randomized controlled trial[Filter] OR review[Filter] OR systematic review[Filter])). Filters applied: free full text, clinical trial, meta-analysis, randomized controlled trial, review, systematic review, in the last 10 years, humans, English, female, male, middle aged + aged 45+ years, and MEDLINE	393
Google Scholar	(Statin therapy OR Statin on cardiovascular OR Cardiovascular on Diabetes patients). Filters applied: studies from 2013 to 2023 and review articles	20,000

TABLE 2: The search strategy, search engines used, and the number of results displayed.

MeSH, Medical Subject Heading; MEDLINE, Medical Literature Analysis and Retrieval System Online

Inclusion and exclusion criteria

We accepted specific criteria to include and exclude participants to achieve our study goals. Our criteria can be summarized in Table 1.

Quality appraisal

To ensure the reliability of our chosen papers, we use various quality assessment tools. We used the PRISMA checklist and Cochrane bias tool assessment for randomized clinical trials for systematic reviews and metaanalyses. Non-randomized clinical trials were evaluated using the Newcastle-Ottawa tool scale. We assessed the quality of qualitative studies, as shown in Table 3, using the Critical Appraisal Skills Programme (CASP) checklist.

Quality Appraisal Tools Used	Type of Studies
Cochrane bias tool assessment	Randomized controlled trials (RCT)
Newcastle-Ottawa tool	Non-RCT and observational studies
PRISMA checklist	Systematic reviews

TABLE 3: Quality appraisal tool used.

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Results

Following the search through three selected databases, PubMed, MEDLINE, and Google Scholar, we extracted 20,393 articles. We then carefully analyzed each paper, applied our specific criteria, and chose not to utilize 19,900 due to duplicates or unsatisfactory titles and abstracts. We closely examined the remaining 16 papers and excluded nine more as their content did not meet our inclusion criteria. Finally, we conducted a thorough quality check on the remaining seven papers, which all met our criteria. These six articles are included in our final systematic review. Table 4 provides a detailed description of each.

Author and Year	Country	Study Design	Databases Used	Conclusions
Ikhsan et al., 2022 [13]	Indonesia	Cross-sectional studies	Google Scholar	DM patients face CVD risk influenced by gender, age, smoking, diabetes, blood pressure, and cholesterol level
Bertoluci and Rocha, 2017 [14]	Brazil	Review	Google Scholar	The improved stratification of diabetes patients enhances treatment quality
Johansen et al., 2014 [15]	USA	Database highlights	Google Scholar and PubMed	There are a considerable number of people that can benefit from statin but did not receive the therapy
Nichols et al., 2019 [16]	USA	Observational longitudinal cohort study	Google Scholar	Despite statin use, CVD risk is higher in DM patients due to high triglyceride level
Ramos et al., 2018 [17]	Spain	Retrospective cohort study	Google Scholar	The effect of statin therapy shows the reduction of CVD risk in DM patients younger than 85 years old
Jung, 2021 [18]	Korea	Retrospective cohort study	PubMed	Proper risk assessment and regular statin use in patients at high predicted risk would reduce outcome risks

TABLE 4: Summary of the results of the selected papers.

CVD, cardiovascular disease; DM, diabetes mellitus

Discussions

Statin reduces the risk of mortality and CVD in individuals at high cardiovascular risk. Statin users reported filling two or more statin prescriptions from a pharmacy during 2010 [19]. According to Johansen et al., that has created multiple logistic regression models for statin use as the dependent variable, with cardiovascular risk factors as independent variables. However, many people at risk of cardiovascular events, including individuals with diabetes, were not receiving statin as an agent that can reduce CVD risk. The undertreatment is due to a focus on the hyperlipidemia profile and not enough on cardiovascular risk [15]. Guidelines, public health messages, and direct-to-consumer advertising have anchored statin to lower cholesterol levels rather than reduce cardiovascular risk.

This overdependence on cholesterol levels shows that those with hyperlipidemia but without DM or heart disease are more likely to be given statin than those without hyperlipidemia who have diabetes or heart disease [20]. Given that individuals with heart disease or diabetes are at considerably higher cardiovascular risk, this suggests that statin use is strongly driven by hyperlipidemia rather than overall cardiovascular risk. Statin significantly reduced cardiovascular events by about seven per 1,000 people treated for one year. Several studies support the benefit of statin on CVD. The Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) trial found a 39% reduction in CVD in statintreated patients over 70 years old but no significant improvement in mortality [21]. Two meta-analyses also addressed the statin effect on CVD. Savarese et al. [22] and Teng et al. [23] found that statin significantly reduces myocardial infarction incidence in patients older than age 65 years. Additionally, Ramos et al. discovered that in diabetic patients, statin medication lowers the risk of atherosclerotic cardiovascular disease (CVD), but its effects disappear in nonagenarians after 85 years [17]. In cardiology practices, statins are prescribed for only about 62% of patients aged 40-75 years, of whom just over 50% continue statin use for an extended period [24]. Statins are recommended for primary CVD prevention in diabetes patients aged 40 years and older and for secondary CVD prevention in all adults [25]. Only 40%-60% of diabetic individuals achieve LDL-C values below 100 mg/dL [26,27]. A regular use of statin was defined as using statin for more than two-thirds of each statin therapy period (from the time medication was started to the year of follow-up), intermittent use as between one-third and three-quarters of each period, occasional use as less than one-third of each period, and nonuse as less than 90 days [28]. According to a study by Jung, regular users saw a 43% risk reduction for major CVD events compared to nonusers, which was close to the secondary analysis's 44% risk reduction (i.e., regular versus occasional users) and the 24%-44% CVD risk reductions seen in statin trials for primary prevention [18]. According to this study, a suitable risk assessment and consistent statin therapy in individuals with high anticipated risks might lower outcome risks. The primary lipid to target in people with diabetes to prevent CVD is LDL-C. Nevertheless, it is common for diabetic people to have high triglyceride (TG) levels [25,29]. The American Diabetes Association (ADA) stated that a post hoc analyses of clinical trials for reducing LDL-C suggest that TG levels are also related to CVD [30]. This statement is supported by Nichols et al. that despite high-density lipoprotein cholesterol (HDL-C) adjustments and statin-controlled LDL-C levels, CV event rates were higher than usual in diabetic patients with elevated TG levels [16]. To account for this finding, mean TG levels were shown to be strongly linked with all-cause mortality in one Italian research of diabetic patients receiving lipid-lowering medication, regardless of other cardiometabolic risk factors [31]. The difference in TG level likely contributed to the extra risk shown in individuals with high TG levels. Patients with DM have a two to four times higher risk of developing incident coronary heart disease and ischemic stroke and a 1.5-3.6 times higher chance of dying. Diabetes has long been regarded as an "equivalent cardiovascular risk." This claim was previously supported by Finnish research, which found that DM patients without coronary heart disease episodes had similar coronary mortality to non-diabetic individuals with a history of coronary events [32,33]. The length of diabetes is a significant factor in determining the risk of CVD. Patients who have had diabetes for more than 10 years may be at an incredibly high risk. Diabetes age of onset and duration are connected; diabetes diagnosis at an early age may impart an extra risk irrespective of diabetes duration [34]. According to Bertoluci and Rocha, the stratification of diabetic individuals increases the precision in predicting future cardiovascular events, silent ischemia, and subclinical coronary artery disease. To prevent overtreating lower-risk individuals, stratification separates greater-risk patients from lower-risk patients who may require intensive CVD prevention [14].

The adoption of a risk factor-based strategy to determine the start of statin medication is encouraged by the 2016 American Diabetes Association (ADA) Standards of Diabetes Care. In essence, it advises risk stratification using age, the history of cardiovascular events, and the presence or absence of risk factors. A family history of early CVD, LDL-C of >100 mg/dL, high blood pressure, smoking, overweight, and obesity are all ADA risk factors [35]. The American Heart Association classifies the statin intensity as low, moderate, and high intensities as shown in Table 5 High-intensity statin treatment should be administered to all patients with certain CVD events, regardless of age. High-intensity statin medication is advised for people between the ages of 40 and 75 who have cardiovascular risk factors but have not experienced CVD events. Depending on the inclination and tolerance of the particular patient, either moderate- or high-intensity statin medication might be recommended for older or younger individuals with risk factors.

Low-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	High-Intensity Statin Therapy
Simvastatin 10 mg	Simvastatin 20-40 mg	Atorvastatin 40-80 mg
Pravastatin 10-20 mg	Pravastatin 40-80 mg	Rosuvastatin 20-40 mg
Lovastatin 10 mg	Atorvastatin 10-20 mg	
Fluvastatin 20-40 mg	Rosuvastatin 5-10 mg	
Pitavastatin 1 mg	Lovastatin 40 mg	
	Fluvastatin 40 mg twice a day	
	Pitavastatin 2-4 mg	

TABLE 5: American College of Cardiology/American Heart Association classification of statin intensity relative to dose prescribed.

Moderate statin medication is recommended for older adults without risk factors or CVD occurrences. The ADA believes that lifestyle treatment alone is more appropriate in younger individuals without CVD or risk factors. ADA recently recommended for those recently diagnosed with acute coronary syndrome that it is appropriate for these individuals to use high-intensity statin [14,35]. Recent research shows that the risk of CVD in people with DM is highly heterogeneous and not always comparable to those with prior cardiovascular disease. A meta-analysis of 13 epidemiological studies with 45,108 patients with and without DM found that the risk of CVD was 43% lower in DM patients without a history of myocardial infarction than in non-diabetics [37].

Limitations

It should be noted that our literature review has certain limitations. Firstly, we focused solely on English articles that were published within the last decade and were aimed at individuals aged 40 years and above. Secondly, we only utilized free articles for our analysis, and our study was confined to examining the impact of statin on patients with cardiovascular and diabetes conditions. It is clear that further research needs to be conducted to arrive at a definitive conclusion.

Conclusions Our study emphasizes the effect of statin medication on cardiovascular results in diabetic individuals. This study on statin therapy aims to maximize the use of statin as a CVD prevention drug. Diabetes is a problem for CVD risk, even though many factors affect how well a statin works to minimize cardiovascular impact. The analysis of the elements that affect a statin's efficacy has been done from various study publications. Some researchers have effectively demonstrated that statin can reduce the risk of heart disease and diabetes can increase the risk of CVD events if they are not used in conjunction with statin therapy.

In another systematic review and meta-analysis of observational studies to extend the current evidence of statin use's association with MACE and all-cause mortality events in T2D patients. To the best of our knowledge, no previous study investigated the potential role of baseline LDL-C levels in the cardiovascular protective effects of statins in T2D patients. This meta-analysis suggests that statin therapy is associated with a significantly lower risk of MACE and all-cause mortality in T2D patients. Statin use compared with statin non-use in T2D patients was associated with greater reductions of MACE and all-cause mortality relative risk, albeit not statistically significant, in studies with higher baseline LDL-C levels. Metaregression analysis showed that studies' mean baseline LDL-C level modestly modifies the association of statin use and MACE events in T2D patients. The current observed data lacks the evidence to prove the significant role of baseline LDL-C levels in the efficacy of statin therapy in T2D patients. A framework tailored to the target population is essential for advancing precision diabetes research from evidence generation to clinical implementation. Sub-classification strategies for T2D have demonstrated meaningful clinical outcomes. Developing treatment decision-support tools that prioritize routine clinical features could offer a costeffective and equitable approach to precision treatment for T2D. However, studies using individual-level data to determine treatment effect heterogeneity are scarce and should be prioritized in future research [39]. Current cholesterol management guidelines recommend statin therapy to reduce baseline LDL-C level by 50% in high and very high-risk CVD risk patients with diabetes mellitus for the management of cardiovascular disease [17,40]. Within this context, the relationship between absolute baseline LDL-C thresholds and the cardiovascular protective effects of statin therapy is not well established. Results of a previous meta-analysis of 34 randomized clinical trials (RCTs) consisting of 270,288 patients from the general population suggested that more attention should be given to the baseline LDL-C in treatments with statins [21]. Navares et al. showed that more intensive vs less intensive LDL-C lowering was associated with a greater reduction in risk of all-cause and cardiovascular mortality in trials with higher baseline LDL-C levels. This association was independent of the magnitude of LDL-C reduction and not present when the baseline LDL-C level was less than 100 mg/dl. Change in the rate ratio of all-cause mortality was 0.91 ([95%CI, 0.86 to 0.96]; P Z 0.001) for each 40 mg/dl increase in baseline LDLC level in the meta-regression model [21]. Higher baseline LDL-C levels were associated with progressively greater relative risk reductions in MACE. However, no lower baseline LDL-C threshold for this benefit was observed in the abovementioned study [21]. The limitation of cardiovascular mortality risk reduction to trials with baseline LDL-C of 100 mg/dl and higher was noted in another meta-analysis of RCTs (Relative risk (RR): 0.85 [95%CI: 0.81 to 0.89], n Z 53, (P Z 0.04 for interaction)) [41]. The risk reduction in MACE was independent of baseline LDL-C levels [41]. Similarly, a meta-analysis of RCTs reported that PCSK9 inhibitor therapy added to background statin use may reduce the risk of total and cardiovascular mortality in studies with baseline LDL-C 100 mg/dl [19]. In our meta-analysis of HRs, the association of statin use with MACE and all-cause mortality events in T2D patients was absent in studies with baseline LDL-C levels lower than 100 mg/dl and 130 mg/dl, respectively.

Another meta-analysis of RCTs comparing the effectiveness and safety of treatment to achieve lower (<70) vs higher (70 mg/dl) LDL-C among patients receiving intensive lipid-lowering therapy revealed that cardiovascular and total mortality benefit was limited in studies with baseline LDL-C of patients 100 mg/dl (P Z 0.01 for interaction) [20]. However, Wang et al. showed that the reduction in major vascular events per 1 mmol/l reduction in LDL-C was consistent between groups of trials with different mean baseline LDL-C levels, with no LDL-C level threshold and no significant between groups interaction (p Z 0.23). The risk reduction of MACE was also independent of the presence of the diabetes [42]. Our meta-analysis varied from previous RCTs [20,21,41,42] as they were conducted among the general population while we included observational studies among T2D patients. Furthermore, previous meta-analyses compared more intensive vs less intensive lipid-lowering medications (including statins, ezetimibe, and PCSK9- inhibitor), but we focused on the statins' effectiveness. Similar to our findings, statin use significantly reduced the risk of all-cause mortality in a meta-analysis of real-world cohorts of adults with different chronic conditions, including diabetes (HR: 0.72 [95%CI: 0.68 to 0.76], I2 Z 95%, n Z 54) [43]. Furthermore, statin therapy was associated with a 14% lower risk of all-cause mortality in an observational meta-analysis of older people (aged 65 years) without cardiovascular disease. This association remained significant only in those with diabetes (HR: 0.82 [95% CI 0.68 to 0.98]) regardless of the baseline LDL-C levels [44]. Our results showed that statin therapy is associated with a reduced risk of all-cause mortality (HR 0.60 [95% CI 0.46 to 0.79]) in the overall T2D population. The Cholesterol Treatment Trialists' Collaboration (CTTC) meta-analysis of statin therapy in participants with diabetes (including both type 1 and 2 diabetes) showed that statin therapy reduced the incidence of major vascular events by about a fifth per each mmol/L (39 mg/dl) reduction in LDL-C, with similar proportional reductions in myocardial infarction or coronary death, stroke, and coronary revascularization outcomes, irrespective of lipid profile [18]. Although previous studies showed that the ARR of cardiovascular events with the same relative LDL-C lowering is more pronounced in individuals with higher baseline LDL-C levels [45], we didn't observe a significant trend in ARRs in our stratified metaanalysis. A possible explanation could be the presence of negative ARR values derived from studies by Ramos et al., (B) [30] among individuals more than 85 years old, and Sasso et al. [34], in T2D patients with nephropathy. This observation highlights the importance of real-world data implementation to make more practical clinical guidelines, as such populations with comorbidities and age limitations are generally excluded from randomized controlled trials. Results of the current study warrant a further focus on the potential mechanisms underlying statin treatment effects on atherosclerosis and the association with pretreatment LDL-C levels. Atherosclerosis, described by the formation of plaques on the inner walls of arteries, is the leading cause of MI and stroke development [46]. Plaque stabilization is characterized by stabilizing plaque content and strengthening the overlying endothelium, and plaque regression focuses on the overall reduction in plaque volume [47]. Based on previous findings, LDL-C levels play a role in plaque progression and instability [48,49]. According to serial intravascular ultrasound data analysis, statin therapy was more effective in inducing coronary plaque regression in those with high cholesterol levels and less effective in patients with low cholesterol levels at baseline [50]. Statin therapy significantly influences plaque composition and volume, external elastic membrane volumes, and dense calcium volumes [51e53]. It should be noted that statins have LDL-Ceindependent cardiovascular protective effects as well [54]. However, considering the overwhelming benefits of LDL-C reduction in cardiovascular event prevention, the clinical importance of statins' pleiotropic effects remains debatable. On the other hand, statins have been shown to raise HDL and reduce plasma TG levels [55].

The HDL/TG ratio has been suggested as a marker of insulin resistance associated with diabetes and atherosclerotic outcomes related to T2D [56e58]. Therefore, future studies should focus further on HDL/TG ratio and LDL-C in novel lipid-lowering approaches, particularly in the T2D target population. The current study has several potential limitations that should be addressed. First, due to the observational setting of the included studies in this meta-analysis, the date of the initial check-ups at the time of inclusion was considered the baseline. Therefore, some studies might have included prevalent statin users instead of new users, which could be a source of heterogeneity. Secondly, all the included studies in this meta-analysis compare statin users vs statin non-users in T2D patients regardless of using other medication types, which could be a major source of bias and heterogeneity. An active comparator design in observational studies of therapeutics is recommended to reduce the unmeasured confounding [59]. However, the results of our meta-regression analysis for the incidence rate of outcomes in the untreated group, as a measure of baseline risk in statin non-users, didn't show any significant associations. Furthermore, physician-based evaluation of T2D patients for cardiovascular risk assessments significantly impacts the treatment approach to achieve LDL-C targets according to guidelines. Physicians' misperception of cardiovascular risk, especially in individuals not taking statins, serves as an unadjustable factor that may potentially influence the association between statin use and MACE outcome in T2D patients beyond the direct effects of statins [60]. A high degree of between-study heterogeneity was reported regarding MACE and all-cause mortality outcomes. We applied a random-effect model to address this heterogeneity and performed meta-regression analyses to find the possible sources. None of the covariates assessed in meta-regression models accounted for heterogeneity, except baseline LDL-C level and year of data collection in MACE outcome. Significant increases in the efficacy of statin therapy in T2D patients by mowing towards more recent data collected studies imply the effectiveness of diabetes guidelines in recent years with more specific recommendations on statin use for the prevention of cardiovascular events in this group of patients. Differences in statin type, treatment dosage, adherence to therapy, comorbidities and setting in primary or secondary cardiovascular event prevention, and model adjustments for different sets of variables in each included study were other possible sources of heterogeneity in our meta-analysis. Moreover, we could not perform a metaanalysis of the individual components of the MACE composite outcome, subgroups of men and women, or a within-study analysis of categorized baseline LDL-C levels because of the data limitation. Despite our efforts to acquire individual-level data, we were limited in getting access and we could not apply further analysis in this regard. Differences in statin efficacy across LDL-C levels in each study may be influenced by various biological and clinical factors such as genetic predispositions and comorbidities considering the observational nature of our included studies. The lack of individual-level data of the included studies makes it challenging to explore these factors and their impact on the observed associations which might introduce unmeasured confounding biases. Therefore, the influence of statin therapy on individual cardiovascular endpoints, gender differences, and stratified within-study analysis remains uncertain. The large number of participants included in the analysis (n Z 403,411), in studies with longer follow-up durations and older populations compared to RCTs and performing sensitivity analyses were the strengths of our study. However, our study argues that future RCTs should validate our observations for making clinical recommendations. Future studies should focus on elucidating the relationship between statin use, baseline LDL-C levels, and cardiovascular outcomes in T2D patients by developing new models that consider baseline LDL-C levels, the magnitude of LDL-C reduction and the risk profile of T2D patients. Rigorous RCTs with extended follow-up periods and diverse patient populations are essential to determine the impact of statin therapy, particularly in individuals with higher baseline LDL-C levels.

Moreover, the next studies should explore potential confounding factors like lifestyle factors and other medications used by T2D patients, employ advanced statistical methodologies e.g., propensity score matching and instrumental variable analysis and consider emerging biomarkers and genetic factors to better understand the observed associations. Attempts to identify T2D patients who would benefit more from statin therapy are clinically and economically significant in the era of precision medicine.

Concluding Points

Statin use compared to statin non-use in patients with T2D is significantly associated with a lower risk of major adverse cardiovascular events and all-cause mortality.

Given the modest absolute risk reductions, without statistically significant differences across studies with different baseline LDL-C levels, it is recommended to consider statin therapy for all T2D patients at risk of cardiovascular events.

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