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Exploring the Use of Diabetic Medications for Non-Diabetic Conditions: A Comprehensive Literature Review

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Abstract

Purpose: Currently, a significant portion of the US population has been impacted by diabetes, and alongside it, heart failure, chronic kidney disease (CKD), obesity, and non-alcoholic fatty liver disease (NAFLD) rates are on the rise. Recent research has highlighted the potential of antidiabetic medications to extend beyond diabetes management. This literature review is aimed at exploring the evolving roles of GLP-1 receptor agonists, SGLT2 inhibitors, and thiazolidinediones. It specifically investigates their applications in cardiovascular disease, chronic kidney disease (CKD), obesity, polycystic ovarian syndrome (PCOS), and NAFLD. As a novel therapeutic approach, their application could reshape treatment strategies for interconnected metabolic disorders, offering a new horizon in patient care.

Methodology: We conducted a comprehensive search of PubMed and Google Scholar for English-language studies published in the United States and Canada between January 1st, 2013, and August 31st, 2023 focusing on trials involving GLP-1RA, SGLT-2i, and thiazolidinediones therapy.

Findings: In our study, GLP-1 receptor agonists emerged as multifaceted pharmaceutical agents, showcasing improvements in cardiovascular disease outcomes, nephroprotective effects, substantial efficacy in obesity management, and promising prospects in addressing nonalcoholic fatty liver disease (NAFLD) and polycystic ovary syndrome (PCOS). Additionally, thiazolidinediones displayed effectiveness in the management of non-alcoholic steatohepatitis (NASH), while metformin exhibited notable benefits in PCOS management. Furthermore, Sodiumglucose Cotransporter-2 (SGLT2) Inhibitors demonstrated remarkable advancements, particularly in terms of cardiovascular and renal benefits. Our findings emphasize the diverse and evolving applications of diabetic medications in addressing a wide range of chronic medical conditions, ultimately leading to enhanced patient care and improved outcomes.

Recommendations: We recommend that healthcare practitioners carefully consider the expanded utility of these medications beyond their conventional diabetic indications and explore their integration into treatment strategies for the indicated medical conditions. This should be done while thoughtfully weighing the associated risks and benefits to ensure the most effective and safe patient care possible.

Keywords: *GLP 1 Agonists, SGLT 2 Inhibitors, Cardiovascular Benefits, Nephroprotection, Obesity*

1.0 INTRODUCTION

In the United States, approximately 11.3% (37.3 million) of the population has diabetes (National Diabetes Statistics Report, 2022), while an estimated 6.5 million adults suffer from heart failure (Dunlay et al., 2019). The prevalence of heart failure in patients with diabetes mellitus is 9% to 22%, which is four times higher than in the general population (Dunlay et al., 2019). Recent clinical trials have demonstrated shared pathophysiological processes between diabetes mellitus and heart failure, as well as the potential for specific diabetes therapies to modulate the risk of heart failure outcomes (Dunlay et al., 2019).

Furthermore, it is estimated that more than 1 in 7, or 15% of US adults, which amounts to approximately 37 million people, have chronic kidney disease. For obesity, its prevalence in the US was 41.9% from 2017 to March 2020, representing an increase from 30.5% in 1999-2000. Notably, the medical costs for adults with obesity were $1,861 higher than those for people with a healthy weight, (Adult Obesity Facts | Overweight & Obesity | CDC, n.d.). Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver condition in the United States, with a prevalence of 25% in adults. Of those with NAFLD, about 20% have non-alcoholic steatohepatitis (NASH), which affects approximately 5% of adults in the U.S. (American Liver Foundation, 2022) (Liver - American Liver Foundation, n.d.). The increased prevalence of NAFLD/NASH in recent years is associated with rises in obesity, type 2 diabetes mellitus (T2DM), and metabolic syndrome (Nouraei et al., 2021,)

Also, polycystic ovarian syndrome (PCOS) is one of the most common causes of female infertility, affecting 6% to 12% (as many as 5 million) of reproductive-age women in the United States. Women with PCOS are at risk of developing serious health problems such as diabetes, gestational diabetes, heart disease, high blood pressure, high LDL and low HDL cholesterol, sleep apnea, stroke, depression, and anxiety. (PCOS (Polycystic Ovary Syndrome) and Diabetes | CDC, n.d.).

Diabetes, as a chronic debilitating medical condition, is often associated with risk factors such as prediabetes (Beulens et al., 2019) overweight, obesity (Essah et al., 2011), and insulin resistance associated with polycystic ovary syndrome (Rocha et al., 2019).

In recent years, there has been significant progress in the development of antidiabetic medications that have proven efficacious not only in managing diabetes but also in addressing non-diabetic medical conditions. These medications have revolutionized the management of certain cardiovascular diseases, chronic kidney disease, obesity, fatty liver disease, and polycystic ovarian syndrome (PCOS (Polycystic Ovary Syndrome) and Diabetes | CDC, n.d.).

For example, GLP-1 agonists, such as liraglutide and exenatide, have shown promising effects in managing cardiovascular diseases (in patients without heart failure), micro vasculopathy, non-fatal myocardial infarction, and non-fatal stroke (Jia et al., 2018; Mikhail, 2018; M. Nauck, 2016). These drugs have also demonstrated significant utility in managing overweight/obesity and fatty liver disease (Alruwaili et al., 2021; Mehta et al., 2017). On the other hand, SGLT2 inhibitors, including dapagliflozin, canagliflozin, and empagliflozin, have shown benefits in managing heart failure (Butler et al., 2020; Pandey et al., 2022; Vaduganathan et al., 2022a) and chronic kidney disease (Toyama et al., 2019).

Due to the increasing incidence of the aforementioned chronic diseases often associated with type 2 diabetes mellitus and the overall burden of health, we saw the need to conduct a comprehensive research endeavor. This review aims to provide valuable insights into the emerging field of repurposing diabetic medications for non-diabetic conditions. It seeks to evaluate the relevance of these anti-diabetic medications, their commonality if any, distinguishing drug characteristics, mechanisms of action, and patient characteristics in which these medications have demonstrated clear benefits. Additionally, the review will explore the potential benefits and limitations associated with this novel therapeutic approach. The findings presented herein are intended to inform future research, clinical decision-making, and the development of evidence-based guidelines for the use of these medications beyond their established indications in diabetes management.

2.0 METHODOLOGY

We conducted a comprehensive search of PubMed and Google Scholar to identify Englishlanguage studies published in the United States and Canada between January 1st, 2013, and August 31st, 2023. Our search focused on trials involving GLP-1RA, SGLT-2i, and thiazolidinediones therapy. To ensure inclusivity, we reviewed various sources, including clinical trials, articles, books, journal publications, summary meta-analyses, US Food and Drug Administration labels, and professional society guidelines. The literature search was performed between May 10, 2023, and July 31, 2023, to ensure the most up-to-date and relevant information for our analysis.

3.0 LITERATURE REVIEW

GLP-1 Receptor Agonists (GLP-1 RA)

Glucagon-like peptide 1 receptor agonists (GLP-1 RA) are analogs of GLP-1, a gut-derived peptide hormone known for its ability to lower glucose levels by stimulating insulin secretion from pancreatic islets in response to an oral glucose load, a phenomenon referred to as the incretin effect (Latif et al., 2023). These agonists also work to decrease glucagon secretion, slow gastric emptying, and enhance satiety through their interaction with the glucagon-like peptide-1 (GLP-1) receptor on pancreatic beta cells (Levin et al., 2017).

Emerging evidence suggests that GLP-1 analogs exert effects on receptors distributed throughout the human body, contributing to arterial vasodilation, blood pressure reduction, increased diuresis, and natriuresis, as well as improvements in endothelial and myocardial function, heart failure, and ischemia (Latif et al., 2023).

Side Effects

The most common adverse effects of GLP-1 RAs are nausea, vomiting, and diarrhea, which stem from their impact on gastric emptying. These symptoms are more frequently observed with shortacting preparations (G. B. J. Mancini et al., 2022). However, to ameliorate gastrointestinal distress, starting GLP-1 agonist medications at the lowest tolerable dose and adjusting it as tolerated can be effective (Honigberg et al., 2020). It's important to note that dulaglutide has been associated with cardiovascular conduction abnormalities like sinus tachycardia, PR interval prolongation, and 1st degree AV block, warranting caution in patients with preexisting arrhythmias. In the PIONEER 0 and 10 trials, reports of nasopharyngitis and upper respiratory infections (URIs) were documented. Others include acute pancreatitis, cholecystitis, and

cholelithiasis, and hence are contraindicated in patients with these conditions (Honigberg et al., 2020). Nevertheless, a systematic review and meta-analysis by (Sattar et al., 2021) revealed no elevated risk of severe hypoglycemia, pancreatitis, or pancreatic cancer.

Contraindications

GLP-1 receptor agonist drugs are contraindicated in patients with hypersensitivity to the drug (Latif et al., 2023), those with a personal or family history of medullary thyroid cancer or multiple endocrine neoplasia syndrome type 2, individuals with gastroparesis, chronic nausea, or a history of gastric surgical procedures, and in pregnant and breastfeeding women. Semaglutide is contraindicated in cases of diabetic retinopathy (Honigberg et al., 2020).

GLP 1 RA and Cardiovascular Disease

Cardiovascular disease is a leading cause of mortality in individuals with diabetes. Those who possess both established atherosclerotic cardiovascular disease (ASCVD) and diabetes are at high risk for recurrent major adverse cardiovascular events (MACE), (Honigberg et al., 2020). Following the demonstrated reduction in MACE from randomized clinical trials of once-daily dosed liraglutide and once-weekly injections of semaglutide, albiglutide, and dulaglutide; the USFDA approved 3 GLP-1 receptor agonists, liraglutide, injectable semaglutide, and dulaglutide for cardiovascular risk reduction. Albiglutide is no longer in use due to withdrawal from the market by its manufacturers for commercial/economic reasons (Latif et al., 2023).

Accumulated data has shown the cardiovascular benefit of selected GLP-1 receptor agonists as a risk reduction in MACE by 12%, cardiovascular death by 12%, all-cause mortality by 12%, stroke by 16%, and myocardial infarction by 9% (Honigberg et al., 2020). The exact mechanism by which some of these agents reduce cardiovascular outcomes remains unclear (Khan et al., 2020a). However, the proposed mechanisms of cardiovascular risk reduction seen with GLP-1 receptor agonists can be attributed to their non-glycemic benefits such as blood pressure and weight reduction (Kelly et al., 2022).

Several cardiovascular outcome trials have been done on the GLP-1 receptor agonists. From the LEADER-6 trial (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results), after a median follow-up of 3.8 years, the primary endpoint of death from cardiovascular causes, non-fatal myocardial infarction, non-fatal stroke, occurred in fewer patients in the liraglutide group compared to the placebo group [(13 versus 14.9%, HR 0.87, 95% CI 0.78 – 0.97), The treatment outcomes of GLP-1 RA use in patients with prevalent Heart Failure demonstrated a consistent reduction in MACE, cardiovascular and all-cause death with liraglutide (M. A. Nauck et al., 2018).

In both the SUSTAIN-6 (Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes) and PIONEER-6 (Peptide Innovation for Early Diabetes Treatment) trials, semaglutide was found to have consistently reduced MACE across subgroups, except in patients with known heart failure (Tuttle et al., 2023). Liraglutide has a cardiovascular benefit in high-risk patients, while subcutaneous semaglutide has been shown to cause a statistically significant reduction in death from cardiovascular events, though there is a discussion about the possibility of confounding from its high HbA1c reduction effect. A reduction in relative risk and absolute risk reduction for major adverse cardiovascular events has been shown

by semaglutide, while liraglutide and dulaglutide have shown significant reductions in cardiovascular outcomes.

However, the EXSCEL (Exenatide Study of Cardiovascular Events Lowering) trial only demonstrated risk reduction in mortality and HF hospitalization in patients without prevalent HF (Holman et al., 2017) (Latif et al., 2023) (Khan et al., 2020b). A reduction in ASCVD was reported with liraglutide, subcutaneous semaglutide, and dulaglutide when compared with placebo. However, these GLP-1 receptor agonists have been found to have no effect on heart failure outcomes and the risk of hospitalizations (OR 0.87, 95% CI 0.79-0.95). Regarding the use of GLP1 receptor agonists for heart failure and its outcomes, a meta-analysis of large cardiovascular outcome trials of patients with T2DM showed a significant 9% reduction in hospitalizations due to heart failure (Khan et al., 2020b).

Professional guidelines recommend the use of GLP-1 receptor agonists in patients with T2DM and established atherosclerotic cardiovascular disease (ASCVD), as well as those with multiple ASCVD risk factors, independent of glucose control or background antihyperglycemic therapy (Honigberg et al., 2020).

GLP 1 RA and CKD

The GLP-1 receptor agonists confer nephron protection through direct effects on the kidneys as well as their direct and indirect effects on glycemic control (Yu et al., 2022). One direct renal protective effect is achieved through optimal glucose control and regulated insulin production. These medications emulate the actions of the naturally occurring hormone, GLP-1. Enhanced glycemic control, therefore, safeguards the kidneys against the direct toxic effects of hyperglycemia on the nephrons and renal arteriolosclerosis (Thomas, 2017).

Gerstein et al. (2019) conducted a post hoc analysis of the REWIND trial from 2013. The REWIND study primarily aimed to demonstrate the benefits of the drug dulaglutide in cardiovascular outcomes. It was a multicenter, randomized, double-blind, placebo-controlled trial where urinary albumin-to-creatinine ratios (UACRs) and estimated glomerular filtration rates (eGFRs) were estimated from urine and serum values measured in local laboratories every 12 months. Their analysis indicated that the renal outcome (defined as the first occurrence of new macroalbuminuria (UACR >33.9 mg/mmol), a sustained decline in eGFR of 30% or more from baseline, or chronic renal replacement therapy) developed at an incidence rate of 3.5 per 100 person-years in the dulaglutide group and an incidence rate of 4.1 per 100 person-years in the placebo group. The authors concluded that long-term use of dulaglutide was associated with reduced composite renal outcomes in people with type 2 diabetes (Gerstein et al., 2019).

Similarly, a study by (Tuttle et al., 2018) aimed to conduct a post hoc analysis on the AWARD trial to determine changes in eGFR while using dulaglutide and insulin glargine. They concluded that in patients with type 2 diabetes and moderate-to-severe chronic kidney disease, once-weekly dulaglutide produced glycemic control similar to that achieved with insulin glargine, with a reduction in eGFR decline. Thus, they suggested that dulaglutide appears to be safe for achieving glycemic control in patients with moderate-to-severe chronic kidney disease.

Tuttle et al. (2019) conducted further analysis to determine if the observed renal protection of dulaglutide was due to changes in body weight. The researchers concluded that the reduction in

eGFR decline observed with dulaglutide was not influenced by body weight loss but was due to the direct effect of dulaglutide. This report further strengthens the position that GLP-1 receptor agonists have direct preservation effects on renal function. In the same vein, (Tuttle et al., 2023) conducted post hoc analysis on the PIONEER 6 and SUSTAIN 6 trials to determine the effects of a GLP-1 receptor agonist - Semaglutide on GFR decline. The researchers concluded that pooled analyses of clinical trial data in patients with T2DM suggest that semaglutide may reduce the rate of eGFR decline.

Furthermore, (Sattar et al., 2021) conducted a systematic review and meta-analysis of the most upto-date evidence on the cardiovascular benefits and risks of GLP-1 receptor agonists from outcome trials in patients with type 2 diabetes. They found that overall, GLP-1 receptor agonists reduced the composite kidney outcome (development of macroalbuminuria, doubling of serum creatinine, or at least a 40% decline in estimated glomerular filtration rate (eGFR), kidney replacement therapy, or death due to kidney disease; worsening of kidney function, based on eGFR change). The GLP-1 agonists have been proven to be beneficial in the management of patients with chronic renal disease, with or without the presence of diabetes. (G. Mancini et al., n.d.)

GLP 1 RA and Obesity

Obesity represents a global health concern associated with several diseases, such as type 2 diabetes mellitus (T2DM), cardiovascular disease, osteoarthritis, certain types of cancers, sleep apnea, asthma, and nonalcoholic fatty liver. According to the CDC, in the United States, obesity medications may be considered for patients with a body mass index (BMI) ≥30 kg/m² or a BMI ≥27 kg/m² in those who have obesity-related health problems and have had unsuccessful lifestyle changes. Different research studies have demonstrated that Glucagon-Like Peptide 1 Agonists provide the most weight-loss benefit compared to other anti-diabetic medications. They not only improve glycemic efficacy without causing hypoglycemia, but they also decrease weight and blood pressure, thereby exerting an overall cardioprotective effect. This led the FDA to approve the use of GLP-1 agonists in obesity management. (Latif et al., 2023). Exenatide was the first GLP-1 receptor agonist to receive FDA approval in 2005, while oral semaglutide was approved in 2019 (Latif et al., 2023).

In a phase 3, double-blind, randomized controlled trial, (Wilding et al., 2021) assigned 1961 individuals to receive either 2.4 mg of semaglutide or a placebo, along with lifestyle modification. Participants in the semaglutide group experienced a mean weight reduction of 14.9%, while the placebo group showed a decrease of 2.4% (95% CI -13.4 to -11.5). In a study conducted by (PiSunyer et al., 2015), high-dose 3 mg liraglutide led to body weight reduction. This 56-week double-blind trial involved 3731 participants with a BMI of 30 or above, or 27 with comorbidities, who were randomly administered 3 mg of liraglutide (2487 patients) or a placebo (1244 patients); both groups received counseling on lifestyle changes. At the study's conclusion, participants in the liraglutide group experienced a mean weight loss of 8.4±7.3 kg, whereas those in the placebo group lost a mean of 2.8±6.5 kg (a difference of -5.6 kg; 95% confidence interval, -6.0 to -5.1; $P<0.001$). Additionally, 63.2% of participants in the liraglutide group achieved at least 5% weight reduction ($P<0.001$) compared to 27.1% in the placebo group. Moreover, 33.1% and 10.6% achieved more than 10% weight loss in the liraglutide and placebo groups, respectively ($P<0.001$).

Semaglutide 2.4 mg once a week and high dose liraglutide have received FDA approval for chronic weight management. Other GLP-1 analogs also possess the favorable side effect of weight loss; however, they have not yet received FDA approval for this indication. (Latif et al., 2023). Tirzepatide, a novel medication recently FDA-approved for type 2 diabetes, holds promise for obesity treatment due to its robust weight loss properties. This dual agonist of GLP-1 and GIP receptors mimics the effects of GLP-1 medications. It is administered as a once-weekly subcutaneous injection. Approved in May 2022, Tirzepatide has exhibited efficacy in reducing hemoglobin A1C levels and weight in trials, notably the SURPASS-5 trial. In this 40-week study, doses of 5mg per week resulted in a remarkable -2.11% reduction in hemoglobin A1C and a 5.4 kg weight loss. Higher doses of 15mg per week achieved a -2.34% reduction in hemoglobin A1C and an impressive 10.5 kg weight loss. (Klein et al., n.d.).

SGLT-2 Inhibitors (SGLT 2 I)

SGLT-2 inhibitors (sodium-glucose cotransporter 2 inhibitors) comprise a class of prescription medicines FDA-approved for use with diet and exercise to lower blood sugar in adults with type 2 diabetes. The SGLT2 inhibitor class includes bexagliflozin, canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin (Weir et al., 2022)/

The sodium-glucose cotransporter 2 (SGLT2) is located in the proximal tubule of the kidney and is responsible for reabsorbing filtered glucose in the kidney. In type 2 diabetes, the kidneys' capacity to reabsorb glucose is increased, which is a maladaptive response linked to heightened SGLT2 expression (Vallon & Thomson, 2017). SGLT-2 inhibitors reduce renal tubular glucose reabsorption, resulting in glucosuria and a reduction in blood glucose without stimulating insulin release, thus providing a beneficial effect for type 2 diabetes mellitus (Hsia et al., 2017) **Side Effects**

SGLT2 inhibitors lower blood glucose by downregulating the renal threshold for glucose excretion and increasing urinary glucose excretion (Geerlings et al., 2014), which may lead to overgrowth of commensal genital microorganisms. Consequently, the risk of genital infections and urinary tract infections (UTIs) is likely to increase in patients taking SGLT2 inhibitors (Bonora et al., 2018). SGLT2 inhibitors are also associated with potential side effects, including lower limb amputations (particularly with canagliflozin), an increased risk of fractures (Menne et al., 2019), potential diabetic ketoacidosis (DKA)(Bonora et al., 2018), acute kidney injury, and hypotension (Pittampalli et al., 2018)

Contraindications

SGLT2 inhibitors are contraindicated in patients with a history of serious hypersensitivity reactions to the drug, pregnancy, breastfeeding, dialysis patients, patients with eGFR <30 ml/min/1.73m² (dapagliflozin), end-stage renal disease (dapagliflozin and empagliflozin), and severe renal impairment (Das et al., 2020). Regular monitoring of renal function, blood pressure, volume status, glycemic indices, and signs of diabetic ketoacidosis is crucial when using SGLT2 inhibitors (Yau et al.,2022).

SGLT 2 Inhibitors and Cardiovascular Disease

Several large clinical trials involving dapagliflozin, canagliflozin, and empagliflozin have shown benefits of SGLT2 I's in cardiovascular disease to decrease the progression of heart failure and

decrease the risk of Atherosclerotic Cardiovascular Disease. In the DECLARE-TIMI 58 trial, dapagliflozin demonstrated a reduction in major adverse cardiovascular events (MACE) in patients with T2DM and atherosclerotic heart disease. compared to placebo (8.8% vs. 9.4%). It also reduced HbA1c by 0.42%. The drug significantly lowered the risk of cardiovascular death or heart failure hospitalization (4.9% vs. 5.8%) and HF hospitalization alone (2.5% vs. 3.3%). However, it carried a slight risk of diabetic ketoacidosis (0.3% vs. 0.1%) and genital infections (0.9% vs. 0.1%) (Furtado et al., 2019) (Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58 - American College of Cardiology, n.d.)

The DAPA-HF study showed a significant improvement in the primary outcome of patients treated with dapagliflozin, which was a combination of cardiovascular death, hospitalization for heart failure, or urgent heart failure visits. The rate of this primary outcome was 16.3% in the dapagliflozin group compared to 21.2% in the placebo group ($p < 0.001$). Dapagliflozin also demonstrated benefits in secondary outcomes, with lower rates of cardiovascular death (9.6% vs. 11.5%) and hospitalization for heart failure (9.7% vs. 13.4%) compared to placebo. The drug showed consistent benefits in different subgroups, including age, risk level, diabetes status, and baseline medication use. The study also found no significant adverse safety events related to dapagliflozin use. Despite the associated decline in estimated glomerular filtration rate (eGFR) with dapagliflozin, it was reported to have better clinical outcomes (McMurray et al., 2019).

The EMPEROR - reduced - trial comparing empagliflozin to placebo showed promising results for patients with symptomatic heart failure with reduced ejection fraction (HFrEF) regardless of their diabetes status. The primary outcome, a combination of cardiovascular death or HF hospitalization, was significantly lower in the empagliflozin group (19.4%) compared to the placebo group (24.7%, $p < 0.001$). There were also positive effects on secondary outcomes, including reductions in cardiovascular death (10% vs. 10.8%), HF hospitalization (13.2% vs. 18.3%), total hospitalizations (388 vs. 553, $p < 0.001$), and composite renal outcome (1.6 vs. 3.1, $p < 0.01$). However, there was no significant difference in all-cause mortality between the empagliflozin group (13.4%) and the placebo group (14.2%) (HR 0.92, 95% CI 0.77-1.10, $p > 0.05$). The trial demonstrated that empagliflozin has significant potential in improving heart failure outcomes in patients with reduced ejection fraction. Empagliflozin also showed benefit in severe left ventricular dysfunction. (McMurray et al., 2019; Packer et al., 2021)

The EMPEROR-Preserved trial comparing empagliflozin to placebo, showed significant benefits in heart failure outcomes among patients with symptomatic stable heart failure with preserved ejection fraction (HFpEF) (EF >40%) regardless of their diabetes status. The primary outcome, a combination of cardiovascular death or HF hospitalization, was lower in the empagliflozin group (13.8%) compared to the placebo group (17.1%, $p < 0.001$). Secondary outcomes also showed positive effects, including reductions in HF hospitalizations, total hospitalizations, and improvement in estimated glomerular filtration rate (eGFR) slope. However, there was no significant difference in all-cause mortality or composite renal outcomes between the two groups. The benefits of empagliflozin were seen in both patients with and without type 2 diabetes. The effect on eGFR decline was more pronounced in patients with diabetes. The improvement in quality-of-life measures was seen early and sustained for 1 year. (Butler et al., 2022; Filippatos et al., 2022)

The SOLOIST-WHF trial evaluated the effects of sotagliflozin, a dual SGLT1 and SGLT2 inhibitor, on cardiovascular outcomes in patients with type 2 diabetes (T2DM) and heart failure (HF). The trial was stopped early due to COVID-19, but the results showed promising benefits. The primary endpoint, a combination of total cardiovascular death, hospitalization for HF, or urgent HF visit was significantly lower in the sotagliflozin group (70 events/100 patient-years) compared to the placebo group (98 events/100 patient-years) ($p = 0.0009$). Secondary outcomes also favored sotagliflozin, including total cardiovascular death and hospitalization for HF, first cardiovascular death and hospitalization for HF, and improvement in the Kansas City Cardiomyopathy Questionnaire (KCCQ)-12 score. Sotagliflozin's benefits were observed irrespective of baseline ejection fraction (EF) and prior history of heart failure, suggesting it may be beneficial for patients with HF with preserved EF (HFpEF) as well (Pitt et al., 2023; Szarek et al., 2021).

Other Cardiovascular Benefits

Studies involving SGLT2 inhibitors have also demonstrated a decrease in systolic, diastolic, and nocturnal blood pressure, along with improved circadian blood pressure rhythm, resulting in enhanced overall blood pressure control (Wilcox et al., 2020). Increased urine production and sodium excretion contribute to reduced plasma volume, alleviating fluid overload and congestion in heart failure patients. SGLT2 inhibitors also facilitate the utilization of fatty acids and ketones as alternative energy sources for the heart, leading to improved cardiac function and efficiency. By reducing inflammatory markers and cytokines, SGLT2 inhibitors mitigate the inflammatory response, potentially preventing adverse cardiac remodeling and protecting against ischemia/reperfusion injury (Lopaschuk & Verma, 2020).

SGLT2 inhibitors promote weight reduction through glucosuria and decreased adipose tissue mass, improving insulin sensitivity, and alleviating cardiovascular burden. Improved glycemic control and reduced HbA1c levels contribute to the overall cardiovascular benefits of SGLT2 inhibitors. Attenuation of sympathetic overactivity by SGLT2 inhibitors leads to reduced vasoconstriction and cardiac workload. SGLT2 inhibitors also inhibit the cardiac Na+/H+ exchanger, reduce hyperuricemia, increase autophagy and lysosomal degradation, decrease epicardial fat mass, elevate erythropoietin levels, boost circulating pro-vascular progenitor cells, reduce oxidative stress, and enhance vascular function (Lopaschuk & Verma, 2020).

SGLT2 Inhibitors and CKD

SGLT2 inhibitors have demonstrated significant renal protective effects in patients with chronic kidney disease, regardless of diabetes presence. These protective effects extend beyond glycemic control, encompassing mechanisms such as blood pressure regulation, uric acid level reduction, and hemoglobin optimization (Solomon et al., n.d.; Vaduganathan et al., 2022b). In the DAPA CKD trial, 4304 participants with an estimated glomerular filtration rate (eGFR) of 25 to 75 ml per minute per 1.73 m^2 and a urinary albumin-to-creatinine ratio of 200 to 5000 were randomly assigned dapagliflozin (10 mg once daily) or placebo. Irrespective of diabetes status, the risk of a composite endpoint consisting of a sustained GFR decline of ≥50%, end-stage kidney disease, or death from renal or cardiovascular causes was significantly lower with dapagliflozin than with placebo (H. J. L. Heerspink et al., 2020)

The EMPA-REG trial evaluated the efficacy, safety, and tolerability of empagliflozin (10 mg and 25 mg) versus placebo as an add-on to existing anti-diabetes treatment in patients with type 2 diabetes and CKD. The study concluded that empagliflozin treatment was associated with a significant 39% reduction in the relative risk of incident or worsening nephropathy compared to placebo (Barnett et al., 2014). Similarly, the DAPA-HF trial, originally cardiovascular-focused, demonstrated that dapagliflozin 10 mg significantly reduced the risk of progression to the secondary renal endpoint in patients with cardiovascular diseases, including those with chronic kidney disease (Kristensen et al., 2019).

In the CVD-REAL trial of 2020 (H. Heerspink et al., n.d.), aimed at assessing the rate of eGFR decline and progression to end-stage renal disease among diabetics, initiation of SGLT2 inhibitor therapy was associated with a slower rate of kidney function decline and lower risk of major kidney events compared with other glucose-lowering drugs (Heerspink et al., 2020). The researchers concluded that the results imply that the benefits of SGLT2 inhibitors on kidney function, as identified in clinical trials, are broadly applicable to real-world clinical practice.

The CREDENCE trial compared 100 mg of canagliflozin and a placebo in terms of renal and cardiovascular endpoints. The trial reported a 34% lower relative risk of the renal-specific composite of end-stage kidney disease and a 32% lower relative risk of doubling creatinine level or death from renal causes in the canagliflozin group (Perkovic et al., 2019). These are consistent with other reports indicating enhanced renal outcomes in patients with chronic kidney disease who use SGLT2 inhibitors. Therefore, SGLT2 inhibitors hold significant potential in diabetes patient management by improving glucose control and slowing the rate of progression of renal disease (Neal et al., 2017)

Diabetic Medications in Non-Alcoholic Fatty Liver Disease (NAFLD)

Non-alcoholic fatty liver disease, now referred to as Metabolic dysfunction-associated steatotic liver disease (MASLD), encompasses a spectrum of conditions (Steatosis, NASH, Fibrosis, and Cirrhosis) characterized by excessive fat accumulation in the liver. While weight loss remains a cornerstone of managing this condition, certain antidiabetic medications have demonstrated potential in ameliorating disease progression and likely reversing its course. Given the escalating global burden of NAFLD and NASH, it is imperative to persist in the search for accurate noninvasive diagnostic and prognostic biomarkers and to develop effective treatments for advanced NASH as well as preventive strategies for those at heightened risk of NAFLD and progressive liver disease (Younossi, 2019). Although no medication has yet been officially FDA-approved for NASH management, some antidiabetic medications have displayed promising outcomes in comparison to placebo concerning NASH progression. Further exploration is required to fully ascertain their potential utility. Among these antidiabetic medications, thiazolidinediones and GLP-1 agonists take precedence.

Research into thiazolidinediones, particularly pioglitazone, in NASH patients has revealed improvements in liver function, liver fat reduction, and NASH resolution, albeit with notable concerns about weight gain. Evidence for other thiazolidinediones has been relatively limited with mixed results, although generally in line with pioglitazone's effects: enhanced liver function and glucose measures. Investigation of GLP-1 receptor agonists has demonstrated their effectiveness in NAFLD management. Evidence indicates that liraglutide contributes to reductions in liver fat,

improved liver function, lowered HbA1c levels, NASH resolution, and weight loss. While Exenatide's efficacy is slightly lower, it still leads to significant reductions in liver fat and weight. Metformin, while improving weight and glucose control, does not substantially impact liver disease. (Blazina & Selph, 2019)

A 52-week double-blind placebo-controlled trial of semaglutide alongside lifestyle modification demonstrated noteworthy weight loss in comparison to liraglutide and placebo (Patrick M O'Neil, 2016). In the LEAN trial (Liraglutide Efficacy and Action in Non-alcoholic steatohepatitis), 52 patients were randomly assigned to liraglutide or placebo. The results indicated a higher rate of NASH resolution (9/23 versus 2/22; P=0.019) and less fibrosis progression (2/23 versus 8/22; P=0.04) with liraglutide, albeit in a small participant pool. A meta-analysis of 6 studies demonstrated that GLP-1 RAs reduce circulating transaminase levels and enhance histology, suggesting potential benefits for NASH treatment (Khan et al., 2020b).

Side effects of Thiazolidinediones primarily encompass mild adverse events related to gastrointestinal distress, lower extremity edema, and general fatigue. These medications should be avoided in patients with heart failure and fluid retention.

Diabetic Medications in PCOS

Polycystic ovarian syndrome (PCOS) stands as the most prevalent endocrine pathology among females of reproductive age worldwide. It is closely linked to various morbidities, including nonalcoholic fatty liver disease/nonalcoholic steatohepatitis (NAFLD/NASH), with women having PCOS being three times more susceptible to NAFLD (Rasquin et al., 2022). A frequent characteristic of women with PCOS is insulin resistance (IR), marked by elevated basal insulin secretion and reduced insulin response to glucose overload (Azziz, 2018).

Diabetic medications have shown promise in treating PCOS patients. This can be attributed to the impaired glucose tolerance (IGT) often observed in PCOS, which can advance to type 2 diabetes mellitus (T2DM). Moreover, obesity is a common factor shared by both conditions. It is worth noting that studies directly establishing the effects of these medications on PCOS are somewhat limited in the USA/Canada. The Endocrine Society advocates the initiation of metformin in PCOS patients with T2DM or Impaired Glucose Tolerance who do not respond to lifestyle modifications, as metformin has demonstrated efficacy in hindering the progression from IGT to T2DM (Rasquin et al., 2022).

In a study by (Niafar et al., 2016) 178 women with PCOS were administered liraglutide and monitored over a 3-month period. The findings indicated reduced basal metabolic index (BMI) and testosterone levels, which correlated with an enhanced ovulation rate in obese women with PCOS. However, further research employing larger sample sizes and extended treatment durations would be valuable. DPP4 inhibitors have also exhibited favorable outcomes in obese women with PCOS through their capacity to induce weight loss and lower blood glucose levels (Devin et al., 2020). Further research examining the use of these medications for PCOS is recommended for the future, as it holds the potential to provide valuable insights for clinical management and treatment strategies in women with this complex endocrine disorder.

SUMMARY

Table 1: Breakdown of Clinical Trials Conducted on Distinct Patient Classes and Their Findings

Patient Type	Clinical Trials	Main Findings
Patients with prevalent Heart Failure	LEADER-6 trial (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results)	Consistent reduction in MACE, cardiovascular and all-cause death with liraglutide
Patients with Type 2 Diabetes	SUSTAIN-6 (Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes)	Semaglutide was found to have consistently reduced MACE across subgroups, except in patients with known Heart Failure.
Patients with Type 2 Diabetes with high cardiovascular risks.	PIONEER-6 (Peptide Innovation for Early Diabetes Treatment)	Semaglutide was found to have consistently reduced MACE across subgroups, except in patients with known Heart Failure.
Patients with type 2 diabetes with or without the risks of cardiovascular events.	EXSCEL (Exenatide Study of Cardiovascular Events Lowering) trial	Only demonstrated risk reduction in mortality and HF hospitalization in patients without prevalent HF
Type 2 Diabetes mellitus with established cardiovascular disease	HARMONY TRIAL	Demonstrated prevention of HF events in at-risk patients with T2DM
Patients with type 2 diabetes. and established cardiovascular disease or multiple risk factors.	REWIND trial of 2013	Long-term use of Dulaglutide was associated with reduced renal composite outcomes, (defined as the first occurrence of microalbuminuria, UACR greater than 33.9mg/mol, a sustained decline in Egfr of 30% or more from baseline or chronic renal replacement therapy
Patients with Type 2 Diabetes mellitus and established atherosclerotic cardiovascular disease or with multiple risk factors for atherosclerotic cardiovascular disease.	DECLARE-TIMI 58 trial	Dapagliflozin demonstrated a reduction in major adverse cardiovascular events (MACE) in patients with T2DM and atherosclerotic heart disease. compared to placebo

Patients with HF and reduced ejection Fraction with or without type 2 diabetes mellitus.	DAPA-HF study	Showed significant improvement in the primary outcome.of patients treated with dapagliflozin, (which was a combination of cardiovascular death, hospitalization for heart failure, or urgent heart failure visit
Patients with symptomatic heart failure with reduced ejection fraction (HFrEF) regardless of their diabetes status.	EMPEROR - reduced - trial	Comparing empagliflozin to placebo showed promising results for patients with symptomatic heart failure with reduced ejection fraction (HFrEF) regardless of their diabetes status. The primary outcome, a combination of cardiovascular death or HF hospitalization, was significantly lower in the empagliflozin group (19.4%) compared to the placebo group (24.7%, $p < 0.001$). There were also positive effects on secondary outcomes, including reductions in cardiovascular death (10% vs. 10.8%), HF hospitalization (13.2% vs. 18.3%), total hospitalizations (388 vs. 553, $p < 0.001$), and composite renal outcome (1.6 vs. 3.1, $p < 0.01$)
Patients with symptomatic stable heart failure with preserved ejection fraction (HFpEF) (EF >40%) regardless of their diabetes status.	EMPEROR-Preserved trial comparing Empagliflozin to placebo, showed significant benefits in heart failure outcomes among patients with symptomatic stable heart failure with preserved ejection fraction (HFpEF) (EF >40%) regardless of their diabetes status.	The primary outcome, a combination of cardiovascular death or HF hospitalization, was lower in the empagliflozin group (13.8%) compared to the placebo group (17.1%, $p < 0.001$). Secondary outcomes also showed positive effects, including reductions in HF hospitalizations, total hospitalizations, and improvement in estimated glomerular filtration rate (eGFR) slope
Patients with type 2 diabetes (T2DM) and heart failure (HF).	SOLOIST-WHF trial evaluated the effects of sotagliflozin, a dual SGLT1 and SGLT2 inhibitor, on cardiovascular outcomes in patients with type	The primary endpoint, a combination of total cardiovascular death, hospitalization for HF, or urgent HF visit, was significantly lower in the sotagliflozin group (70 events/100 patient-years) compared

	2 diabetes (T2DM) and heart failure (HF).	to the placebo group (98 events/100 patient-years) (p = 0.0009). Secondary outcomes also favored sotagliflozin, including total cardiovascular death and hospitalization for HF, first cardiovascular death and hospitalization for HF, and improvement in the Kansas City Cardiomyopathy. Questionnaire (KCCQ)-12 score. Sotagliflozin's benefits were observed irrespective of baseline ejection fraction (EF) and prior history of heart failure, suggesting it may be beneficial for patients with HF with preserved EF (HFpEF) as well.
Patients with chronic kidney disease, regardless of the presence or absence of diabetes	DAPA CKD trial, randomly assigned 4304 participants with an estimated glomerular filtration rate (GFR) of 25 to 75 ml per minute per 1.73 m2 of body-surface area and a urinary albumin-to-creatinine ratio (with albumin measured in milligrams and creatinine measured in grams) of 200 to 5000 to receive dapagliflozin (10 mg once daily) or placebo.	Among patients with chronic kidney disease, regardless of the presence or absence of diabetes, the risk of a composite of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes was significantly lower with dapagliflozin than with placebo
Patients with type 2 diabetes and CKD	The EMPA-REG trial aimed to establish the efficacy, safety, and tolerability of empagliflozin 10 mg and 25 mg once daily versus placebo over 52 weeks as an add-on to existing antidiabetes treatment in patients with type 2 diabetes and CKD	The trial concluded Empagliflozin treatment (10-mg and 25-mg pooled dose group) was associated with a statistically significant 39% reduction in relative risk of incident or worsening nephropathy vs placebo
Patients with HF and reduced ejection Fraction with or without type 2 diabetes mellitus.	The DAPA-HF trial (McMurray et al 2019) also a primarily cardiovascular-based trial reported that the use of SGLT2 inhibitor dapagliflozin 10 mg in patients with	Significantly lowered the risk of progression to the secondary renal endpoint, even in patients with chronic kidney disease

	cardiovascular diseases, significantly lowered the risk of progression to the secondary renal endpoint, even in patients with chronic kidney disease	
Patients with Type 2 Diabetes mellitus and chronic kidney disease with and without known cardiovascular disease.	The CREDENCE TRIAL, Perkovic et al, 2019, compared 100mg canagliflozin and placebo to renal and cardiovascular endpoints by assessing the relative risk of the renal specific composite of end-stage kidney disease.	They reported that doubling the creatinine level or death from renal causes was lower by 43%, and the relative risk of end stage kidney disease was lower by 32% in the canagliflozin group.

Table 2: Diabetic Drug Class and Non-Diabetic Uses

Drug Class	GLP I RA	SGLT2 Inhibitors	Thiazolidinediones
Non-Diabetic Conditions	Cardiovascular Disease	Cardiovascular Disease	PCOS
	Chronic Kidney Disease	Chronic Kidney Disease	
	Obesity		
	NAFLD/NASH		
	PCOS		

4.0 CONCLUSION AND RECOMMENDATIONS

Conclusion

In recent years, diabetes management has evolved beyond glycemic control, with medications revealing multifaceted benefits. GLP-1 receptor agonists display notable cardiovascular impact, independently of A1C levels, potentially curbing nonfatal stroke, myocardial infarction, and cardiovascular mortality. Tailored use among these agonists is crucial for distinct cardiovascular outcomes. They also reshape chronic kidney disease and obesity management, offering renal protection and novel avenues for intervention. SGLT2 inhibitors redefine therapeutic landscapes, delivering significant cardiovascular and renal advantages, albeit with monitored side effects. Trials like DECLARE-TIMI 58, DAPA-HF, EMPEROR-Preserved, and EMPEROR-Reduced reinforce their potential. In renal health, they slow GFR decline and microalbuminuria. This progress underscores a new era in holistic patient care where medications' extended capabilities offer optimism for improved outcomes and enhanced quality of life, with ongoing research promising further innovations. Future research holds promise in exploring and expanding the utility of these medications for various conditions, providing hope for enhanced patient outcomes and improved quality of life.

Recommendations

Based on our comprehensive review of diabetic medications and their diverse applications in various medical conditions, we recommend that healthcare practitioners consider the potential expanded utility of GLP-1 receptor agonists, thiazolidinediones, metformin, and Sodium-glucose

Cotransporter-2 (SGLT2) Inhibitors beyond their traditional diabetic indications. Clinicians should explore the incorporation of these medications into treatment strategies for cardiovascular disease, chronic kidney disease, obesity, non-alcoholic fatty liver disease (NAFLD), and polycystic ovary syndrome (PCOS) in the presence or absence of T2DM. However, it is essential to base such decisions on individual patient profiles while keeping in mind the contraindications, risks and benefits associated with these medications.

Research Gaps and Limitations

Our research journey encountered notable gaps in the available literature, particularly in relation to the benefits of GLP-1 receptor agonists (GLP-1 RAs) in chronic kidney disease (CKD). A significant portion of trials primarily focused on cardiovascular disease (CVD), and the renal benefits emerged through post hoc analysis, underscoring a need for more dedicated investigations in this specific context. Additionally, we identified a limitation in the landscape of available research papers in the USA and Canada concerning the direct effects of diabetic medications on non-alcoholic fatty liver disease (NAFLD) and polycystic ovary syndrome (PCOS). To address these gaps and enhance our understanding of the direct impacts of diabetic medications on NAFLD and PCOS, further dedicated research in this specific direction is paramount. These research gaps represent opportunities for future studies to advance our knowledge and improve patient care in these critical areas.

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