REVIEW ARTICLE

Pharmacological therapy and cardiovascular risk reduction for type 2 diabetes

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SUMMARY

The pharmacological therapy for type 2 diabetes mellitus has presented important advances in recent years, which has impacted the treatment of patients with established cardiovascular disease or with high cardiovascular risk. In this scenario, two drug classes have emerged and demonstrated clear clinical benefits: SGLT-2 inhibitors and GLP-1 agonists. The present review discusses the pharmacology, adverse effects, and clinical trials that have demonstrated the benefits of these medications in reducing cardiovascular risk.

KEYWORDS: *Diabetes mellitus, Hypoglycemic agents, Heart disease.*

INTRODUCTION

Type 2 diabetes mellitus (DM-2) is a prevalent condition that affects approximately 450 million people worldwide. It is expected that approximately 640 million people will be affected in 2040. Until recently, scientific evidence has indicated that pharmacological therapy for DM would be able to reduce only microvascular complications (retinopathy, nephropathy, and neuropathy). However, in 2008, after 10 years of follow-up, the UK Prospective Diabetes Study (UKPDS) observed potential for reducing cardiovascular events, including death, by improving the glycemic control of DM-2[1]. These observations were a milestone in cardio-diabetology since cardiovascular disease (CVD) is the main cause of death among diabetics.

In 2007, the results of a meta-analysis raised great concern about the use of oral antidiabetics by demonstrating a higher risk of acute myocardial infarction and mortality with the use of rosiglitazone[2]. Since then, the Food and Drug Administration and the European Medicines Agency have become concerned about the cardiovascular risk associated with new therapies for DM and have established that new drugs for the treatment of DM-2 should be tested in randomized, prospective, and controlled studies. Two classes of drugs, sodium-glucose co-transporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP-1) agonists, have shown not only safety but also great potential for reducing macrovascular events.

For decades, two key ways of treating diabetes were sulfonylureas,[3] which have controversial safety, and DPP-4 inhibitors, which are neutral in terms of cardiovascular endpoints. These characteristics were shown in the EXAMINE[4] and CAROLINA[5] studies. The only therapeutic target was glycemic control, and not the reduction of cardiovascular clinical events.

SGLT2 inhibitors

SGLT-2 transport protein inhibitors are the first class of medication for DM-2 therapy that has demonstrated a reduction in cardiovascular risk. SGLT-2 is a protein found in the proximal convoluted tubules of nephrons and is responsible for the reabsorption of 90% of the filtered glucose in the glomerulus. Another carrier protein found in nephrons is SGLT-1, which reabsorbs the remaining 10% of filtered glucose. Through this mechanism of action, SGLT2 inhibitors are able to reduce glycated hemoglobin (HbA1c) levels by 0.5-1%, in addition to reducing systolic (± 4-6 mmHg) and diastolic blood pressure (± 1-2 mmHg). The latter effect is due to greater osmotic diuresis and possibly also the promotion of nephron remodeling, improvement of endothelial function, reduction in arterial stiffness, and weight loss due to the caloric loss caused by glycosuria[6 - 10].

The SGLT2 inhibitors available so far are empagliflozin, canafliflozin, dapagliflozin, and ertugliflozin (table 1). All of these drugs are administered once a day due to their prolonged half-life. Furthermore, they have similar pharmacokinetic and pharmacodynamic characteristics except for the degree of selectivity of blocking SGLT-2 receptors in relation to SGLT-1 receptors (empagliflozin> ertugliflozin> dapagliflozin> canagliflozin). Among these, ertugliflozin is the only one with no studies demonstrating a reduction in cardio-vascular events thus far.

TABLE 1

SGLT-2 inhibitor	Doses available
Empagliflozin	10-25 mg once daily
Dapagliflozin	5-10 mg once daily
Canagliflozin	100-300 mg once daily
Ertugliflozin	5-15 mg once daily

The EMPA-REG OUTCOME study was the first large study to demonstrate a reduction in CV risk. This study tested the administration of empagliflozin in patients with DM and established CVD. After a 3.1-year follow-up, there was a 14% reduction in the incidence of the primary composite outcomes in the form of major adverse cardiac and cerebrovascular events (MACCE), which include cardiovascular death, stroke, and acute myocardial infarction (AMI). Emphasis was placed on the 38% reduction in the general mortality rate and the 32% reduction in the cardiovascular mortality rate. In addition, a 35% reduction in hospitalizations for heart failure has been reported, suggesting that the benefit of this class of drug is mainly due to its hemodynamic effects[7].

In 2017, the CANVAS study on canagliflozin was published. Unlike the EMPA-REG OUTCOME study, the CANVAS study included a mixed population of patients with DM-2 and CVD or without CVD, as well as multiple risk factors. Canagliflozin therapy reduced the primary endpoint composed of MACCE by 14%, but unlike the EMPAREG-OUTCOME study, there was no difference in the isolated analysis of mortality. Hospitalization rates for heart failure were also reduced by 33%[6]. The use of canagliflozin was also evaluated in patients with DM-2 and chronic kidney disease by the CREDENCE study. This study was conducted because of the possible benefits of SGLT2 inhibitors in reducing the progression of diabetic nephropathy. After an average follow-up of 2.6 years, a 39% reduction in hospitalization for heart failure and a 20% reduction in the outcome rates of MACCE were demonstrated, in addition to benefits in reducing the progression of diabetic nephropathy[11].

The DECLARE-TIMI 58 study published in 2019 analyzed the use of dapagliflozin in a mixed population with less severe conditions compared to previous studies. The population was composed of patients with CVD and DM-2 (40%) or with DM-2 and multiple risk factors. The results of 4 years of follow-up showed a 17% reduction in cardiovascular death and hospitalization for heart failure, which were mainly driven by a 27% reduction in hospitalization for heart failure. However, there was no significant decrease in cardiovascular death or the primary composite outcome[12].

An important difference is apparent in the reduction of clinical events among these four studies: a significant reduction in cardiac death was only observed in EMPAREG-OUTCOME. This could possibly be explained by the different populations included in each of these trials. EMPAREG-OUTCOME included only patients with established CVD, while the other three included heterogeneous populations of patients with or without CVD and different high risk factors.

The most recent major study to demonstrate the cardiovascular benefits of ISGLT2 is the DAPA-HF study. This study looked at the use of dapagliflozin in an exclusive population of patients with heart failure and reduced left ventricular ejection fraction (≤40%). The motivations for this study were the previous results demonstrating a significant reduction in the occurrence of hospitalization for heart failure and the biological mechanisms that could justify the use of this class of medication in patients with heart failure. It is important to highlight that the presence of DM-2 was not mandatory for inclusion in this trial and was not diagnosed in 58.2% of the participants. After a follow-up of only 18 months, dapagliflozin reduced hospitalization for heart failure by 30%, cardiovascular death by 18%, and all-cause mortality by 17%. Additionally, there was a symptomatic improvement in heart failure assessed by the Kansas City Cardiomyopathy Questionnaire[13].

Despite the clear documented benefits of the use of SGLT2 inhibitors, especially in a population with established CVD, some major side effects should be discussed. The glycosuric effect of this class of drugs causes an increased risk of infections of the genital tract, especially urinary infections and vulvovaginal candidiasis[14]. Osmotic diuresis with a consequent contraction of intravascular volume can trigger arterial hypotension in more susceptible patients[15]. Another adverse effect reported is the risk of lower limb amputations, particularly with the use of canagliflozin in the CANVAS study. This means that patients using SGLT2 inhibitors should be monitored and adequately oriented about foot care[6]. The CANVAS study also identified higher rates of bone fracture with canagliflozin, which seems to be explained by greater bone loss with this SGLT2 inhibitor[6]. Finally, there are reports of cases of diabetic euglycemic ketoacidosis[16, 17].

GLP-1 receptor agonists

In addition to pancreatic hormones (insulin, glucagon, and amylin), blood glucose homeostasis depends on gastrointestinal peptides, such as GLP-1 and glucose-dependent insulinotropic polypeptide (GIP). The production of these substances illustrates incretins' effect of greater stimulation of insulin secretion with an oral supply of glucose than an equivalent dose intravenous infusion[18]. GLP-1 is produced by L cells in the ileum and colon in response to hyperglycemia after caloric intake. After binding to its specific receptor, the peptide acts on various tissues, with the effect being greater on pancreatic beta cells. This leads to glucose-dependent insulin secretion and inhibits the release of glucagon. However, GLP-1 is rapidly degraded by the enzyme dipeptidyl peptidase-4 (DPP4)[19].

Synthetic analogues are resistant to the action of DPP4 and accentuate pleiotropic events that favor weight loss, such as delayed gastric emptying and reduced appetite. Defects in this regulation are possibly associated with the development of diabetes. Currently, six drugs have been approved for the treatment of DM2: exenatide, liraglutide, albiglutide, lixisenatide, dulaglutide, and semaglutide. All of them cause a significant reduction in glycated hemoglobin (0.55 - 1.21%), and long-acting ones are usually more effective in glycemic control[20]. One factor that can hinder adherence is the route of administration, since all of these medications are administered subcutaneously except for semaglutide, which can be taken orally (table 2).

TABLE 2

GLP-1 receptor agonists	Doses available
Ezenatide	5-10 mcg twice daily or 2 mg 1 once a week
Liraglutide	0.6-1.8 mg once daily
Lisenatide	10-20 mcg once daily
Albiglutide	30-50 mg once a week
Dulaglutide	0.75-1.5 mg once a week
Semaglutide	Subcutaneous: 0.25-1 mg once a week Oral: 7-14 mg once daily

Initial evidence has shown conflicting results regarding the reduction of CV risk. Only liraglutide and semaglutide have demonstrated superiority to standard therapy. The LEADER study published in 2016 showed a significant reduction (13%) in the primary outcomes (MACCE) when comparing the administration of liraglutide at 1.8 mg (or the maximum tolerated dose) over an average follow-up of 3.8 years[21]. This result was mainly driven by a reduction in CV death (22%), and unlike ISGLT2, there was no significant reduction in hospitalization rates for heart failure. The SUSTAIN-6 study tested semaglutide and showed an even more expressive reduction in the same composite outcome, with a 26% reduction in comparison to the control group. This result was mainly driven by stroke. However, there was no significant decrease in CV mortality or AMI[22]. The difference between these two studies may have occurred due to the shorter follow-up period (2.1 years) and the

lower number of participants in SUSTAIN-6. Both studies included patients with high cardiovascular risk, and 80% of them had established CVD and an average HbA1c of 8.7%.

Despite the encouraging results of the trials mentioned, other studies have failed to find a significant reduction in cardiovascular events with GLP-1 receptor agonists, and only the cardiovascular safety has been proven for some of these new drugs in comparison to a placebo. These studies were EXSCEL, which randomized 14,752 patients to use exenatide weekly; PIONEER 6, which examined oral semaglutide; and ELIXA, which included patients in a secondary prevention scenario for the evaluation of lixisenatide, and hospitalization for angina was part of the primary composite outcome[23-25].

More recently, the class effect theory for protection from cardiovascular events has gained strength since the publication of the HARMONY and REWIND studies[26, 27]. The first of these studies assessed albiglutide and demonstrated a 22% reduction in MACCE, which even led to the resumption of production of this medication, which had previously been discontinued. The REWIND study observed a reduction of only 12% in MACCE driven by stroke, but it included most patients in primary prevention, and only 31.5% had evidence of established atherosclerotic disease.

A meta-analysis published in 2019 demonstrated that GLP-1 RA reduces MACCE (NNT 75) and its individual components, in addition to reducing the risk of hospitalization for heart failure and worsening renal function (mainly by reducing macroalbuminuria). These benefits were achieved without increasing the risk of severe hypoglycemia[28]. It is important to highlight the relevant association between obesity and CVD, as well as the average weight loss of 2.9 kg that occurs when taking this class of drug[29].

GLP-1 RA slows the progression of kidney disease and the possible dysfunction of incretins in type 1 DM, but it should not be used in patients with terminal CKD or type 1 DM[30]. The adverse effects are mainly related to the gastrointestinal tract, particularly nausea, which tends to improve with time of use or with dose reduction. Increased progression of retinopathy was observed in SUSTAIN-6 but has not been reproduced in other trials and may be the result of type I error or associated with significant glycemic reduction[31, 32]. After reports of acute pancreatitis in users of GLP-1 RA, there was an initial concern that has not been confirmed in prospective and randomized

studies, and a relationship has only been reported with calculous cholecystopathy. Despite this, GLP-1 RA should not be prescribed for patients with a history of pancreatitis[33]. Another raised concern is the action of AR-GLP1 on C cells of the thyroid based on experiments on animal models, which has led to it being banned for use in patients with personal or family history of medullary thyroid cancer or multiple endocrine neoplasia type 2A or 2B[34-37].

Present Recommendations

The studies mentioned show a clear benefit of using SGLT2 inhibitors and GLP-1 RA to reduce cardiovascular events. Since the dissemination and wide discussion of these studies, there have been changes in the recommendations of guidelines for first-line medical therapy for DM. The 2019 European Society of Cardiology (ESC) guidelines recommend monotherapy with SGLT2 inhibitors or GLP-1 RA for the initiation of treatment in patients with CVD or high-risk CV. If a patient is already using metformin, the addition of one of these classes is advised if HbA1c ≥ 7.0%.

On the other hand, the American Academy of Diabetes (ADA) favors metformin as an initial therapy for all patients, given its wide availability and low cost. However, it points out that in patients with CVD, chronic kidney disease, heart failure, or indicators of high CV risk (> 55 years of age with ventricular hypertrophy or stenosis > 50% in coronary, carotid, or peripheral vascular territory), it is recommended that treatments include an SGLT2 inhibitor or GLP-1 RA with proven cardiovascular benefit, with a preference for SGLT2 inhibitors in patients diagnosed with heart failure, regardless of glycated hemoglobin levels (Figure 1).

FIGURE 1
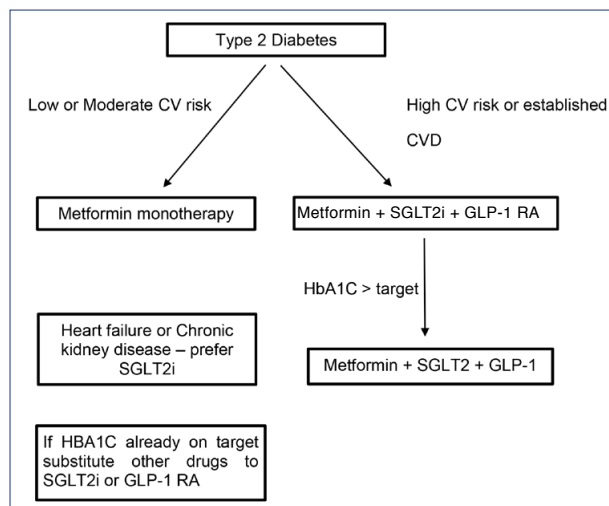
We are even considering replacing medications that have a neutral cardiovascular effect with drugs that have proven prognostic benefit in patients with established CV disease, even among those with good glycemic control.

CONCLUSION

DM treatment has changed substantially in recent years. Evidence supporting a transition from glycemic control as a therapeutic target to the reduction of cardiovascular events has been demonstrated in various clinical studies and must be reflected in clinical practice. Therapeutic inertia should be avoided with the use of medications that are known to be associated with the reduction of clinical events in populations with established CVD or high cardiovascular risk. This approach appears to be not only reasonable but also the most appropriate approach based on the available evidence.

Funding Sources
None.

Conflicts of Interest
The authors declare that there are no conflicts of interest.

Authors' Contributions
EBM and EGL conceived, wrote, and revised the entire final manuscript, FGP wrote the introduction and revised the final manuscript, LNSC wrote and revised the GLP-1 analogue section, TDQ wrote and reviewed the section on GLP-1 analogs, and CVSJ reviewed the final manuscript and participated in the conception.

RESUMO

A terapia farmacológica do diabetes mellitus tipo 2 apresentou avanços importantes nos últimos anos, impactando principalmente o tratamento dos pacientes com doença cardiovascular estabelecida ou com alto risco cardiovascular. Nesse cenário, surgiram duas classes de fármacos com claros benefícios clínicos; os inibidores da SGLT-2 e os agonistas do GLP-1. Na presente revisão os autores discutem desde a farmacologia, efeitos adversos e também os estudos clínicos que demonstraram os benefícios dessas medicações na redução de risco cardiovascular.

PALAVRAS-CHAVE: diabetes mellitus, hipoglicemiantes, cardiopatias.

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