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Best Second Oral Agent to Metformin to Manage Type 2 Diabetes

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by

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Abstract

Diabetes is a major health concern in the United States with many long-term complications, such as heart disease, stroke, kidney failure, blindness, and amputation. According to the Center for Disease Control, as of 2020, 34.1 million of US adult had diabetes and 88 million were prediabetic. Due to the severe complications, it is important to manage diabetes with lifestyle changes and pharmacotherapies. Many oral agents such as metformin, sodium glucose transporter 2 inhibitors (SGLT2i), and sulfonylureas are used in the management of type II diabetes. Metformin is typically the first line pharmacotherapy. However, when metformin alone is not enough to adequately control hyperglycemia, combination therapy is recommended. The goal of this literature review is to investigate differences in safety and efficacy when using monotherapies (metformin, SGLT2i, sulfonylureas) and combination therapy (metformin-SGLT2i versus metformin-sulfonylureas) in management of type II diabetes. A comprehensive literature review was done using different electronic databases such as Pub-Med, Clinical Key, Cochrane Library, access medicine, CINAHL Complete and Dynamed Plus. Review of the literature showed each monotherapy reduces A1c to some extent. SGLT2i users had better cardio-protectiveness than sulfonylureas. The use of metformin-SGLT2i has significantly greater reduction in hemoglobin A1c (HbA1c), and body weight compared to metformin-sulfonylureas. However, sulfonylureas are more widely used because they are cheaper and well-studied. Studies also stated that sulfonylurea cause more hypoglycemic episodes compared to metformin or SGLT2 inhibitors.

Keywords: type II diabetes, metformin, SGLT2i, sulfonylureas, metformin-SGLT2i, metformin-sulfonylureas, combination therapy, monotherapy

Introduction

According to the Centers for Disease Control and Prevention (CDC) 2020 diabetes statistics report, 34.1 million adults in the United States had diabetes. Diabetes is a chronic health condition that can lead to many long-term complications such as cardiovascular disease, nephropathy, retinopathy, foot damage, hearing impairment, and increased mortality. Risk of complications increase if diabetes is left untreated. There are many oral medications that can be used in the management and treatment of type two diabetes (DMII) such as sulfonylureas, biguanide, alpha-glucosidase inhibitors, dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors), and SGLT2 inhibitors. Metformin, a biguanide, is the preferred initial medication for most patients with type 2 diabetes. However, in patients with type 2 diabetes and HbA1c $\geq$ 1.5%-2% above the glycemic target, combination therapy is recommended. There are many factors such as cost, adherence, compliance, reduction in HbA1c, body weight, etc. that play a role in selecting and adding a second agent to metformin in the treatment of DMII. The purpose of the study is to conduct a comprehensive literature review investigating any statistically significant differences in safety and efficacy when using metformin-SGLT2i versus metformin-sulfonylureas. This study will also investigate the effects of metformin, sulfonylureas, and SGLT2i in the reduction of HbA1c, body weight, and fasting plasma glucose.

Statement of the Problem

Management of glycemic control early on can reduce many long-term complications of diabetes; thus, the choice of a second drug is an important one. As stated above, there are many factors that play a role in selecting and adding a second agent to metformin in the treatment of type 2 diabetes. Therefore, to make an informed decision in helping patients with type 2 diabetes, it is important for a medical provider to understand factors affecting patient's choice, as well as

the safety and efficacy of each oral agent (metformin, sulfonylureas, and SGLT2i), safety and efficacy when combined with other oral agents (metformin-SGLT2i versus metformin-sulfonylureas), and the effects of oral agents in reduction of HbA1c and body weight.

Research Question

In adult patients with uncontrolled type 2 diabetes mellitus (DMII), are sulfonylurea or SGLT2i a better choice to combine with metformin to reduce HbA1c and cardiovascular comorbidity?

Methods

For this paper, a comprehensive literature review is done using an electronic database such as Pub-Med, Clinical Key, Cochrane Library, access medicine, CINAHL Complete and Dynamed Plus. Specific keywords and Medical Subject Headings terms (MeSH terms) were used to search literatures on monotherapy of metformin, SGLT2i, and Sulfonylurea when treating patients with DMII and the differences in safety and efficacy when using combined therapy (metformin-SGLT2i versus metformin-sulfonylureas). Keywords and MeSH terms were also used to investigate the effect of metformin, sulfonylureas and SGLT2i in the reduction of HbA1c, body weight, and fasting plasma glucose. Literature reviewed was based on four themes and resulted more than 3000 search results. Studies that dealt with infant and children were excluded. Multiple other studies were excluded as they dealt with other oral agents beside metformin, sulfonylureas and SGLT2is.

Literature Review

A review of the literature recommends metformin as the initial glucose lowering therapy, if tolerated and not contraindicated. In patients with type 2 diabetes and HbA1c $\geq$ 1.5%-2% above the glycemic target, combination therapy is recommended. SGLT2 inhibitors are strongly

recommended in patients with or risk of developing atherosclerotic cardiovascular disease, heart failure or kidney disease (Grade A). When comparing the all-cause mortality and serious adverse events there were no significant differences between patients using metformin-SGLT2i versus metformin-sulfonylureas. However, compared to patients using metformin-sulfonylureas, a study done by Gebrie et al. found out that "participants taking metformin-sodium glucose co-transporter-2 inhibitors showed a significantly greater reduction in HbA1c, body weight, systolic blood pressure, diastolic blood pressure, and fasting plasma glucose." Therefore, for patients with type 2 diabetes and who are at risk for cardiovascular comorbidity, metformin-SGLT2 inhibitors are safer and more efficacious compared to metformin-sulfonylureas. (Gebrie, 2021)

Metformin Monotherapy in management of DMII in adults

Metformin is usually the first medication prescribed for type 2 diabetes patients. Providers generally aim for a target dose of 2 x 1000 mg metformin in all stages of the disease, including the combination with other oral antidiabetic drugs (Maruthur, 2016). A systematic review and meta-analysis performed by Maruthur et al., evaluated the comparative effectiveness and safety of monotherapy in adults with type 2 diabetes. Metformin, sulfonylureas, and sodium–glucose cotransporter 2 [SGLT-2] inhibitors were few among many antidiabetic drugs that were evaluated.

Sources of the data and searches used in the study came from MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials. Furthermore, they searched ClinicalTrials.gov to identify relevant registered trials and reviewed the Food and Drug Administration website for any unpublished additional studies relevant to the topic. All reviewed studies were in the English language and were done between April 2009 and March 2015. Study

selection was done by two reviewers. They independently screened titles, abstracts, and full-text articles for inclusion and resolved differences through consensus.

A total of 214 studies were reviewed, out of which 50 studies were multicontinental, 55 studies were conducted in Europe, 39 studies were conducted in Asia, and 34 studies were conducted in the U.S. Eighty-one percent of studies were randomized control trials. Participants were either overweight or obese with A1c levels between 7% and 9%. However, most studies excluded older participants with clinically significant comorbid conditions. Most studies used the last-observation-carried-forward approach for analysis of intermediate outcomes.

Their study compared the effectiveness of each monotherapy on HbA1c, body weight, and cardiovascular comorbidities. When comparing metformin to sulfonylureas, there were no significant reductions in A1c levels, and both monotherapies reduced A1c to a similar degree. Medications expected to maintain or decrease weight such as metformin or SGLT2 inhibitors were favored compared with medications expected to increase weight such as sulfonylureas. Metformin reduced weight by about 2.5 kg; however, SGLT-2 inhibitors decreased weight more than metformin. Metformin monotherapy was associated with lower long-term (≥2 years) cardiovascular mortality compared with sulfonylurea monotherapy. Metformin monotherapy was associated with more gastrointestinal side effects such as nausea and diarrhea compared to sulfonylurea and SGLT2i monotherapy.

This systemic review of 204 studies (179 trials and 25 observational studies) provides well organized information that compares the effectiveness and safety of diabetes medications to help providers make informed treatment choices. This study used reliable sources such as MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials to find to find relevant and unbiased articles and systematic reviews on diabetic monotherapy. The entire

review article was well organized and provides detailed information on data sources, data synthesis, study selection, grading of the evidence, method, and the results.

A major limitation of this systemic review is that only articles published in the English language are included. They reviewed articles published in Asia, Europe, and the United States and if they had included articles published in different languages, they would have more articles to review thus a bigger sample size. Also, participants were limited to non-pregnant, overweight, or obese with an A1c between 7% and 9%. The result of this review is not applicable to diabetic pregnant women, and individuals, regardless of weight, whose A1C is greater than 9%. Maruthur et al., also revealed in their study that most of the articles they reviewed were short "with limited ability to assess rare safety and long-term clinical outcomes." (Maruthur, 2016)

One of the common comorbidities in people with diabetes mellitus is heart failure. Risk of heart failure significantly increases with elevation in A1c. People with diabetes mellitus have a 2 to 5 times higher risk of cardiovascular comorbidities compared to the general population. (Eurich, 2013) A systemic review of observational studies done by Eurich et al. looked at the safety and effectiveness of metformin in patients with diabetes mellitus and heart failure.

Eurich et al. used Systematic Reviews and Meta-Analyses (PRISMA) guidelines to analyze articles on the association between metformin treatment and morbidity and mortality in people with heart failure and diabetes mellitus. As measures of overall safety, Eurich et al. examined all-cause mortality and all-cause hospitalizations. The electronic database used in search strategy were Health Star, EMBASE, Allied and Complementary Medicine Database, Cumulative Index to Nursing and Allied Health Literature, International Pharmaceutical Abstracts, Medline, Web of Science, and Cochrane Central Registry of Controlled trials. Two reviewers (D.L.W. and S.E.V.) were selected for inclusion criteria and data abstraction. They

independently “identified citations and included them if they described original research, included subjects with both diabetes mellitus and HF, evaluated the effect of metformin on hospital admission (all-cause or HF-specific) or mortality, and included a contemporaneous control group for comparison. Any discrepancies were resolved by consensus after review by a third investigator (D.T.E.).” (Eurich, 2013)

Eurich et al. started the review with a total of 12,994 observational studies, but only 9 were the part of the final meta-analysis. Final nine studies consisted of 35,000 patients with diabetes mellitus and heart failure, of which 6624 patients (19%) were using metformin. Only two of nine studies specifically evaluated the use of metformin as monotherapy. Three of the nine studies compared the metformin to sulfonylureas (n=4605). Specific criteria for selection of observational studies are depicted by the figure below:

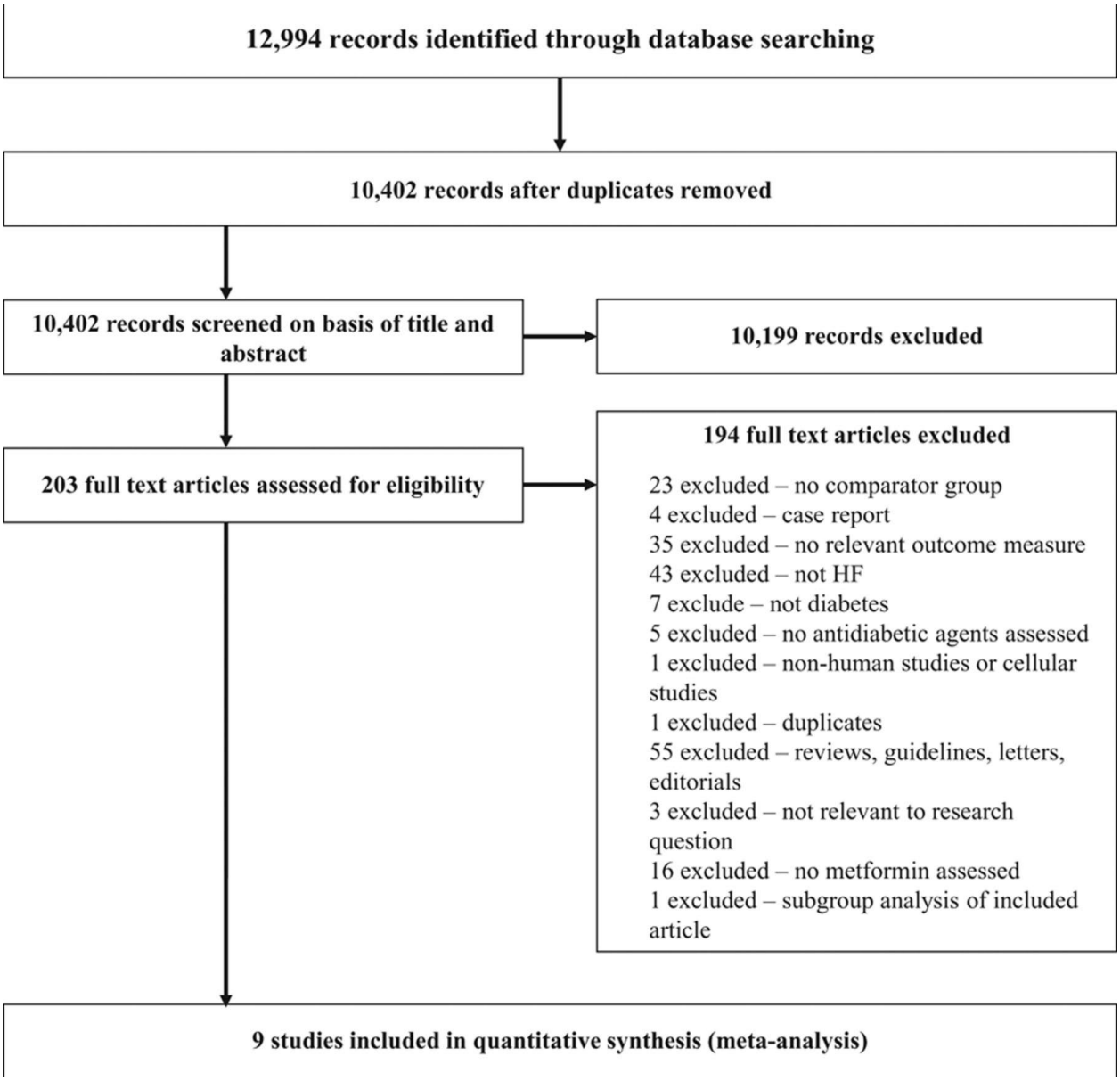

Figure 1. PRISMA diagram of systematic search (Eurich, 2013)

The study done by Eurich et al. included total of 35,000 from variety of settings including clinical registries, hospital discharges, and community and primary care settings patients. The average age of cohort patients ranged from 56 to 78 years of age.

Eurich et al. concluded that metformin-based regimens reduced the risk of all-cause mortality. Compared to sulfonylureas, metformin-based regimens were associated with a 20% relative reduction in all-cause mortality (pooled adjusted risk estimates: 0.80; 0.74–

0.87; I^2=15%; P<0.001). They also stated that compared with other treatments, metformin is a safe option for glycemic control in patients with heart failure. Two of nine studies evaluated the use of metformin in patients with reduced left ventricular ejection fraction (LVEF<30) and concluded that there was no increase in mortality associated with metformin compared with non-metformin-based therapies, thus metformin is safe to use in patients with reduced LVEF. Overall, metformin is at least as safe as other glucose lowering therapies in patients with diabetes mellitus and heart failure. (Eurich, 2013)

One of the limitations of this study is the absence of randomized control trials. Nine observational studies were included in the study; no randomized controlled trials were identified. We know that randomized trials are considered the best study design to confirm the efficacy of the experiment, thus this study could have failed to examine unmeasured confounding variables. Eurich et al. themselves mentioned that there could have been a publication biased on studies they reviewed, which can be another limitation to the study. Even though they were only able to do a meta-analysis of nine studies out of 12,994, Eurich et al. did a good job eliminating unnecessary studies and only focused on studies that evaluated the safety and effectiveness of metformin in patients with diabetes mellitus and heart failure. Another strength of the review was the studies they evaluated came from reliable search engines like Health Star, EMBASE, Allied and Complementary Medicine Database, Cumulative Index to Nursing and Allied Health Literature etc.

Sulfonylurea Monotherapy in management of DMII in adults

Even though sulfonylureas are a very widely used antidiabetic medications, the extent to which they improve glycemia is poorly documented. Hirst et al. states that in the United Kingdom, sulfonylureas are the second-line choice of oral antidiabetic medications after

metformin. Previous studies have shown that sulfonylurea and metformin combination therapy can reduce the A1c by 1.5%. However, the effects of sulfonylurea monotherapy are still not well-known. A systemic review done by Hirst et al. evaluates the effect of sulfonylurea on HbA1c in diabetes and glycemic control.

Hirst et al. used Medline, Embase and the Cochrane Central Register of Controlled Trials, as well as two clinical trials registries—Clinicaltrials.gov and the EU Clinical Trials Register, as the source of their data. The review included randomized control trials with no language restriction. To assess the change or effect of sulfonylurea in A1c and other secondary outcomes, such as change in body weight, Hirst et al. searched articles that included fixed-dose sulfonylurea monotherapy or sulfonylurea added on to other glucose-lowering treatments. Study selection was done by two reviewers. Each article must include "patients with diabetes, be randomized, be double-blinded, be at least 12 weeks in duration, have a fixed dose of sulfonylurea either as monotherapy, as an add-on to another oral glucose-lowering therapy or as an add-on to insulin therapy, have the same sulfonylurea and background oral therapy dose for each participant, and report participants' HbA1c levels after baseline." (Hirst, 2013)

Using the databases listed earlier, they searched total of 4,308 articles, but only 31 were included on final analysis. Figure 2 describes the flow chart of the searches and reason why 4277 articles were omitted from final review.

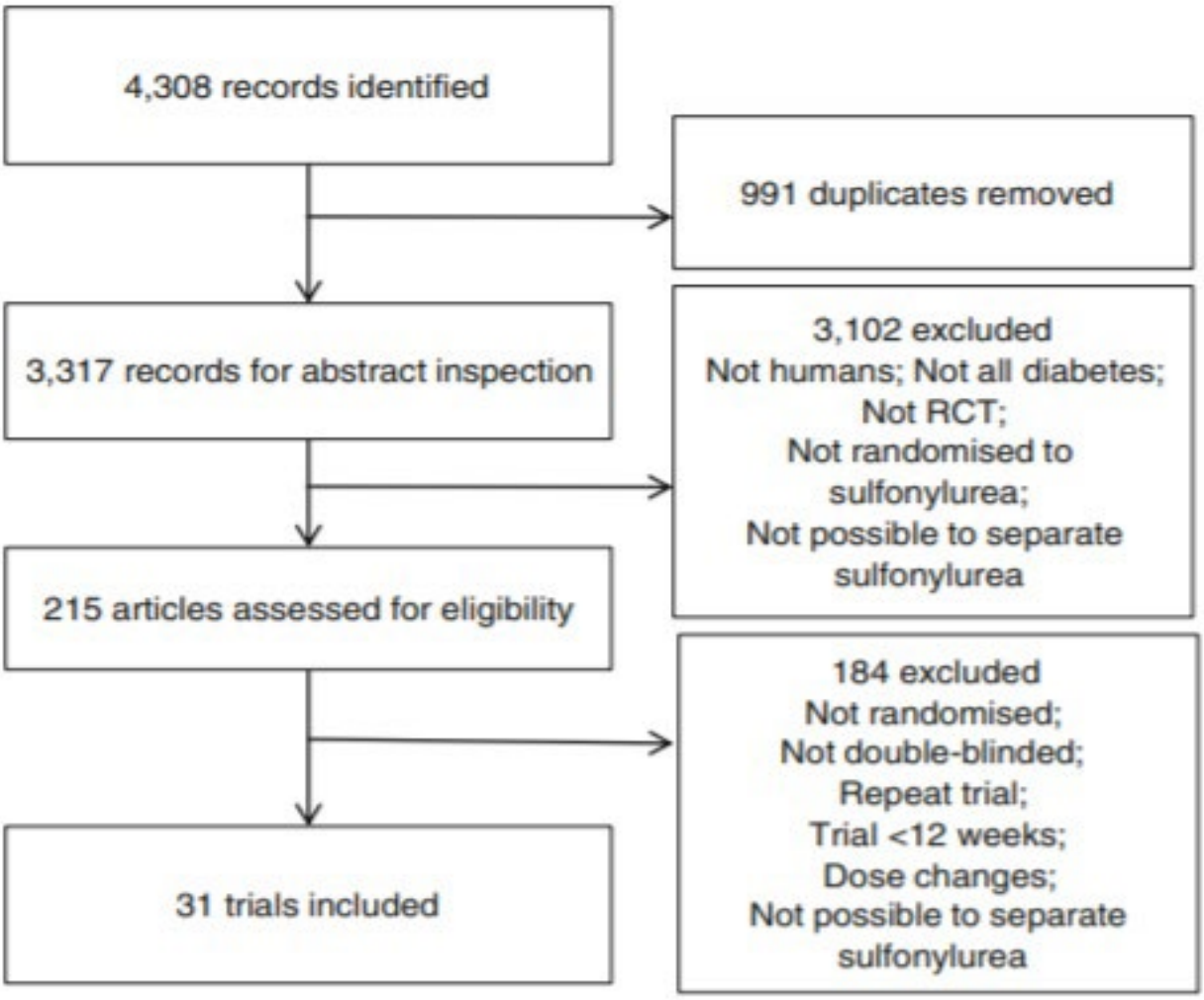

Figure 2. Flow chart of the searches. (Hirst, 2013)

As you can see from Figure 2, 31 studies were included in final meta-analysis. Nine out of 31 studies reviewed sulfonylurea monotherapy, 4 out of 31 studies reviewed sulfonylureas added to oral diabetes treatment and remaining 17 studies reviewed sulfonylurea added to insulin. Studies they reviewed varied in length from 12 weeks to 3 years, mean baseline HbA1c varied from 4.6% to 13.6%, and mean patient age varied from 34 to 66.5 years.

The HbA1c level was 1.51% lower in participants using sulfonylurea monotherapy compared to placebo group (95% CI 1.25, 1.78, I^2 =59.8%). HbA1c was 1.62% (95% CI 1.00, 2.24; I^2=94.1%) lower in participants using sulfonylurea added to oral diabetic treatment

(studies did not reveal what oral agents were combined with sulfonylurea). Sulfonylurea in combination with insulin resulted in reduction in HbA1c by 0.46% (95% CI 0.24, 0.69, I^2 =43.6%). Twelve studies reported mean increase in weight of 2.31 kg (95% CI 1.31, 3.32) in the sulfonylurea-treated groups compared with comparator groups (result of comparator group was not revealed by the study). Common adverse event among different studies was that sulfonylurea treatment resulted in an increased number of hypoglycemic events. There was no evidence of other adverse events from sulfonylurea treatment.

All the articles they reviewed for meta analysis included randomized control trials with no language restriction. To address possible publication bias, they used Egger's test for funnel plot asymmetry wherever possible (including at least 10 trials in the analysis). To address possible attrition bias, they conducted sensitivity analyses to exclude trials in which fewer than 75% of participants completed the trial. (Hirst, 2013) One other way they tried to minimize the bias was by using only double-blinded randomized controlled trials in their review. One limitation that Hirst et al. mentioned in their review was that most of the reviewed articles had less than 100 participants especially in the insulin trial which may have led to publication bias. Another limitation of the review was that they never mentioned which oral antidiabetic agents were combined with sulfonylurea during the research. It would have been helpful for a reader if they had mentioned specific oral agents to better understand the combination therapy.

A cohort study done by Roumie et al. compares the effectiveness of sulfonylurea and metformin monotherapy on cardiovascular events (acute myocardial infarction and stroke) in patients with type 2 diabetes mellitus. Setting of their chort study was National Veterans Health Administration (VHA) databases linked to medicare files.

The patient population studied was comprised of veterans aged 18 years or older who received regular VHA care for at least the past 365 days and who initiated metformin or sulfonylurea therapy for diabetes. Patients with heart failure, HIV, cancer (except for nonmelanoma skin cancer), organ transplantation, endstage kidney or liver disease, or respiratory failure were excluded. They started with 364,865 patients and out of 364,865 patients, 253,690 were included for final review. Among 253, 690 patients initiating treatment , 98,665 patients did sulfonylurea therapy (glyburide or glipizide) and 155,025 patients did metformin therapy. Ninety seven percent of the patient population were men and 75% were white. Median age of the participant was 62 years old. The average HbA1c level was 7.0% among those who began metformin therapy and 7.3% among those who began sulfonylurea therapy.

An increase in CVD events, or death, were associated with sulfonylurea therapy, compared to metformin therapy. Unadjusted rates of CVD events (AMI and stroke, excluding deaths) were 13.5 per 1000 person-years for sulfonylurea users and 8.2 per 1000 person-years for metformin users. They also found 21% increased hazard of hospitalization for AMI or stroke associated with initiation of sulfonylurea compared with metformin therapy. Their study concluded that metformin monotherpy is more effective than sulfonylurea monotherapy on cardiovascular events in type 2 diabetes mellitus.

A large sample size was the strength of the study. A large sample size allowed them to come up with the more precise estimate of the treatment effect. The entire study was well organized and easy to follow, but it also had many limitations. One of the primary limitations was the patient population. Ninety seven percent of the patients were men and 75% were white. Data on women and minority groups were limited, thus this study is not applicable to those populations. The study states that there is a higher risk associated with sulfonylurea monotherapy

compared to metformin, but the reason for the difference in risk between metformin and sulfonylurea users was never explained in the study.

SGLT2i Monotherapy in management of DMII in adults

Sodium–glucose cotransporter 2 (SGLT2) inhibitors are antidiabetic medications that work by inhibiting glucose reabsorption by the kidney, inducing glucosuria. SGLT2 inhibitors are known to reduce HbA1c, fasting and postprandial blood glucose levels, body weight and blood pressure. As of now, few SGLT2 inhibitors such as empagliflozin and canagliflozin, are shown to improve cardiovascular outcomes in high-risk individuals. However, there are also risks associated with the use of SGLT2 inhbitors, such as genitourinary infections, diabetic ketoacidosis and amputation. An article published by Lupsa et al. discucsses the risks and benefits of SGLT2 inhibitors in type 2 diabetes.

Beneficial effects of SGLT2 inhibitors:

1. **Glucose lowering**

   SGLT2 inhibitors are associated with a low incidence of hypoglycemic and can be used as monotherpay or add on to other antidiabetic medications such as metformin or sulfonylurea. SGLT2 inhibitors achieve a reduction in HbA1c of 0.4–1.1%, depending on the baseline HbA1c and the specific drug and dose used. Among all the SGLT2 inhibitors, canagliflozin reduces the HbA1c to slightly greater extent.

2. **Cardiovascular benefits**

   Two specific SGLT2 inhibitors, empagliflozin and canagliflozin, have shown significant reduction in cardiovacular disease.

3. **Weight loss**

   Weight loss caused by SGLT2 inhibitors is due to glucosuria-induced energy loss. "A meta-analysis of randomised controlled trials involving participants treated with canagliflozin 300 mg, empagliflozin 25 mg or dapagliflozin 10 mg daily showed a weight loss of 2.66 kg, 1.81 kg and 1.80 kg, respectively, compared with placebo" (Lupsa, 2018)

Adverse effects of SGLT2 inhibitors

1. **Genitourinary infections**

   Based on the meta-analysis of randomised trials comparing SGLT2 inhibitors with placebo or other antidiabetic medications, SGLT2 inhibitors increase the risk of genital mycotic infections by fivefolds.

2. **Diabetic ketoacidosis**

   One of the complications of SGLT2 inhibitor use is diabetic ketoacidosis. However, it happens more frequently with type 1 patients than type 2 diabetes patients.

3. **Amputation**

   Risk of amputation is associated with only one SGLT2 inhibitor, canagliflozin, especially lower extremity amputation. Absolute risk of amputation increases with the participants with a history of amputation or peripheral vascular disease.

This study did a great job explaning the details the benefits or risks associated with SGLT2 inhibitors. However, this is not a cohort study, systematic review or meta analysis, so detailed statistical data on each specific benefits and risks were not provided.

To prevent the increase of cardiovascular events in patients with type 2 diabetes, glycemic control is critical. There are lot of antidiabetic medications that work by either enhancing insulin secretion or by improving insulin sensitivity. SGLT2 inhibitors work via insulin-independent mode of action by reducing glucose renal reabsorption in the kidney. Zou et al. did a comprehensive meta-analysis of data from 42 randomized placebo-controlled trials to understand the effects of SGLT2 inhibitors on cardiovascular outcomes and mortality in patients with type 2 diabetes.

Meta-analysis was conducted under PRISMA guidelines using reliable search engines such as Medline, Embase, and Cochrane Library. There were total of 42 trials (published between 2010 and 2019) and 61,076 patients with type 2 diabetes included in the meta-analysis. Participant populations included the ages ranging from 52.20 to 68.50 years; HbA1c, from 7.17% to 8.94%; body mass index (BMI), from 25.39 to 54.00; and follow-up period, from 12 to 338 weeks. (Zou, 2019)

Systematic search of scientific literature in the databases was done by two reviewers (Zou and Liu). Specific keywords and Medical Subject Headings terms (MeSH terms) were used to search literatures on SGLT2 inhibitor monotherapy or SGLT2 inhibitor add-on therapy to other non-SGLT2 inhibitor. Statistical analysis was conducted using RevMan statistical software for dichotomous data with a Mantel-Haenszel fixed-effects model. The heterogeneity across studies was examined using the Chi-squared test, with $P<.10$ indicating significant heterogeneity. Variables with P values$<.05$ were considered statistically significant.

Based on 37 studies, out of 42, that compared the effects of SGLT2 inhibitors and control treatments on cardiovascular outcomes, Zou et al. concluded that SGLT2 inhibitors significantly reduced the incidence of major adverse cardiovascular events compared with control treatment

(OR=0.86, 95% CI 0.80–0.93, P<.0001). The risk of myocardial infarction in patients with type 2 diabetes was evaluated by 25 out of 42 studies. Compared to placebo group, diabetic patients on SGLT2 inhibitors monotherapy showed lower incidence of myocardial infarction (OR=0.28, 95% CI 0.12–0.64, P=.003). Zou et al. did not find any evidence of SGLT2 inhibitors reducing or increasing the risk of ischemic stroke based on 26 studies compared with control treatment (OR=0.95, 95% CI 0.85–1.07, P=.42). When comparing SGLT2 inhibitor monotherapy vs placebo, SGLT2 inhibitors showed reduced cardiovascular mortality (OR=0.86, 95% CI 0.78–0.95, P=.003). Based on a finding from 25 studies, SGLT2 inhibitor monotherapy significantly reduced the risk of all-cause mortality compared with placebo (OR=0.85, 95% CI 0.79–0.92, P<.001). Several studies also showed that SGLT2 inhibitors have favorable effects on reducing fasting blood sugar, HbA1c, body weight, acute kidney injury, and blood pressure.

Most of the comprehensive literatures they reviewed were moderate-to-high quality. Studies were selected by two different investigators according to strict inclusion criteria. All their studies provided detailed information on the effect of SGLT2 inhibitors on major adverse cardiovascular events, myocardial infraction, ischemic stroke, cardiovascular death, and all-cause mortality which made it easier to draw conclusions from this meta-analysis. One of the limitations of the study was the sample size. Although they reviewed 42 studies with 61,076 total patients, each study was almost all single-center trials with a relatively small number of patients. Also, the latest approved SGLT2 inhibitors, such as ertugliflozin, was not included in meta-analysis, so more studies need be done in future to investigate cardiovascular effects of new SGLT2 inhibitors.

Combined therapy in management of DMII in adults

Many people with uncontrolled type two diabetes are treated with more than one antidiabetic medication. Metformin and sulfonylurea combination therapy for adults with type 2 diabetes mellitus is a common one. Madsen et al. "investigate the effects of metformin plus sulfonylurea on patient-important outcomes such as complications of diabetes (for example kidney and eye disease, heart attacks, strokes), death from any cause, health-related quality of life and side effects of the medications." (Madsen, 2019) The comparator used in the study was metformin plus another glucose-lowering intervention as a combination therapy (e.g., metformin plus dipeptidylpeptidase-4 inhibitor, metformin plus insulin).

A review 32 randomized articles came from the search engines like CENTRAL, MEDLINE, Embase, ClinicalTrials.gov and WHO ICTRP. There were total of 28,746 participants aged 18 or older. Articles were independently reviewed by two different reviewers to assess the risk of bias. They used random-effects model to perform meta-analysis. All trials included both genders. The percentage of women ranged from 29% to 65%. The mean age of the participants ranged from 52 years to 73 years. Mean HbA1c at baseline ranged from 7.3% to 9.3%.

Madsen et al. compared metformin and sulfonylurea combined therapy to many comparators such as metformin monotherapy plus placebo, DPP-4 inhibitor, metformin plus glinide, metformin plus SGLT-2 inhibitor, metformin plus thiazolidinedione etc. When looking at mortality, serious adverse effects, macrovascular and microvascular complications, they found inconclusive evidence whether metformin and sulfonylurea combination therapy compared with metformin plus another glucose-lowering intervention results in benefit or harm for most patients.

Due to the progressive nature of diabetes, treating it with monotherapy is becoming challenging. Uncontrolled diabetes can lead to diabetic retinopathy, neuropathy, kidney damage, and microvascular and cardiovascular complications. To achieve and maintain specific glycemic targets, most patients require glucose-lowering drugs in addition to lifestyle interventions (exercise, healthy eating, smoking cessation, and weight reduction). Efficacy, risk of hypoglycemia, patient's comorbid conditions, impact on weight, side effects, and cost plays important role when choosing a second antidiabetic drugs. To better understand the combination therapy, Gebrie et al. did a "systematic review and meta-analysis of randomized controlled trials (RCTs) to compare the cardiovascular safety and efficacy of combination therapy of metformin-SGLT2Is and metformin-sulfonylureas in patients with T2DM."

For the design and reporting of the results, Gebrie et al. followed the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA 2015) guidelines. They used MEDLINE-PubMed, Embase, the Cochrane Library, and ClinicalTtrials.gov to find completed studies. Two reviewers were selected to examine the title and abstract of all searched studies. They found total of 3,190 citations, out of which 30 were fully assessed. Only nine of them fulfilled the inclusion criteria. Below is the figure 3 that shows the inclusion criteria:

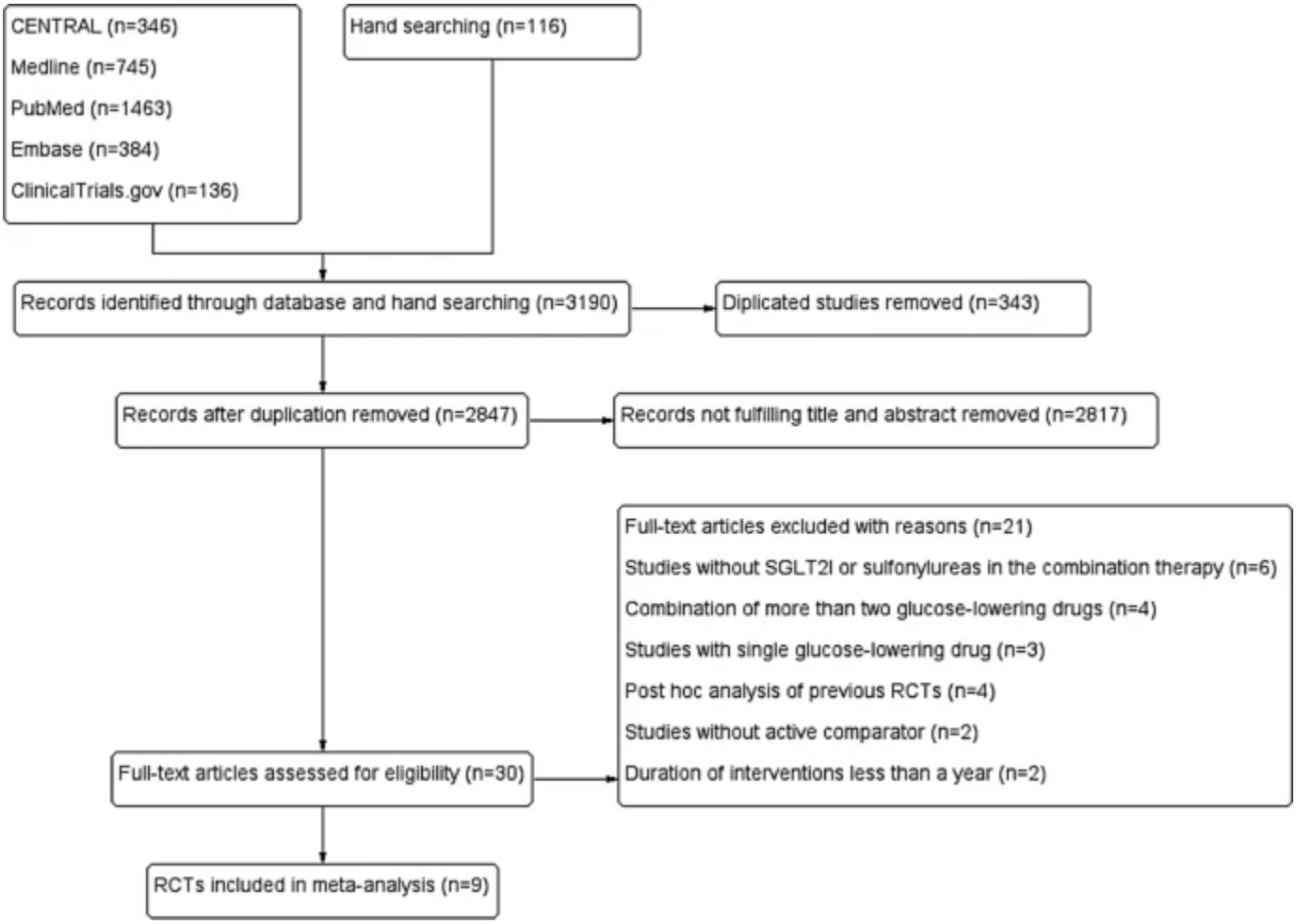

Figure 3. PRISMA flow diagram of the study (Gebrie, 2021)

There were total of 10,974 patients with type 2 diabetes who were in either of the two combination therapies at least for a year.

All nine studies looked at all-cause mortality and deaths events and found no significant difference in all-cause mortality/death events between patients with T2DM who were on metformin-SGIT2Is and metformin-sulfonylurea combination therapies (RR = 0.93, 95% CI [0.52, 1.67], P = 0.81). Two out of nine trials looked at the cardiovascular efficacy especially coronary artery disease and acute myocardial infarction and found no significant difference between patients on metformin-SGIT2I versus metformin-sulfonylurea combination therapies. Result of serious adverse events yield no significant difference between two groups. They looked

at the hypoglycemic events on 10,794 patients and concluded that patients under metformin-SGIT2I combination therapy were found to experience significantly fewer hypoglycemic events as compared to patients under metformin-sulfonylureas combination therapy (RR = 0.13, 95% CI [0.10, 0.17], P < 0.001) I2 = 67%, P = 0.002). Data also showed significant difference in the mean difference of HbA1c between patients on metformin-SGLT2I and metformin-sulfonylureas combination therapies; MD = − 0.10, 95% CI [− 0.17, − 0.03] %, p = 0.005), I2 = 63%, P = 0.006. They concluded that body weight and fasting plasma glucose of patients in the metformin-SGLT2I was significantly reduced from baseline compared to patients in the metformin-sulfonylureas.

This study did an excellent job illustrating cardiovascular safety, efficacy, and cardiovascular risk factors between the two combination therapies. However, the sample size is too small, and studies were limited, therefore further long-term trials comparing the overall safety, efficacy, and cost-effectiveness of metformin-SGLT2Is and metformin-sulfonylureas combination therapies is needed.

When treating a patient with type 2 diabetes, metformin is first line drug, but uncertainty remains regarding the choice of second-line therapy once metformin is no longer effective. Singh et al. did a review to discuss what could possibly be the best option as a second line oral agent, once metformin monotherapy becomes ineffective. (Singh, 2014)

Singh et al. did a systemic reviews and met-analysis to analyze what would be the best second agent to metformin between sulfonylurea, DPP-4 inhibitors, and SGLT-2 inhibitors.

Comparing SUs versus DPP-4 inhibitors

This meta-analysis suggested a marginal superiority of sulfonylureas, especially glimepiride, in A1c over DPP-4 inhibitors. DPP4I were clearly superior to sulfonylureas in any

adverse effects, hypoglycemia, weight gain, and CV events (Singh, 2014). They found that sulfonylurea may cause (severe) hypoglycemia, whereas DPP4I do not.

Comparing SUs versus SGLT-2 inhibitors

SGLT-2 inhibitors are new drugs used in the management of type two diabetes. There were only few studies that compared sulfonylureas with SGLT-2 inhibitors. Studies they reviewed show non-inferiority of SGLT-2 inhibitors in A1c reduction compared to SUs but with significant weight loss and blood pressure reduction. (Singh, 2014)

Sulfonylureas are still popular because of the cheap cost; however, they also cause severe hypoglycemia at times, with significant weight gain. SGLT-2 inhibitors are better at lowering A1c compared to sulfonylureas and DDPP4 inhibitors with added benefit of weight loss and blood pressure reduction, which seems to be consistent.

One of the strength of the study was clearly and concisely written risks and benefit associated with each antidiabetic medications: sulfonylureas, DDPP4 inhibitors and SGLT-2 inhibitors. However, this study did not provide any information on patient populations, how many studies they reviewed, inclusion criteria and information reviewers. They fail to list methodology. Without understanding the patient population, it will be difficult to implement the information in real world.

Sulfonylureas and SGLT2 inhibitors are often used after metformin as second-line antidiabetic agents. Xie et al. used the US Department of Veterans Affairs electronic health care databases to evaluate the comparative effectiveness of SGLT2 inhibitors vs sulfonylureas associated the risk of all-cause mortality in persons receiving metformin therapy. (Xie, 2021)

This was a cohort study done with a total of 23,870 individuals with new use of SGLT2 inhibitors and 104,423 individuals with new use of sulfonylureas were enrolled

between October 1, 2016, and February 29, 2020, and followed up until January 31, 2021. Mean age was 64.60 years; 122 096 men (95.17%) and 6197 women (4.83%) were included. To estimate the risk between initiation of SGLT2 inhibitors and sulfonylureas on all-cause mortality, a Cox proportional hazards model with the overlap weighting was applied.

Xie et al concluded that compared with new use of sulfonylureas, new use of SGLT2 inhibitors was associated with a reduced risk of all-cause mortality (HR, 0.81; 95% CI, 0.75-0.87). In addition, SGLT2 inhibitor use with metformin was associated with a reduced risk of all-cause mortality (HR, 0.70; 95% CI, 0.50-0.97) as well.

One of the strengths of the study was that they used large-scale real-world data from the US Department of Veterans Affairs, which operates the largest integrated healthcare system in the US. Articles they reviewed were from October 1, 2016, to February 29, 2020, which means their findings are relatively new and the results may help the provider choose right antihyperglycemic therapy in people with type 2 diabetes. One of the limitations of the study was the population. Majority of the patients were white and male participants, which may limit the generalizability of study findings.

Discussion

A major goal of antihyperglycemic medications such as metformin, sulfonylureas and SGLT2i is to reduce long term complications of diabetes and death. Evidence from this literature review indeed support the theory that pharmacotherapy intervention can reduce severe long-term complications of diabetes and death from it.

When treating patient with type two diabetes, metformin is considered first-treatment because of glycemic control, weight neutrality, and low cost as well as low risk for hypoglycemia. When looking at macrovascular and microvascular outcomes, Maruthur et al.

"found moderate strength of evidence that metformin monotherapy was associated with lower long-term (≥2 years) cardiovascular mortality compared with sulfonylurea monotherapy" However, there were no significant differences in reduction of A1c between metformin and sulfonylurea. One of the serious comorbidities in patients with type 2 diabetes is heart failure. An observational study done by Eurich et al, found out that out of 1497 of 6624 metformin users (23%) died compared with 10221 of 27880 (37%) in the control group suggesting reduced risk of all-cause mortality with metformin-based regimens. When comparing patients with advanced systolic heart failure on metformin vs control group, Eurich et al. found no significant improvement with metformin use, however metformin uses also did not increase the mortality. So, it is fair to conclude that metformin is at least as safe as other glucose-lowering treatments in patients with diabetes mellitus and heart failure.

Sulfonylureas are another antidiabetic agents that are used either as monotherapy or combination with another diabetes medication. Systemic review done by Hirst et al. looked at the effect of sulfonylurea on HbA1c. They found out that compared to placebo group, the HbA1c level was 1.51% lower in the sulfonylurea group. However, sulfonylurea also led to mean increase in weight of 2.31 kg and more hypoglycemic episodes compared to placebo group. Another studyby Roumie et al., investigated the effect of sulfonylurea and metformin on cardiovascular events in people with type 2 diabetes. It is evident that increased CVD events or death was associated with the use of sulfonylureas compared with metformin for initial treatment of diabetes. In addition, metformin compared with sulfonylureas resulted in decreases of 2.7 kg in weight, 0.259 mmol/L (10 mg/dL) in LDL cholesterol levels, and 0.1 mmol/L (8.6 mg/dL) in triglyceride levels and no difference in HbA1c levels. Therefore, when treating type 2 diabetes

patients with cardiovascular comorbidities such acute myocardial infraction or stroke, it is safer to go with metformin than sulfonylurea as an initial treatment.

Sodium–glucose cotransporter 2 (SGLT2) inhibitors are new antidiabetic drugs that reduce plasma glucose concentrations by increasing urinary glucose excretion. Study done by Lupsa et al. found out that, beside lowering plasma glucose, SGLT2i also causes weight loss, provides renal and cardiovascular benefits, and carry low risk of hypoglycemia. If good glycemic control has not been achieved with metformin monotherapy, SGLT2i should be considered reasonable second line therapy especially with diabetic patient that has increased risk of cardiovascular events. However, one of the major drawbacks of SGLT2i is that it is very expensive. In the USA, for example, retail costs are more than 100-fold higher than for generic metformin or sulfonylureas. Another study done by Zou et al. on effects of SGLT2 inhibitors on cardiovascular outcomes and mortality in type 2 diabetes had similar findings as above. SGLT2 inhibitors significantly reduced the incidence of major adverse cardiovascular events, myocardial infarction, and cardiovascular death compared with control treatment. However, SGLT2 inhibitor monotherapy had no effects on cardiovascular events or all-cause mortality. Therefore, SGLT2 inhibitor as an add-on therapy could be beneficial for type 2 diabetes patients.

When metformin monotherapy is inadequate at controlling blood sugar, combination therapy is recommended. A systematic review and meta-analysis of randomized controlled trials performed by Gebrie et al. investigated the cardiovascular safety and efficacy of metformin-SGLT2i versus metformin-sulfonylureas in type 2 diabetes. Their finding indicated that the body weight, fasting plasma glucose, and HbA1c of patients in metformin-SGLT2I group was significantly reduced from baseline compared to patients in the metformin-sulfonylureas. However, there was no evidence of significant difference in all-cause mortality/death events and

developing coronary artery disease (CAD) and acute myocardial infarction (AMI) between patients with type two diabetes who were on metformin-SGIT2Is and metformin-sulfonylurea combination therapies. The risk of experiencing hypoglycemic events was much higher under patients on metformin-sulfonylureas combination therapy versus patients under metformin-SGIT2I combination therapy. SGLT2I showed added benefit of weight loss, whereas sulfonylureas are reported to increase body weight. In their study, Gebrie et al. found out a 4.57 kg weight loss in metformin-SGLT2Is group than the metformin-sulfonylureas. In conclusion, Gebrie et al. stated "both metformin-SGLT2Is and metformin-sulfonylureas combinations are effective to control HbA1c for a short duration of follow-up. However, for a long duration of follow-up, metformin-SGLT2Is are more effective than metformin-sulfonylureas." Therefore, when treating a patient with type two diabetes who are at risk of cardiovascular comorbidity metformin-SGLT2Is are better choice than metformin-sulfonylureas.

Unlike the study done by Gebrie et al. that found no evidence of significant difference in all-cause mortality/death events, the study done by Xie et al. found out that SGLT2 inhibitor treatment was associated with a reduced risk of all-cause mortality compared with sulfonylureas. Compared with sulfonylureas, SGLT2 inhibitors were associated with a reduced risk of death, regardless of cardiovascular disease status.

Another study done by Singh et al. had similar conclusion on metformin-SGLT2I vs metformin-sulfonylureas combination therapy. Sulfonylureas are popular because of the cheap cost; however, they also cause severe hypoglycemia at a time, with significant weight gain thus limiting its compliance and wider utility in current clinical practice. SGLT-2 inhibitors are better at lowering A1c compared to sulfonylureas and with added benefit of weight loss and blood pressure reduction.

Conclusion

In summary, findings from this literature review strongly imply that SGLT2i a better choice to combine with metformin to reduce HbA1c and cardiovascular comorbidity. For patients with type 2 diabetes and who are at risk for cardiovascular comorbidity, metformin-SGLT2i is a better combination therapy than metformin-sulfonylureas. When looking at individual monotherapies, all of them lowers the HbA1c in patient with type II diabetes. Metformin and SGLT2i seem to aid in weight reduction, whereas sulfonylureas cause weight gain. Increased events of cardiovascular comorbidity are associated with sulfonylurea monotherapy compared to metformin and SGLT2i monotherapy. Even though SGLT2i inhibitors are superior to sulfonylurea considering weight & HbA1c reduction and cardio-protectiveness, they are also expensive. Sulfonylureas are well studied antidiabetic medications and are less expensive compared to SGLT2i inhibitors.

There are many studies done with metformin and sulfonylureas in treatment of type II diabetes, but further studies are warranted to assess benefits and effects of SGLT2i. Only few SGLT2 inhibitors such as empagliflozin and canagliflozin are well studied. Since SGLT2i has greater potential to reduce cardiovascular comorbidities, further research will be beneficial.

Applicability to Clinical Practice

The information provided within this literature review will help medical providers make an informed decision when treating an adult with uncontrolled type II diabetes. They will be able to consider many factors such as cost, compliance, reduction in HbA1c, effects on body weight etc. when considering adding an oral agent to metformin to manage type 2 diabetes. They will

also be able to understand if there are any statistically significant differences in safety and efficacy when using metformin-SGLT2i versus metformin-sulfonylureas.

This paper also highlights the importance of a provider to look at patient profile in entirety such as additional health issues, socioeconomic status, health insurance etc. before prescribing antidiabetic medications to provide better care and increase patient compliance.

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