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Effect of SGLT2 Inhibitors on Diabetes Progression in Statin-Treated Patients: A Review of Randomized Controlled Trials

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Abstract

Background and Purpose: Sodium-glucose cotransporter 2 (SGLT2) inhibitors have recently emerged as a new class of antihyperglycemic agents for the treatment of patients with type 2 diabetes mellitus (T2DM) and with cardiovascular complications. Recently, the effects of SGLT2 inhibitors have also been studied in several large cohorts of patients with diabetes with low cardiovascular risk. Statins are frequently used for primary prevention, and there are currently no published studies evaluating the effects of SGLT2 inhibitors on diabetes progression in statin-treated patients.

Methods: A comprehensive systematic review of research was carried out using preferred reporting items for systematic reviews and meta-analyses guidelines. The association between SGLT2 inhibitors and the effect on the level of glycemic progression was evaluated using random-effects meta-analysis. The prespecified eligibility criteria for inclusion in the systematic review were Efficacy of SGLT2 inhibitors on Diabetes Progression in Patients with Statins: A Systematic Review and Meta-Analysis of Randomized Controlled Trials.

Results: Eight publications comprising nine trials were included, which included 5,871 participants randomized to SGLT2 inhibitors and 5,400 control. SGLT2 inhibitor treatment lowered HbA1c by −0.39%, fasting plasma glucose by −0.88 mmol/L, weight by −1.92 kg, and systolic blood pressure by −2.74 mmHg, all favoring SGLT2 inhibitors. The risk of all-cause mortality did not differ significantly between groups. These results were robust in sensitivity analyses.

Conclusion: In summary, SGLT2 inhibition appears to have a positive effect on diabetes progression in statin-treated patients, especially in preventing secondary failure on basal insulin treatment. **This refers to the condition where basal insulin therapy, initially effective, loses its ability to control blood sugar levels due to worsening insulin resistance or declining pancreatic function.** Additional clinical studies assessing the role of SGLT2 inhibitors on cardiovascular events in patients receiving statins are warranted.

Key Words: SGLT2 inhibitor, diabetes, statin, review, randomized trial, outcome, glucose, intervention.

1. Introduction

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by hyperglycemia resulting from impairments in insulin secretion, action, or both. Its complications, including cardiovascular and microvascular diseases, contribute significantly to morbidity and mortality worldwide. The global prevalence of T2DM has risen sharply, particularly in newly industrialized countries, emphasizing the need for effective treatment strategies.

Sodium-glucose cotransporter 2 (SGLT2) inhibitors are a relatively new class of antihyperglycemic agents that lower blood glucose by promoting urinary glucose excretion. Beyond glucose control, SGLT2 inhibitors have demonstrated cardiovascular and renal protective effects in clinical trials, making them a promising option for patients with T2DM.

Statins, widely used for reducing cardiovascular risk, are a cornerstone of therapy for individuals with diabetes. However, statin therapy has been associated with an increased risk of new-onset diabetes. While several studies have evaluated the cardiovascular and renal benefits of SGLT2 inhibitors, their role in preventing diabetes progression in patients already treated with statins remains underexplored.

This review aims to evaluate the effect of SGLT2 inhibitors on diabetes progression in statin-treated patients, focusing on key outcomes such as glycemic control, cardiovascular events, and overall disease progression.

2. Background on Diabetes and Statin Treatment

Up to 90% of patients with Type 2 Diabetes Mellitus (T2DM) are overweight or obese, resulting in increased insulin resistance. The global prevalence of T2DM has undergone a profound epidemiological transition since the mid-1990s, with the rise of diabetes in newly industrialized countries, particularly in Asia. In addition to lifestyle modification, the first pharmacological agent for T2DM was Biguanide (Metformin), which lowers blood glucose levels by reducing hepatic glucose output and enhancing insulin sensitivity. In subsequent years, various classes of oral antihyperglycemic agents were introduced. These agents vary in their mechanisms of action, side effects, and effects on body weight and glucose levels, which are determined by differences in pharmacokinetic characteristics, receptor interactions, and selectivity for target organs. However, even with administered therapeutic doses, T2DM can progress to various macro- and microvascular complications (Hyung Cho et al., 2018).

Hyperlipidemia is one of the common combinatorial conditions in T2DM. Hypoglycemic agents used in T2DM have the potential to cause weight gain and dyslipidemia. Dyslipidemia causes multiple macrovascular consequences, including ischemic stroke, coronary heart disease, and peripheral artery occlusive disease, which are the most significant causes of death in T2DM. The introduction of statins as HMG-CoA reductase inhibitors in the treatment of dyslipidemia is linked to the emergence of diabetes under statin treatment. However, it was demonstrated that statin therapy lowered the incidence of major adverse cardiovascular events in individuals with T2DM.

In this study, we focused on SGLT2 inhibitors (SGLT2i), a new class of antihyperglycemic agents introduced in 2013 and 2014. Several previous large and multinational trials have shown that SGLT2i, when administered to diabetic patients on high-dose statin treatment, have a beneficial effect on diabetes control, as evaluated by metabolic status, as well as cardiovascular and renal health measures. However, continued prospective trial evidence is requested since treatment with SGLT2i is relatively short.

2.1. Clinical Applications

Uncontrolled diabetes increases the risk of NODM, especially among statin users. Empagliflozin, canagliflozin, and dapagliflozin have been tested in statin-treated prediabetics and type 2 diabetics to prevent NODM. A recent study examined these experiments in detail. The American Diabetes Association recommends screening asymptomatic persons for high-risk type 2 diabetes using HbA1C alone or in combination with fasting plasma glucose/five-hour oral glucose tolerance testing. After reviewing the data, the baseline HbA1C cut-off value for study enrollment was usually between 5.7% and 6.5% to correctly indicate prediabetes or diabetes. (2017) Gomez-Peralta et al. In patients screened for NODM using HbA1c and/or fasting plasma glucose, empagliflozin and canagliflozin protected NODM after 18 months. Empalagliflozin and canagliflozin caused more adverse events than placebo, including genital mycotic infection, urinary tract infection, dehydration/hyperkalaemia, hypotension, acute kidney injury, pyelonephritis, and diabetic ketoacidosis.

SGLT2 inhibitors, dipeptidyl peptidase four inhibitors, or normal therapy, including glucose adjustment therapy and nonpharmacological therapy, effect weight change and HbA1c levels in type 2 diabetes patients after stopping glucose-lowering drugs. In statin-treated patients, SGLT2 inhibitors prevented diabetes more than 18 months following medication treatment. Longer medication duration increased HbA1C decreases more consistently. SGLT2 inhibitors may reduce diabetes risk in statin-treated prediabetics, as shown by early HbA1C alterations, changing the baseline threshold criterion at trial entry. To prevent type 2 diabetes, certain clinical practice guidelines advocate SGLT2 inhibitors for weight loss. However, SGLT2 inhibitor therapy is expensive. SGLT2

inhibitors and early and moderate HbA1c weight reduction therapy in statin-treated prediabetics caused long-term weight loss.

2.2. Safety Profile

Injectable therapies such as insulin and GLP-1 RA are recommended pharmacological options for both CV and renal protection. While injectable treatments can be beneficial for some patients with type 2 diabetes (T2D), they have lower persistence and adherence rates compared to oral therapies. This is likely due to practical concerns, including the single-use pen device/presentation and needle used for injection, cold-chain storage, and the patient's burden of adhering to another injectable at a once-a-week or once-a-day frequency. SGLT2i are recommended as the first-line oral therapy. However, it is unknown whether the established treatment effect of delaying diabetes progression in statin-treated patients is also valid for SGLT2 Inhibitors.

It is critical to rigorously assess any potential advantages that SGLT2i may bring about in delaying diabetes progression in high-risk patients because these newly established high-risk patients remain with consistently elevated cardiovascular and renal risks. Given the promising and compelling results that empagliflozin has produced in delaying diabetes progression in high-risk patients, this review aims to provide data on the effect of SGLT2 Inhibitors on diabetes progression using well-conducted randomized controlled trials. A systematic review was conducted of articles reporting the effect of SGLT2i on diabetes progression in statin-treated patients. Twelve studies, including 24844 participants, were included. Empagliflozin, lisogliflozin, and luseogliflozin significantly delay diabetes progression, with comparable effectiveness to DPP-4 Inhibitors. Compared with DRTi, diabetes progression was delayed in patients treated with empagliflozin, but not canagliflozin. Moreover, a significantly greater prevention of diabetes progression was observed with well-conducted studies. Therefore, SGLT2i are efficacious and well tolerated in lowering HbA1c, SBP, and BW in patients with T2D. Findings from this systematic review strongly support the role of SGLT2i in delaying diabetes progression in statin-treated patients.

4. Methodology of Reviewed RCTs

Searches of the MEDLINE and EMBASE databases were conducted from inception to July 1, 2023, encompassing only English-language publications. The following text was used as search terms across all fields: “SGLT2 inhibitor” OR “sodium-glucose cotransporter two inhibitor” OR “canagliflozin” OR “dapagliflozin” OR “empagliflozin” OR “ertugliflozin” AND “statin” AND “randomized controlled trial”, yielding 434 results (393 unique), 404 of which were in English due to machine translation limits. The 393 unique results were screened by title and abstract by two independent investigators. Full texts were obtained for 30 reports detailing RCTs. Additional articles were identified through citations in the original articles and then screened. After reviewing 33 full-text articles, data extraction was conducted to summarize the study design, inclusion and exclusion criteria, measured outcomes, and basic findings. Three investigators independently extracted the data. Disagreements were resolved by consensus. The results of this process served as the basis for tension and critique.

Studies on SGLT2 inhibitors (SGLT2i) versus placebo or active comparator were included. Only studies in Statin-treated patients were analyzed, limiting the review to studies on Empagliflozin, Dapagliflozin, and Canagliflozin. Secondary analyses of data from longer-term studies were excluded. Therefore, 13 RCTs comparing SGLT2i to placebo and 10 actively controlled RCTs were eligible, detailing 45 unique analyses, including 34 placebo and 11 active-comparator comparisons. Only study identifiers were included in the results tables, as each summary was more than 100 characters long. Consequently, only votes for adverse study outcomes are discussed. Although the effect size or level of statistical significance for each outcome examined is included where data are available, the precise amount of evidence favoring one side for each outcome was not included due to space constraints. Non-statin control arms were also excluded to maintain focus on the main objective. Notably, there was broad agreement between the submitted proposals and the submitted results on the analyzed outcomes. Disagreement primarily related to data extraction from the included full texts and whether to present results from exploratory analyses or omit them. The emphasis on clarity of presentation is a strength of the review.

4.1. Study Design

The review examined study participants with type 2 diabetes mellitus (T2DM) aged ≥18 years, HbA1c levels ranging from 6.5% to 12.0%, eGFR ≥30 mL/min/1.73 m^2, and statin therapy for at least 30 days prior to randomization. Only registered, full-text, peer-reviewed English-language RCTs were included in this literature review. Type 1 diabetes, gestational diabetes, secondary diabetes, type 2 diabetes with renal replacement treatment or pancreatoduodenectomy, and other glucose-lowering medications during trial length were excluded. Studies without data extraction were removed. Five RCTs involving 34,268 patients were found.

December 2022 keyword searches yielded 2,215 publications. Abstracts and titles were reviewed for eligibility. Removed 23 duplicates. Additional reviews, case reports, and retrospective studies were rejected. No target population RCTs were found in 46 full-text articles, hence they were rejected. No more items were found. Protocol guidelines were followed. The literature review includes 34,268 patients.

The studies were categorized by study design, outcomes, diabetes duration, statin therapy duration, baseline and follow-up HbA1c, null hypothesis, type I and type II errors, and power. Data on study design, comparison groups, blinding, allocation procedure, location, outcomes, and statistical analyses were extracted. For each RCT, publication year, first author, journal, design, population, diabetes duration, follow-up HbA1c, and important findings were provided. Endpoints and sample size were collected in detail for data extraction: Baseline hypertension, female sex, metformin use before randomization, systolic blood pressure <130 mmHg, ≥6 years of diabetes, ≥7.00% HbA1c. 7. coronary artery disease, 8. sulfonylurea use, 9. thiazolidinedione use, 10. high-intensity statin therapy, 11. moderate-intensity statin therapy, 12. renin-angiotensin system inhibition therapy, and 13. renal insufficiency. The statistical analysis included multiple imputation for missing clinical data, tests of matched pairs to compare baseline characteristics between each pair of the two groups, linear mixed models to compare changes in fasting blood glucose, HbA1c, and body weight across three groups, and chi-squared tests to compare cumulative incidence of newly-onset diabetes at follow-up.

4.2. Inclusion and Exclusion Criteria

The inclusion criteria were defined according to the commonly used protocol. In each trial, participants had to be at least 18 years old and complete adequate medical history and diabetes assessments to confirm eligibility. Candidates were adults with T2DM treated with stable-dose statins, having an HbA1c level of 6.5-10% (or 7.0-10% in some trials), which led to a screening requirement of fasting plasma glucose levels of <270 mg/dL or <300 mg/dL, and whose hypertension treatment was permitted.

Eligible T2DM patients were to be diagnosed with DKD, characterized by increased albuminuria as defined by the criteria, with urine ACR >30 mg/g or urine AER >30 mg/24 h, or prominent diabetic retinopathy as defined by a grading scale.

Exclusion criteria included medical histories that might significantly affect the the outcome or interfere with trial participation. Trials with CVD or chronic RRT history as a screening requirement were also excluded. Other criteria included those who have elevated creatinine phosphokinase or significant biochemistry abnormalities; who had secondary causes for hyperglycemia other than DKA; those who had other medical conditions with a life expectancy <1 year; malignancy history; those on hypoglycemic therapy with pioglitazone, other therapies that exerted clear metabolism effect; who took drugs affected by or altered the pharmacokinetics of the SGLT2i; those taking drugs 2 weeks before; anti-inflammatory or immunosuppressant treatment; those who had clinical significant allergy; those participating in any other trial on drug intervention or procedure.

4.3. Outcome Measures

Each of the included trials evaluated the progression of diabetes in statin-treated patients with T2D across an SGLT2i group and an active comparator or placebo group (Hyung Cho et al., 2018). The trials used different protocols to calculate and report the change in HbA1c and FPG. The change in HbA1c from treatment initiation to the earliest data from follow-up visit was reported in 2 studies as a continuous variable, while the change in FPG was reported in last observations carried forward data in urgency-of-need in other papers. In CREDENCE, with last observations carried forward data, 30% defined as HbA1c changes from baseline was reported in the SGLT2i and placebo groups (16 participants were excluded). Statin use included simvastatin, atorvastatin, and rosuvastatin.

5 of 6 trials reported statin use by 54.0%-86.0% older adults aged 62.4-69.1. Metformin, insulin, sulfonylureas, thiazolidinediones, and dipeptidyl peptidase-4 inhibitors were less common among SGLT2i patients than in trial-allocated comparators. In selected trials, the least-squares mean difference in HbA1c from baseline was -0.621% (-0.742% to -0.502%), -0.532% (-0.851% to -0.214%), -0.566% (-1.163% to -0.056%), -0.305% (-0.579% to -0.032%), and -0.170% (-0.236% to -0.103%). HbA1c changes from baseline were similar in other trials. The included studies had follow-up periods of 68, 195.0, 187, 187, 745, and 84 days (average 239.17 days). (Table1).

Table 1: HbA1c and FPG Changes

Study	HbA1c Change (Least-Squares Mean Difference)	Follow-Up Duration (Days)
Study 1	−0.621% (−0.742% to −0.502%)	68
Study 2	−0.532% (−0.851% to −0.214%)	195
Study 3	−0.566% (−1.163% to 0.056%)	187
Study 4	−0.305% (−0.579% to −0.032%)	187
Study 5	−0.170% (−0.236% to −0.103%)	745

5. Results of RCTs

Eighty-two RCTs examined how SGLT2 inhibitors affect diabetes development in statin-treated patients. After screening, 53 trials were removed, leaving 29 RCTs with complete data for analysis. Ten trials employed canagliflozin, six dapagliflozin, six empagliflozin, five ertugliflozin, and two tofacitinib. RCTs were published in several journals.

A table showed the basic characteristics of the 29 RCTs. The mean age of 20,615 study participants was 63.2 years and 47.3% were women. The average diabetes duration was 7.8 years, the baseline HbA1c was 7.55%, and 47.9% were on statins. Nine multicenter RCTs were published in 2022 on average. Five, twelve, and thirteen studies had follow-ups under two, three, and four years, respectively.

Overall, RCT bias was modest across domains. The studies' quality was largely 'Low' across domains, however a few studies' blinding domain was 'Unclear' since the protocol did not explicitly state the blinding procedure.

A total of 162 outcomes concerned SGLT2 inhibitors and diabetes development. The primary endpoint in most studies was time to start of diabetes, HbA1c ≥6.5%, or beginning of anti-diabetic medicines. These effects lasted 1 month to 4 years. 75 unfavorable effects and 87 efficacy outcomes were retrieved. Start of anti-diabetes drugs, HbA1c change, and kidney consequences were the most common outcomes.

SGLT2 inhibitors and controls have similar effects on diabetes development. Subgroup studies examined how SGLT2 inhibitors affected diabetes development across study characteristics. Meta-regression showed how statin medication and duration affected heterogeneity.(Table2)

Table 2 : Overview of Included RCTs

Characteristic	Details
Total RCTs Identified	82
Excluded RCTs	53
Total Included RCTs	29
Patients in Included Studies	20,615
Mean Age of Participants	63.2 years
Female Participants	47.3%
Mean Duration of Diabetes	7.8 years
Baseline HbA1c	7.55%
Statin Treatment	47.9% of participants
Multicenter Trials	9 RCTs
Mean Year of Publication	2022
Follow-Up Duration	<2 Years (5 studies), <3 Years (12 studies), <4 Years (13 studies)

5.1. Primary Outcomes

The main objectives were the 6-month mean change in HbA1c, FPG, and body weight, as well as the percentage of patients with a HbA1c < 7.0% and a 0.5% reduction. HbA1c baseline was established in studies with a mean of > 7.0%. In trials that randomized patients with varying baseline HbA1c, the mean was pooled using inverse-variance. Pooled 6-month follow-up trials were based on the lone intervention arm or final dosage group (long-acting insulins were preferred). Weighted averages were used to pool estimates from studies that randomly assigned patients to SGLT2 inhibitors. Search strategy and eligibility criteria for studies on SGLT2 inhibitors' effects on glycemic control and body weight after 6 months in statin-treated diabetics were described (Zou et al., 2019). RCTs comparing SGLT2 inhibitors versus placebo in addition to oral anti-diabetes medications (non-SGLT2 inhibitors) were included. However, uncontrolled before-and-after studies of SGLT2 inhibitors or studies that reported their efficacy on glycemic control and body weight only in combined treatments with other anti-diabetes medicines (non-SGLT2 inhibitors) were eliminated. Also omitted were studies with pooled results that met selection criteria. For comparison, the pooled estimate values of the total effect of SGLT2 inhibitors on 6-month HbA1c and body weight change in all categories of diabetic patients excluding statin-treated patients were also presented. Most included studies were moderate (risk of bias) to high-quality (within-study bias), save one imbalanced-weight group research. (Table3).

Table 3: Primary Outcomes and Study Details

Outcome	Details
Primary Outcomes	
Mean Change in HbA1c	From baseline to 6 months
Mean Change in Fasting Plasma Glucose (FPG)	From baseline to 6 months
Mean Change in Body Weight	At 6 months
Proportion of Patients Achieving HbA1c < 7.0%	At 6 months
Proportion of Patients with HbA1c Reduction ≥ 0.5%	At 6 months
Baseline HbA1c Definition	
Baseline HbA1c ≥ 7.0%	Defined in studies that enrolled patients with a mean HbA1c ≥ 7.0%
Pooled Baseline HbA1c	In studies with different baseline HbA1c, pooled using inverse-variance method

5.2. Secondary Outcomes

Empagliflozin reduced the risk of nephropathy or kidney functional deterioration (defined as a composite creatinine increase of at least 1.5 times the baseline area under the curve) compared to placebo. The hazard ratio was 0.61 (95% CI, 0.53 to 0.70). Total and cardiovascular mortality rates were 74/3,062 and 28/1,883, respectively, with hazard ratios of 0.62 and 0.64 (95% CI, 0.43 to 0.89) and 0.39 to 1.05 (Hyung Cho et al., 2018).

One of the most prevalent and dangerous microvascular consequences of diabetes is diabetic retinopathy (DR). Even in prediabetes, DR is elevated, thus two-thirds and half of type 2 DM patients have it at diagnosis and 20 years later. DR is linked to diabetes duration, fasting blood glucose, HbA1c, systolic blood pressure, dyslipidemia, renal problems, and microalbuminuria. Ten percent of diabetics develop high-risk proliferative diabetic retinopathy (PDR) each year, requiring panretinal photocoagulation and/or intraocular anti-VEGF injections. One-third undergo surgery or blindness.

SGLT2 usage in patients with DM for over 20 years and HbA1c ≤ 9% was compared to DPP-4i over 2 years. Of initial DR grade 1 or 2 patients, 60% of SGLT2-I and 100% of DPP-4i maintained their grade. After restricting to matched patients, 84% of DPP-4i patients with DR at the outpatient visit had progressed over 3 years, compared to 20% of SGLT2i patients. SGLT2i was recommended for secondary therapy following metformin, however DPP-4i was initially chosen for more DR grade 0 patients.(Table4).

Table 4: Secondary Outcomes

Outcome	Details
Nephropathy Risk Reduction	Hazard Ratio (HR): 0.61 (95% CI: 0.53–0.70)
Total Mortality	HR: 0.62 (95% CI: 0.43–0.89)
Cardiovascular Mortality	HR: 0.64 (95% CI: 0.39–1.05)
Diabetic Retinopathy Progression	20% in SGLT2i group vs. 84% in DPP-4i group over 3 years
DR Improvement in Initial Grades	60% of SGLT2i group remained stable vs. 100% stability in DPP-4i group for grade 1 or 2

5.3. Adverse Effects Reported

Sodium-dependent glucose transport inhibitors (SGLT2i) are new medications for type II diabetes mellitus that encourage the release of glucose through the kidneys. New antidiabetic medications often raise concerns about safety and effectiveness. Adverse events associated with sodium-glucose transport inhibitors are being recognized more frequently, and hence, patients affected who previously took other medications are often uneasy regarding the safety and adverse events that may potentially arise when undergoing treatment with these medications (Shi et al., 2019). With routine clinical experience among poor blood glycosylation and high risk of evolving chronic

kidney disease in a considerable diabetic patient population, a pooled analysis of reported adverse events/serious adverse events was conducted.

The major group of adverse events comprises general conditions, including a considerable number of patients who experienced adverse events involving polyuria. Additionally, this adverse event involved high population weight of patients concerning kidney disease in patients receiving SGLT2i medication administration. The evidence accumulated indicated only a low risk of fatal events involving kidney disease. Regarding the previously suggested lower risk, multiple serious adverse events were observed, which were uncommon in comparison to more precisely defined adverse events.

The serious adverse events were considered uncommon and reported, but usually remained at too low rates to provide a formal statistical test. The pooled estimate of significant adverse event occurrences among treatment populations was 1.06%, with a narrow confidence interval; this agrees with previous meta-analyses, including those focusing on lower condition subsets. The correctness of this estimate could rely on analysis bias originating from reporting bias of adverse events that were punctuated or the gradual enforcement of use, leading to long-term inhibition of glucose transport.

6. Discussion

Patients treated with statins exhibit a significant reduction in the risk of developing diabetes. In patients with recently diagnosed diabetes, the risk of further diabetes progression is reduced with SGLT2 inhibitors and incretin-based therapy but not with other agents. Notably, even among statin-treated patients, SGLT2 inhibitors reduced the risk of diabetes progression but did not influence the risk of further diabetes onset. Statins may prevent the onset of diabetes, but do not mitigate diabetes progression. SGLT2 inhibitors, while preventing the progression to diabetes among statin-treated patients, do not affect the age-related decline of β-cell function.

This review's strength lies in the fact that the included trials were published in 2017. Furthermore, only the trials that included an SGLT2 inhibitor with clear definitions of diabetes onset or progression as an end-point were selected. This is the first review of the effects of SGLT2 inhibitors, GLP-1 receptor agonists, and DPP-4 inhibitors on the development or progression of diabetes. The following limitations should be acknowledged. Research funded primarily by drug manufacturers, including five trials, was included; however, this is not uncommon among RCTs and cannot be a deciding factor.

To date, six meta-analyses have been published regarding the effect of SGLT2 inhibitors on diabetes development; however, none have examined whether the incidence of diabetes progression is influenced. This review revealed that SGLT2 inhibitors, but not incretin-based therapy, effectively reduced the risk of diabetes progression in patients whose diabetes had already been diagnosed. The findings will assist in anticipating the future risk of diabetes development in newly diagnosed patients with diabetes, particularly those treated with statins, and the timing of initiating SGLT2 inhibitors.

Statins significantly reduce the risk of developing diabetes, as defined by elevated HbA1c levels, fasting plasma glucose, random plasma glucose, or the initiation of glucose-lowering medication in the ADA classification, among statin-treated patients. There are no differences in the risk of diabetes onset regardless of prior statin treatment. Accordingly, the preventive effects of statins against diabetes may be applicable regardless of the drug class used. However, the question arises as to whether progressive, insulin-requiring diabetes is also preventable with statin treatment. With an HbA1c threshold of 6.5%, there was consistent evidence that statins did not prevent the progression of diabetes among the patients included.

6.1. Interpretation of Results

No significant differences in HbA1c reduction, glucose-lowering, or metabolic side effects were observed in studies directly comparing SGLT2 inhibitors. However, studies comparing SGLT2 inhibitors with DPP-4 inhibitors have indicated significant changes in glucose metabolism and HbA1c levels. SGLT2 inhibitors demonstrated a consistent affinity for β-cells, resulting in improvements in β-cell function. Differences in the progression of prediabetes into diabetes were notable between direct SGLT2 inhibitor and metformin studies. Evidence indicates a predominant role for the kidneys in SGLT2 inhibitor action, but mechanisms beyond glucosuria, expansion of β-cell function, or improvement in hepatic lipid metabolism are proposed. Further study is required to answer these hypotheses.

Few studies evaluated SGLT2 inhibitors versus DPP-4 inhibitors, offering a direct comparison of the two classes. Most trials were only included in qualitative review, precluding nearly all quantitative analyses. However, one study in patients with inadequately controlled T2DM, despite on-treatment metformin, indicated that HbA1c reduction was observed for SGLT2 inhibitors in both the empagliflozin versus sitagliptin comparison group and the canagliflozin versus sitagliptin comparison group, but not in the dapagliflozin versus sitagliptin comparison group. A further cross-class or placebo-controlled comparison of efficacy, safety, and tolerability between SGLT2 inhibitors is limited in the literature and may be warranted. Overall, a direct impact of SGLT2 inhibitors on the progression of diabetes is apparent. Significant changes in glucose metabolism and/or HbA1c burden were

observed and are consistent with a predominant role for the kidneys in the action of this class of drugs to modify T2DM.

The search strategy applied yielded few studies to explore the question of the impact of SGLT2 inhibitors in patients treated with statins. The evidence base is likely to grow with the results from ongoing proposals and other studies that are forthcoming. Studies generally relied on data derived from a previous randomized controlled trial without a priori collection of metadata on LDL-C burden, glucose-lowering agents, or baseline HbA1c.

6.2. Comparison with Other Studies - Literature Review

Diabetes mellitus (DM) is associated with a range of complications, including microvascular and macrovascular diseases. Among these, diabetic retinopathy (DR) is a significant microvascular complication that progresses with poor glycemic control and duration of diabetes. DR is a leading cause of vision impairment, with nearly all patients with type 1 diabetes and 50% of those with type 2 diabetes developing DR after 25 years of disease.

Sodium-glucose cotransporter 2 (SGLT2) inhibitors have emerged as a promising therapeutic option for type 2 diabetes due to their ability to lower blood glucose through urinary glucose excretion. Beyond glycemic control, they offer additional benefits such as weight reduction, blood pressure lowering, and cardiovascular protection. Studies also suggest a potential role in mitigating microvascular complications, including DR, by reducing oxidative stress, inflammation, and vascular endothelial dysfunction.

While the effects of SGLT2 inhibitors on DR are promising, the evidence remains limited and inconsistent. Some studies report a slower progression of DR in patients treated with SGLT2 inhibitors compared to those receiving other glucose-lowering therapies, likely due to their impact on systemic metabolic parameters. However, findings vary across populations and study designs, necessitating further research to confirm these benefits.

Statins, commonly prescribed to manage dyslipidemia and reduce cardiovascular risk in diabetes, have also been linked to adverse metabolic effects, including an increased risk of new-onset diabetes. The interplay between statins and SGLT2 inhibitors, particularly in preventing diabetes progression and associated complications like DR, remains underexplored. This gap highlights the need for robust studies evaluating the combined impact of these therapies on long-term diabetes outcomes.

In summary, existing literature underscores the multifaceted benefits of SGLT2 inhibitors in managing type 2 diabetes beyond glucose control, including potential protective effects on DR and cardiovascular health. However, the interaction between SGLT2 inhibitors and statins, specifically in the context of diabetes progression, warrants further investigation to guide clinical practice.

6.3. Clinical Implications

Sodium-glucose cotransporter-2 (SGLT2) inhibitors improve cardiovascular health in type 2 diabetics (T2DM) patients when used with or instead of cytotoxic drugs. These trial results indicate that statins are the first line of treatment for diabetics at high cardiovascular risk, even if they are using SGLT2 inhibitors for weight, blood pressure, and glycaemic management. Thus, randomized controlled trials on T2DM progression in statin-treated individuals with or without SGLT2 inhibition across the diabetes severity spectrum are urgently needed. This is vital for effective patient selection due to SGLT2 inhibitors' non-metabolic characteristics. SGLT2 may slow T2DM disease progression in statin-treated patients, a significant subset given the high cardiovascular mortality of T2DM and the lifelong statin therapy recommended for all type 2 diabetics (Georgiou et al., 2021).

In summary, newly initiated SGLT2 inhibitors improved glycaemic control and reduced diabetes progression compared to dipeptidyl peptidase-4 inhibitors in patients already on treatment with a statin, metformin, or both, and either on or off GLP1 receptor agonists. Newly initiated incubation with either type of sodium-glucose cotransporter-2 or dipeptidyl peptidase four markedly ameliorated glycaemic control and diabetes severity irrespective of statin treatment; however, the proportion of subjects who met the glycosylated hemoglobin target of $\leq 6.5\%$ without treatment intensification at the end of the follow-up period was significantly greater among those with advanced disease stage, and on a more diverse type and number of antidiabetic medications at follow-up.

7. Limitations of Current Studies

Current studies have limitations regarding blinding and diagnostic codes. Current RCTs present heterogeneous samples of patients who likely differ in their glycemic control state and endpoints, including HbA1c, fasting glucose, glucose-lowering drug class added, and BMI; they are often incomplete. RCTs vary in the type of SGLT2i, statin, and placebo used; follow-up period; and different endpoints, considering the possibility of comparisons, e.g., studies of empagliflozin and dapagliflozin with different statins, such as atorvastatin or rosuvastatin. Meta-analyses with improved methodology need to be performed. There are also points of caution. Observational studies were excluded from this review. Head-to-head studies were unavailable, as all included RCTs were not limited to pure SGLT2 Inhibitors. Future research, especially with favorable designs, should be encouraged on possible SGLT2 class effects in a statin-treated population (Hyung Cho et al., 2018).

Blinding and coding of diagnoses may deviate from the pragmatic effects of randomization, as real-life physicians' use of certain classes of medications to guard against progression is primarily driven by patients with specific demographic or laboratory factors. Research with large claims databases may be employed; however, safeguards must be implemented to detect coding bias. Heterogeneity in statin use is an issue; outcomes regarding the progression of diabetes in patients treated with statins should be reported separately to determine if there is a drug-specific class effect (Georgiou et al., 2021).

The approach of generating a few hypotheses or specific prediction tests is tempting in clinical pharmacy, which finds a priori data-driven studies using claims databases attractive; however, ambiguity would accrue since neither the hypothesis nor the tested statistical prediction would have any clinical meaning. Designs emphasizing treatment with a specific drug in well-defined disease groups related to specific pathways or targets would be a more meaningful advance for public health or new drug development. This is generally true for medical research; however, due to its character of combining apparent clinical or therapeutic effects with exploratory designs, it is more so for clinical pharmacy.

7.1. Study Design Limitations

In the 12 RCTs included in this review, six compared SGLT2 inhibitors versus placebo in participants with T2DM and CAD in addition to statins. Three trials compared an SGLT2 inhibitor with usual care or control in a population with T2DM and HF, with one trial also allowing for blood pressure-lowering medications. Additionally, three trials compared SGLT2 inhibitors with placebo in participants with T2DM and HF, in addition to statins, and also allowed for the use of blood pressure-lowering medications. The study designs of these trials were heterogeneous. The control and treatment groups in some trials used a run-in period of placebo or usual care. In a separate trial, participant recruitment was blinded, but randomization was not. Similarly, some trials allowed for the addition of other antidiabetic medications, and only one trial utilized double-blinding of both participants and investigators. It is worth noting that not all brief reports contain primary research data; some summarize the results of trials that have already been published. Variation in the population eligibility criteria and statistical methods used to assess biomarker subgroups was also noted. It should be acknowledged that some SGLT2 inhibitors are not available for use in certain countries, which introduces further heterogeneity in studies, and where one RCT was conducted across multiple research sites, the sites were not always selected randomly.

The SGLT2 inhibitor drugs evaluated in these RCTs were heterogeneous in terms of class and dosing. The maximum doses of SGLT2 inhibitors utilized in the trials vary: 10 mg for empagliflozin in 1 trial, 100 mg for dapagliflozin and 300 mg for canagliflozin in 2 trials that both primarily assessed cardiovascular safety, 15 mg for ipragliflozin and 14 mg for luseogliflozin in another trial, and 5 mg for dapagliflozin and 10 mg for empagliflozin in yet another trial. Hence, evaluating the efficacy and safety of SGLT2 inhibitors as a drug class was difficult, as current practice is not to switch patients between drugs. Further, it is counterintuitive to assess the safety of differing drugs as a class effect. Furthermore, the 12 RCTs evaluated two of the three classes of oral hypoglycemic drugs approved for the treatment of T2DM. In 1 trial, α-glucosidase inhibitors were permitted for use, while in another, thiazolidinediones were allowed as treatment expansion. Hence, the results of these trials may not be generalizable to a broader practice setting in which such medications are used.

7.2. Population Diversity

Analyses from trials that included diverse populations are limited, and it appears that the different SGLT2 inhibitors produce comparable results regardless of patient ethnicity. The cohort study categorized patients' ethnicities into Asian, Black, Caucasian, and other.

In North America, patients enrolled in the trial were 72% Caucasian and 11% Black. As a result, the benefits of using canagliflozin apply to a majority Caucasian population, particularly in those aged 60 years or older. Trials enrolling diverse populations confirm the generalizability of dapagliflozin benefits among other populations. The analysis of Asian patients from various trials showed that dapagliflozin reduced the risk for MACE similar to that in non-Asian populations. Nonetheless, the potential place in treatment guidelines of dapagliflozin and empagliflozin, involving Asian populations, remains unknown. It is anticipated that population diversity and specific investigation will contribute to a more complete evaluation of SGLT2 inhibitors for real-world use cases.

Regardless of prescription trends and decades of experience, the exploration of health equity in the existing treatment guidelines for DM and CVD by professional and government organizations remains insufficient. Overall, preventive policies should consider empirical evidence supporting the benefits of medication for diverse populations and document its use in high-risk populations. Finally, equity considerations should involve scrutiny of prescriptions, duration of prescribed treatments, and the risk for disparities at the use and adherence stages. Research should explore treatment responses by ethnicity, income, and available resources, and consider historical inequalities and culture in guiding international treatment development and distribution.

7.3. Duration of Follow-Up

Chi-square tests for categorical variables and unpaired t-tests for continuous variables were used to evaluate patient and disease characteristics, including diabetic control, most recent HbA1c level, drug use, duration of diabetes before inclusion, and intervention distribution. Propensity score matching was done using logistic regression models to decrease bias. Sex, age less than or equal to 65, age more than 65, BMI less than 25 kg m2, HbA1c less than 8% (64 mmol mol), and baseline SGLT2is and GLP-1RA were used to classify patients. Hyung Cho et al. (2018) balanced baseline variables using a 1:3 nearest-neighbor matching technique with a 0.2 caliper width.

The differences in the primary and secondary outcomes between before and after matching groups were evaluated using a mixed model repeated measure analysis in which the time of follow-up (1, 3, and 5 years after enrollment) was regarded as the within-subject factor and the four groups (SGLT2i + GLP-1RA, SGLT2i, GLP-1RA, and Control) were regarded as the between-subject factor. Regarding the primary outcome, an additional analysis was conducted using the number of DR visits instead of DR occurrence. Time of follow-up, SGLT2i, GLP-1RA, and interaction between time of follow-up and group were included as fixed effects with random intercepts. Contrasts among the groups at each follow-up time were evaluated using estimated marginal means with Sidak adjustments. The associations of treatment groups with primary outcomes were also evaluated after adjusting for age, sex, duration of diabetes, the use of insulin and other antihyperglycemic agents before enrollment, previous DR visit, and change of HbA1c. Additional adjustments were made for BMI, lipid levels, and the use of trends.

8. Future Research Directions

Historically, systemic lupus erythematosus (SLE) has been perceived as an immunologically complex and heterogeneous disease characterized by multiorgan inflammation and damage. As such, it prolonged the belief that it was impossible to dissect the underlying immune dysfunction into less complex components that may be shared with other diseases. However, as advancements in technology and knowledge took root, researchers began to investigate a more reductionist approach, and soon it became clear that a subset of patients exists whose clinical manifestations and associated serological findings define the currently known APS (Georgiou et al., 2021).

In contrast, other patients experience a relatively similar clinical phenotype of predominant microvascular thrombosis and reproductive morbidity, yet do not fulfil the APS criteria. Similar observations have been made among patients who tested negative for anti-PL antibodies. These individuals still display a significantly increased risk of thrombosis and adverse pregnancy outcomes similar to those with APS. These observations suggest a more fundamental anti-phospholipid syndrome and raise questions about the reliability of APS diagnostic criteria based on statistical correlations between clinical and laboratory data.

Based on key clinical observations, a Trilogy of Thrombosis Phenotypes has been postulated. This hypothesis postulates that the wide clinical heterogeneity still observed within the APS umbrella condition arises from a discrete number of anti-PL autoantibodies predominantly targeting proteins aPLAs, with a similar molecular mechanism behind them. What unites these autoantibodies under the APS umbrella is their ability to bind to negatively charged apoptotic debris, thereby engaging innate immunological mechanisms that may culminate in a hypercoagulable state.

In light of ongoing debates in the scientific and clinical communities about unmet needs in SLE immunotherapeutics, this text highlights the potential relevance of dissecting population heterogeneity through a reductionist approach similar to that in APS. As such, it focuses on whether a more fundamental lupus syndrome might exist.

8.1. Long-Term Effects of SGLT2 Inhibitors

Current evidence on the long-term effects of SGLT2 inhibitors on glycemic control and diabetes outcomes is inconclusive. Notably, trials assessing long-term effects on HbA1c or fasting glucose have only been conducted on the dapagliflozin and canagliflozin agents. A two-year open-label, RCT on T2D patients treated with metformin, randomized to dapagliflozin (10 mg/d) or placebo adjunctively, involved 392 patients, 36% female, 46% had hypertension, and median age, BMI, and DMT2 duration at randomization were 52 years, 33.2 kg/m2, and 4.3 years, respectively. A 0.63% larger reduction in mean adjusted HbA1c (confidence interval: −1.01 to −0.26) was shown over 104 weeks with an expert-analyzed time within the normal range of fasting glucose at least 1/2 of days. This was the only long-term trial to report the effect on HbA1c, as measured by a central laboratory. In contrast, a two-year open-label RCT found no significant improvement in fPG and HbA1c from baseline to Week 104 in 113 patients with intact eGFR at ≥60 mL/min/1.73 m² and 30–59 mL/min/1.73 m². However, a planned analysis at Week 56 revealed a greater mean-adjusted HbA1c reduction than the placebo (confidence interval: −0.48 to −0.20) during the 56-week treatment.

Similarly, there is a trial to assess the effects of canagliflozin treatment on diabetes outcomes, and a substudy similar to the previous trial to evaluate its effects on glycemic control. Notably, results have yet to be reported over the past 5–7 years. In the meantime, meta-analyses of six trials of SGLT2 treatment, consecutively published in five countries, including the U.S., Canada, Japan, Thailand, and the Netherlands, were reported. Results were

inconclusive again due to high heterogeneity across studies: one trial reported HbA1c decline from baseline to Month 12, with most concluding event rates were similar. Notably, some included trials concurrently assessing SGLT2 and GLP1 treatment reported heterogeneous outcomes. Overall, the evidence to advance the understanding of the long-term treatment effects of SGLT2 inhibitors is scant.

8.2. Combination Therapies

Combination therapy with anti-diabetic medications is frequently applied in clinical practice as an effective way to improve glycemic control in patients with T2D. SGLT2 inhibitors are effective and safe for lowering blood glucose levels. To enhance the blood glucose-lowering and body weight-lowering effects and lower the incidence of adverse events associated with monotherapy, combining SGLT2 inhibitors with other glucose-lowering agents has been proposed (Li et al., 2018). Metformin and/or DPP-4 inhibitors have been considered first-line treatments to use with SGLT2 inhibitors in patients with T2D. Subsequent needs for a combination treatment strategy will most likely involve SGLT2 inhibitors together with thiazolidinediones, meglitinides, or GLP-1 receptor agonists. A growing body of literature has been published regarding the effects of combination therapy that includes SGLT2 inhibitors. However, it is not yet fully clear whether combination therapy that includes SGLT2 inhibitors is more effective than monotherapy or placebo. The objective of this study was to summarize and analyze randomized controlled trials (RCTs) on combination therapies involving SGLT2 inhibitors for type 2 diabetes (T2D) published since 2012.

The findings of this systematic review and meta-analysis revealed that combination therapy, including SGLT2 inhibitors, decreased the HbA1c levels to a larger extent than monotherapy with DPP-4 inhibitors or GLP-1 receptor agonists. SGLT2 inhibitors, when combined with metformin or a DPP-4 inhibitor, reduced HbA1c levels. The effect sizes of HbA1c lowering were greater than previously reported for combination therapies of other second-line glucose-lowering agents for T2D. In addition, combination therapy involving SGLT2 inhibitors with other glucose-lowering agents has been shown to reduce body weight compared to their respective monotherapies, suggesting that combining agents with distinct pathophysiologic targets is a crucial method for treating T2D. However, the included studies had various limitations. Most studies included patients with mild forms of type 2 diabetes or early stages of the disease. The duration of the trials was only short- to mid-term. The long-term effects of SGLT2 inhibitors on glucose metabolism and cardiovascular diseases remain uncertain.

8.3. Real-World Evidence Studies

Sodium glucose cotransporter-2 inhibitors (SGLT2i) are gaining popularity among physicians and patients due to emerging evidence that SGLT2i can reduce mortality in patients with diabetes and cardiovascular disease. A total of 165 patients using SGLT2 inhibitors (SGLT2i) were recruited from eight diabetes clinics in India between December 2017 and December 2018. A computer-assisted personal interview format was used to record the prescription pattern, demographic data, efficacy, and side effects. The study concluded that the use of SGLT-2 Inhibitors in the treatment of patients is associated with statistically significant decreases in HbA1c, body weight, fasting plasma glucose, systolic blood pressure, and diastolic blood pressure. It was more efficacious than randomized controlled trials that had a relatively low side effect profile.

Although limitations exist in the design of this study, a careful approach was taken to select the study parameters and the methodology to assess them in a real-world setting. The duration of the study was relatively long compared to the majority of similar studies already published. Non-obesity was the primary reason for SGLT2i prescription, which may be because SGLT2i is the first sodium-glucose cotransporter inhibitor registered in India. At the same time, other classes of antidiabetic medications have been marketed for several years. Most safety concerns, particularly genitourinary infections, were observed during the first 3 months of exposure to SGLT2i, after which they seemed to abate. Similar findings have also been reported in earlier studies. It is mandatory for every patient prescribed an SGLT2i to receive guidance on adequate hydration and maintaining good genital hygiene.

9. Conclusion

The evaluated RCTs examine how SGLT2 inhibitors affect diabetes development in statin-treated high-risk individuals. As they lower cardiovascular risk in the general population, statins are the cornerstone of secondary prevention in type 2 diabetes. Statins are also advised for prediabetics. Therefore, this demographic has a higher diabetes risk than others.

SGLT2 inhibitors are a promising treatment for type 2 diabetes (T2D), hence statin-treated individuals should be studied. SGLT2 inhibitors have been shown to prevent diabetes in the general population and other high-risk populations, although statin-treated individuals have not been studied. The approval of SGLT2 inhibitors as a diabetes prevention medication underscores the relevance of this issue.

In conclusion, this review aims to investigate the effect of SGLT2 inhibitors on diabetes progression as a secondary outcome in RCTs within this patient population. Seven studies with 33,843 participants were reviewed. Four studies (with 21,947 participants) on CVOTs demonstrated the effect of SGLT2 inhibitors on diabetes prevention. Three studies (with 11,896 participants) on non-CVOTs reported that SGLT2 inhibitors appeared to be promising

treatment alternatives, yet may require more extensive RCTs with stricter inclusion criteria. Overall, SGLT2 inhibitors reduced diabetes progression, providing important evidence for the management of the substantial statin-treated population at a high risk of developing diabetes.

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