Original article

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Effect of pharmacological therapies for glycemic control in patients with type 2 diabetes mellitus on vascular outcomes

Efecto de terapias farmacológicas para el control glicémico en pacientes con diabetes mellitus tipo 2 en los desenlaces vasculares

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Abstract

Introduction: In the last 5 years the publication of knowledge related to vascular disease and type 2 diabetes mellitus (T2D) has been increasing. However, due to the absence of a review that collects all the vascular outcomes of T2D, the current review of the literature aims to group all vascular outcomes related to T2D and describe how hypoglycemic drug therapy can be effective for the control of these outcomes. Cardiovascular events as the main outcome show that innovative antidiabetic drugs such as empagliflozin and liraglutide can add significant benefits for patients with T2D.

Materials and methods: Systematic search of the literature, from which 141 references were obtained, after eliminating duplicates, for paired screening. Subsequently, 21 references were identified that met the inclusion criteria to be considered in the analysis.

Results: The effect of good glycemic control on clinical outcomes, specifically in the progression of diabetic kidney disease, has been the objective of multiple large-scale studies, both in type 1 diabetic patients and type 2 diabetics. Micro and macrovascular outcomes are the primary results of T2DM, which increase the incidence of comorbidities and in turn represent greater morbidity.

Conclusions: Among the main causes of morbidity and mortality of patients with T2D, are those with vascular damage, especially cardiovascular disease and renal involvement. In this context, the pharmacological treatment of diabetes mellitus has focused on finding drugs that reduce the importance of cardiovascular events and that at the same time delay the onset of nephropathy or its progression. Thiazolidinediones, DPP4 inhibitors (alogliptin, saxagliptin and sitagliptin), insulin glargine and degludec have demonstrated cardiovascular safety, but not incremental cardiovascular benefits, in patients with T2D who are at high risk of atherosclerotic cardiovascular disease.

Key words: Liraglutide, empagliflozin, vascular diseases, diabetes mellitus, type 2, hypoglycemic agents.

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Resumen

Introducción: en los últimos 5 años la publicación de conocimiento relacionado con la enfermedad vascular y la diabetes mellitus tipo 2 (DT2) ha ido en aumento. Sin embargo, debido a la ausencia de una revisión que recopilara todos los desenlaces vasculares de la DT2, la presente revisión de literatura tiene como objetivo agrupar todos los desenlaces vasculares relacionados con la DT2 y describir cómo la terapia farmacológica hipoglicemiante puede ser eficaz para lograr el control de estos desenlaces. Los eventos cardiovasculares como desenlace principal demuestran que los medicamentos antidiabéticos innovadores como la empagliflozina y la liraglutida pueden agregar un beneficio significativo para pacientes con DT2.

Materiales y métodos: búsqueda sistemática de la literatura, de la cual se obtuvieron 141 referencias, después de eliminar duplicados, para la tamización pareada. Posterior a esto, se identificaron 21 referencias que cumplían con los criterios de inclusión para ser considerados en el análisis.

Resultados: el efecto de un buen control glucémico, sobre los resultados clínicos, específicamente en la progresión de la enfermedad renal diabética, ha sido objetivo de múltiples estudios a gran escala, tanto en pacientes diabéticos tipo 1 como en diabéticos tipo 2.

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Los desenlaces micro y macrovasculares son los principales desenlaces de la DMT2, que incrementan la incidencia de comorbilidades y representan, a su vez, una mayor morbilidad.

Conclusiones: dentro de las principales causas de morbilidad y mortalidad de los pacientes con DT2, se encuentran las relacionadas con daño vascular, en especial enfermedad cardiovascular y compromiso renal. En este contexto, el tratamiento farmacológico de la diabetes mellitus se ha enfocado en encontrar medicamentos que reduzcan de manera significativa los eventos cardiovasculares y que al mismo tiempo retrasen la aparición de nefropatía o su progresión. Las tiazolidinedionas, los inhibidores de DPP4 (alogliptina, saxagliptina y sitagliptina), la insulina glargina y degludec han demostrado seguridad cardiovascular, pero no beneficio cardiovascular incremental en pacientes con DT2 que tienen alto riesgo de enfermedad cardiovascular aterosclerótica.

Palabras clave: liraglutida, enfermedades vasculares, diabetes mellitus tipo 2, hipoglucemiantes.

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Introduction

The prevalence of type 2 diabetes *mellitus* (T2D) is increasing worldwide, with the consequent increase in morbidity and mortality associated with its vascular complications. These vascular disorders increase with the severity of hyperglycemia and the time of evolution, which is related to metabolic alterations.[1] The goal of the treatment of diabetes *mellitus* is to decrease the hyperglycemia, thus avoiding acute and chronic (microvascular and macrovascular) complications.

The complications of diabetes have traditionally been divided into macrovascular (coronary artery disease added to cardiomyopathy and diabetic dysautonomia; cerebrovascular disease and peripheral vascular disease) and microvascular (albuminuric or non-albuminuric nephropathy, proliferative or non-proliferative retinopathy, and neuropathy). According to the literature, half of patients with T2D present microvascular complications and 27% macrovascular complications, that are usually already advanced or established at the time of diagnosis.[2] The relative risk of microvascular and macrovascular involvement in patients with diabetes is at least 10 to 20-fold higher and 2 to 4-fold higher, respectively, compared with non-diabetic individuals.[3]

T2D and its complications contribute significantly to the burden of mortality and disability, the latter with a substantial increase in recent years, adding a decrease in general productivity. 10.7% of all deaths in the population between 20 and 79 years of age worldwide are attributed to this condition and it is one of the top 10 causes of decreased life expectancy across the world, which represents a high impact on the global public health.[4]

Recent clinical studies dedicated to evaluate cardiovascular events as the main outcome show that innovative antidiabetic drugs such as empagliflozin[5] and liraglutide[1] can add a significant benefit for patients with T2D, even for those with already established atherosclerotic cardiovascular disease, especially in reducing mortality due to cardiovascular causes.

This article provides an updated view of the cardiovascular and renal ((two of the most affected target systems) impact of T2D, and in turn, of the therapeutic role of the current pharmacological agents for the treatment on these specific outcomes.

Materials and methods

A generic search strategy was designed based on the key terms for the development of the literature review of the effect of pharmacological therapies for glycemic control in T2D on cardiovascular and renal outcomes. Therefore, the terms «Diabetes Mellitus, Type 2», «Cardiovascular Diseases», «Diabetic Nephropathies», «Hypoglycemic Agents» and «Diabetes Complications» were included. Subsequently, a systematic and exhaustive literature search was carried out, from which 141 references were obtained after eliminating duplicates, for the execution of the paired screening. Then, 22 references were identified for review in full text, of which 21 met the inclusion criteria to be considered in the analysis. The selection of systematic reviews of clinical trials or observational studies in the last five years, all available as a full publication, was prioritized.

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Main target organs affected

Cardiovascular disease

Cardiovascular disease (coronary heart disease, peripheral arterial disease and cerebrovascular disease) is one of the leading causes of morbidity and mortality worldwide.[6] (Patients with T2D have twice the risk of developing cardiovascular disease,[7] which has an early onset (14.6 years earlier than in the general population), a greater clinical severity[8-10] and higher mortality.[10] Thereby, men of 60 years of age with T2D and a history of cardiovascular disease (myocardial infarction or cerebrovascular event) will have a life expectancy 12 years shorter, mainly due to a 58% increase in the risk of death of cerebro-cardio-reno-vascular origin.[11]

The incidence of cerebrovascular attack in patients with T2D is two to four times higher than that of the population without this pathology; in addition, diabetic patients have a worse prognosis and a higher risk of recurrence. Subcortical cerebrovascular disease is significantly associated with the presence of T2D and the panorama becomes complicated, as both hyperglycemia and hypoglycemia cause cognitive impairment.[12]

Diabetic cardiomyopathy, coronary atherosclerosis, valvular heart disease or congenital heart disease are the main cardiac diseases related to T2D and represent a major impact on the health of these patients. Diabetic cardiomyopathy is associated with an incidence of heart failure 2 to 4 times higher than in the general population, which manifests in its early stages with systolic dysfunction and microvascular angina or coronary small vessel disease.[13,14]

Kidney disease

The incidence of diabetic kidney disease has doubled in the last decade, mainly due to the increase in the prevalence of patients with T2D, in whom kidney involvement is frequent; it is estimated that about 25% have diabetic kidney disease at some point in their life, defined as persistent albuminuria, a decreased estimated glomerular filtration rate (eGFR), or both.[15] Diabetes mellitus causes approximately 44% of incident cases of end-stage chronic kidney disease[6] and is the most frequent cause of dialysis. Nearly 10% of the mortality in diabetic patients is attributed to kidney failure.[16] The advent of new classes of drugs for the treatment of T2D, including renal sodium-glucose cotransporter 2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists, which besides lowering the glycemia, they have other beneficial effects for the cardiovascular and renal systems, such as weight loss and the reduction of the blood pressure. The outcome trials showed that SGLT-2 inhibitors and GLP-1 receptor agonists can reduce cardiovascular events and all-cause mortality, as well as the progression of kidney disease, in patients with T2D. The available evidence on the cardioprotective and nephroprotective effects of SGLT-2 inhibitors and GLP-1 analogs is overwhelming; today, in light of these clinical studies, the guidelines of the American Diabetes Association (ADA), the European Association for the Study of Diabetes (EASD) and the American Association of Clinical Endocrinology (AACE) include them in their different algorithms and recommendations as first-line drugs in the treatment of patients with chronic kidney disease (CKD) and T2D with diabetic kidney disease (DKD) and CKD.[5,17]

Vascular disease

The vascular complications of diabetes, initiated by endothelial dysfunction, are serious manifestations of the disease. Systemic atherosclerosis and diabetic kidney disease are the main reasons for the shorter life expectancy in patients suffering from this condition. Although the decrease in hyperglycemia delays the onset of nephropathy and retinopathy, its impact on cardiovascular disease is less clear, since a lesser benefit of glycemic control on these macrovascular changes has been observed. Thus, insulin resistance and its biological effects on various tissues might be a more important factor than hyperglycemia in mediating atherothrombotic complications. Despite the advances in prevention, diagnosis and treatment of diabetes, complications are still a serious public health problem.[18]

Meanwhile, peripheral arterial disease has a prevalence of 20 to 30% in diabetic patients. Both

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the duration of the diabetes and the degree of glycemic control are related to the incidence and severity of peripheral arterial disease.[19] In a meta-analysis conducted in 2016 that evaluated the impact of diabetes on peripheral arterial disease outcomes, it was found that diabetes is associated with a statistically significant increase in the risk of critical limb ischemia (Odds Ratio: 2.38, 95% CI: 1.22- 4.63, P<0.001) as the most serious form of peripheral vascular disease,[20] and is the most common cause of amputations.

At the end of August 2019, the guidelines for diabetes, prediabetes and cardiovascular diseases of the European Society of Cardiology, developed in conjunction with the European Association for the Study of Diabetes, were published.[21] A strong point of these guidelines is the categorization of cardiovascular risk, which allows favoring the comprehensive treatment of cardiovascular risk factors in individuals with T2D. Another strong point of the guidelines is the discussion addressed to the management of the different cardiovascular risk factors such as hypertension, dyslipidemia, CKD, coronary heart disease, and so on. One of the most notable aspects related to a change in the treatment paradigm is the establishment of a specific classification of cardiovascular risk for people with diabetes (Table 1).

The purpose of the classification is that the management will be oriented towards cardiovascular risk and the control of risk factors, even moving away from the concept of primary and secondary prevention.

Atherosclerosis

The nature of the atherosclerotic lesions in patients with diabetes is similar to that of patients with other characteristics, although the lesions are earlier, and more accelerated and aggressive. Apolipoprotein B and oxidized LDL cholesterol, accumulated in the arterial intima are recruited by adhesion molecules expressed in the endothelium. The cytokines and chemokines released from foam cells and other immune cells recruit others with similar characteristics. Additionally, insulin resistance causes endothelial dysfunction, which is manifested by increased expression of adhesion molecules.[22] In summary, the alterations in vascular homeostasis due to dysfunction of the endothelium and the vascular smooth muscle cells are the main characteristics of diabetic vasculopathy that favors a prothrombotic and pro-inflammatory state that ultimately leads to atherothrombosis.[9]

The main microvascular and macrovascular effects of hyperglycemia are described in Figure 1.

Effects of glycemic control on vascular outcomes

HbA1c and estimation of the mean blood glucose

Based on two international studies that sought to evaluate the correlation between the glycated hemoglobin (HbA1c) levels and blood glucose, the

Table 1. Classification of cardiovascular risk in diabetic individuals. Modified from ESC Guidelines 2019.[21]

Category	Data
Very high cardiovascular risk	With any of the following items: • Established cardiovascular disease. • Target organ damage. • Three or more risk factors (age, hypertension, tobacco, dyslipidemia, obesity). • Early onset of long-standing type I diabetes (>20 years).
High cardiovascular risk	Patients with disease duration of more than 10 years, without target organ damage plus a risk factor.
Moderate cardiovascular risk	Young people (type 1 diabetes <35 years; type 2 diabetes <50 years) with less than 10 years of disease duration and without risk factors.

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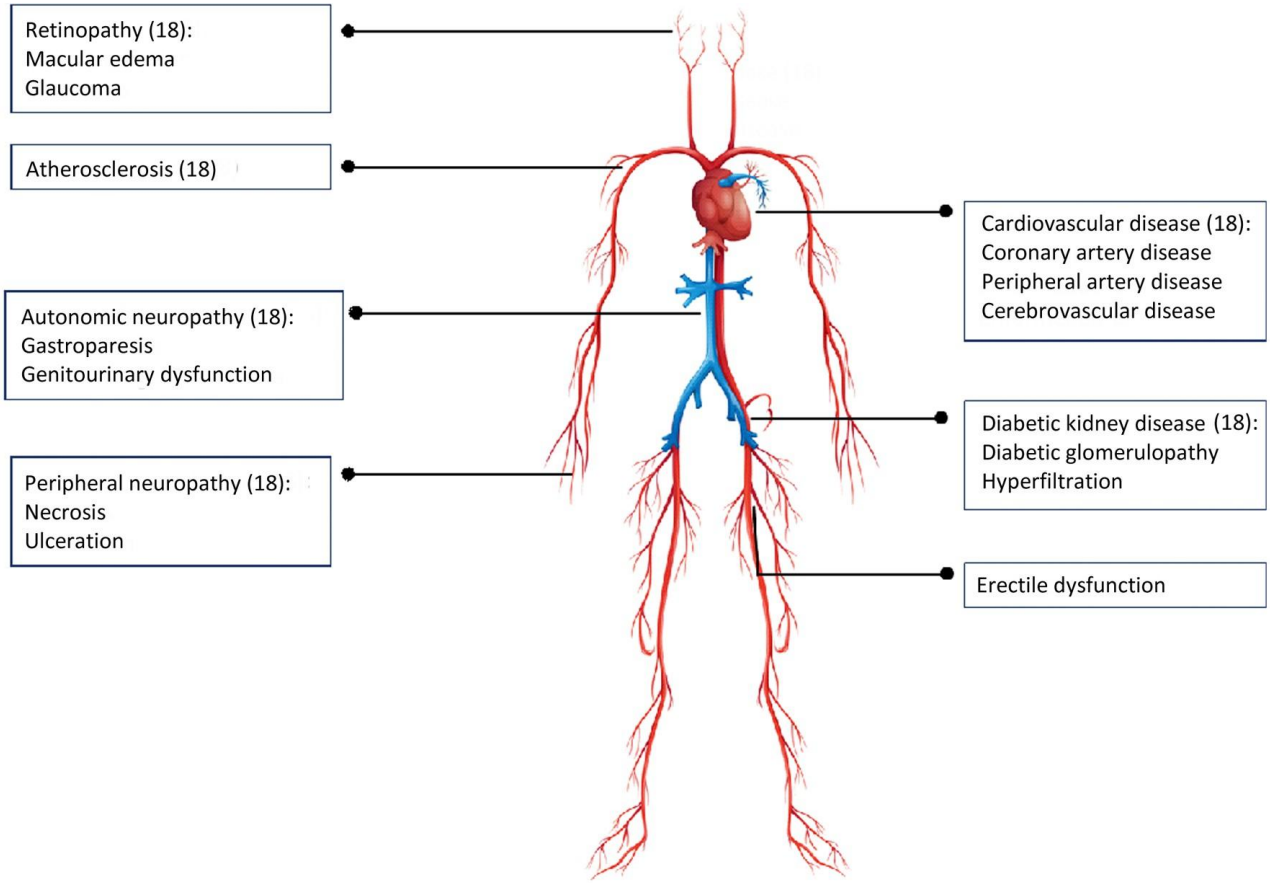

Figure 1. Micro and macrovascular manifestations of type 2 diabetes mellitus. Source: own elaboration. Image taken from vectorstock.com/1855392

American Diabetes Association (ADA) and the American Association for Clinical Chemistry determined that the correlation found in the studies (r 0.92) was strong enough to report the HbA1c result with a figure of the estimated average blood glucose.[23] However, recent studies have demonstrated that HbA1c can underestimate or overestimate the mean blood glucose level, due to factors that can alter the results (e.g. intra- and interlaboratory measurement variability, duration of exposure of the erythrocyte to glucose, and the effect of frequent pathologies in diabetics such as chronic kidney disease and anemia).

HbA1c goals

Despite its limitations (for example, it does not detect or discriminate patients with postprandial peaks, which generate greater endothelial damage), it is accepted that HbA1c reflects the average glycemia of the last three months and has a strong predictive value for the complications of diabetes.[18,24]

The assessment of the levels of HbA1c should be individualized according to the characteristics of the patient and the non-glycemic factors that can affect the HbA1c. In addition to this measurement, the clinician must rely on clinical data and ideally on blood glucose monitoring to optimize medical management.[25,26] According to the Standards of Medical Care in Diabetes, published in 2018 by the American Diabetes Association (ADA), the recommendations for measurement and goals of HbA1c are the following:

- Twice a year in patients with T2D with stable glycemia and within the treatment goals.[25]

- Approximately every 3 months in patients with treatment modifications on in those who have not reached the treatment goals.[25]

- Unstable patients or those who are under intensive management may require tests more frequently than every 3 months, remembering that HbA1c does not detect glycemic variations, which are the most vasculotoxic. [25]

- A reasonable goal for HbA1c is 7.5-8%; except in pregnant women, which is 7%. Stricter HbA1c goals (6.5%) in some cases.[25]

Even though the ADA proposes optimal HbA1c ranges, it is necessary to individualize the goals for each patient, taking into account their preferences, and always in order to avoid hypoglycemia and any other adverse effect related to the treatment.[1] Intensive glycemic control plays an important role in primary prevention in patients with type 1 and newly diagnosed type 2 diabetes.[22] However, in advanced disease it is not beneficial and it could be potentially deleterious. Thus, patients with long-standing diabetes, a known history of hypoglycemia or advanced atherosclerosis, as well as elderly or frail patients, may benefit from less aggressive goals.[27]

There is evidence of endothelial damage caused by hypoglycemia, which increases the production of reactive oxygen species (oxidative stress) and inflammatory biomarkers such as C-reactive protein and interleukins 6 and 8; favors platelet aggregation, the production of factor VIII, Von Willebrand factor and the processes involved in atherothrombosis; potentiates vasoconstriction and endothelin production, and acutely enhances the sympathetic-adrenergic response with an increased incidence of arrhythmias and sudden cardiac death.[28,29]

Pharmacological strategies for glycemic control and their effects on vascular outcomes

As described in previous sections, patients with diabetes have an increased risk of vascular morbidity and mortality, and consequently, risk stratification is currently recommended in clinical practice for the prevention of such events.[30] It is considered that glycemic control should be multifactorial and individualized with intervention in the lifestyle, therapeutic management of blood pressure, lipids, antithrombotic agents and glycemic control.[27,31,32] The main pharmacological strategies are summarized in Table 2.

In recent years, regulatory bodies such as the U.S. FDA and the European Medicines Agency (EMA) have required studies to demonstrate the cardiovascular safety of the new drugs for glycemic control.[27] The available evidence on the vascular impact of the drugs for glycemic control, by pharmacological class, highlighting the studies that support their vascular safety and their location in current treatment guidelines is described below.

Biguanides

They are oral hypoglycemic molecules, and metformin is part of this pharmacological group. This drug is the most commonly prescribed oral medication in the world for the management of T2D, because it has a good safety profile, even among patients with kidney failure.[33] Early combination with other drugs should be considered on individual basis to achieve good glycemic control, reduction of cardiovascular risk and renal protection.[1,30] If metformin is tolerated and not contraindicated, it should be continued when used in combination with other agents, including insulin.[25]

Sulphonylureas

Sulfonylureas are another very important and very effective oral hypoglycemic agent in glycemic control. These molecules stimulate insulin secretion from pancreatic beta cells and reduce fasting plasma glucose by 36 to 72 mg/dL and HbA1c levels by 1 to 2%.[9] The available sulfonylureas are variably associated with events of moderate and severe hypoglycemia (20-40% and 07.01%, respectively). They also alter ischemic preconditioning, and therefore they are contraindicated in patients with coronary artery disease (except for gliclazide).

Thiazolidinediones

These molecules are oral hypoglycemic agents that were originally developed as lipid-lowering agents.[34]

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Table 2. Comparison between the different therapeutic alternatives for the treatment of type 2 diabetes *mellitus*.

Pharmacological class	Drug for glycemic control	Study	intervention	Comparator	Primary outcome	n	Cardiovascular status	Follow-up mean (years)
Biguanides	Metformin	UKPDS (UKPDS34 subgroup analysis)	Intensive control of blood glucose with metformin (fasting glucose below 6 mmol/L)	Conventional therapy	All-cause mortality	17704	Time until the first diabetes-related outcome (sudden death, death from hyperglycemia or hypoglycemia, fatal or non-fatal myocardial infarction, angina, heart failure, stroke, kidney failure, amputation [for at least one digit], vitreous hemorrhage , retinopathy requiring photocoagulation, blindness in one eye or removal of cataracts),	10.7
Thiazolidinediones	Pioglitazone		Pioglitazone		Death, MI, stroke, ACS, vascular intervention, amputation	5238	Macrovascular disease	2.9
	Rosiglitazone	RECORD	Addition of Rosiglitazone to metformin or sulfonylurea	Combination of metformin and sulfonylurea	CV death, MI, cardiovascular hospitalization	4447	Exclusion in the presence or history of heart failure. ischemic heart disease 5-20%	5,5
Insulins	Insulin glargine	ORIGIN	Insulin glargine	Conventional therapy	CV death, MI or cerebrovascular event	12537	CV risk factors (recent angina, stroke, MI, or revascularization)	6.2
	Insulin degludec	DEVOTE	Insulin degludec	Insulin glargine	CV death, MI or cerebrovascular event	7637	CVD or kidney disease or CV risk in ≥ 60 years	1.9
Sulfonylureas	Sulfonylureas	Meta-analysis	First and second generation sulfonylureas as a group	Placebo/no intervention or other hypoglycemic therapies	All-cause mortality, CV death, MI or cerebrovascular event			
SGLT2 inhibitors	Empaglifozin	EMPAREG OUTCOME	Addition of empaglifozin (10 mg and 25 mg)	Placebo	CV death, MI or cerebrovascular event	7000	CVD or high cardiovascular risk	3.1
	Canaglifozin	CANVAS program	Canaglifozin (100 mg and 300 mg)	Placebo	CV death, MI or cerebrovascular event	10142	Pre-existing CVD or high cardiovascular risk	1.5
DPP-4 inhibitors	Sitagliptin	TECOS	Addition of sitagliptin	Placebo	CV death, MI, unstable angina or stroke	14724	Pre-existing CVD	3
	Saxagliptin	SAVOR-TIMI 53	Addition of saxagliptin	Placebo	CV death, MI or cerebrovascular event	18206	CVD or high cardiovascular risk	2.1
	Alogliptin	EXAMINE	Addition of alogliptin	Placebo	CV death, MI or cerebrovascular event	5380	Acute coronary syndrome (15-90) days before	1.5
GLP-1 receptor agonists	Liraglutide	LEADER	Liraglutide	Placebo	CV death, MI or cerebrovascular event	9340	CVD or vascular disease, heart or kidney failure in ≥ 50 years or high CV risk in ≥ 60 years	3.8
	Semaglutide	SUSTAIN-6	Semaglutide (0.5 mg and 1.0 mg)	Placebo	CV death, MI or cerebrovascular event	3299	Pre-existing CVD in ≥ 50 years or pre-CVD in ≥ 60 years	1.9
	Exenatide	EXSCEL	Exenatide once a week	Placebo	CV death, MI or cerebrovascular event	14752	73.1% with previous CVD	3.2
	Lixisenatide	ELIXA	Addition of lixisenatide	Placebo	CV death, MI,unstable angina or cerebrovascular event	6076	ACS (<=180) days before	2.1

CV cardiovascular. CVD Cardiovascular disease. CKD Chronic kidney disease. ACS Acute coronary syndrome. MI Myocardial infarction. Conventional therapy: lifestyle modification and/or metformin and/or sulfonylurea

PPAR gamma receptors (PPARg) are expressed mainly in adipocytes, muscle, and liver, and are involved in glucose and lipid metabolism; and it is through these receptors that thiazolidinediones exert their pleiotropic effect.[34] The action of thiazolidinediones is focused on stimulating insulin sensitivity in skeletal muscle, liver, and adipose tissue due to their ability to activate the peroxisome proliferator-activated receptor.

DPP-4 inhibitors

Dipeptidyl peptidase-4 (DPP4) inhibitors are analogs of these peptides and act by inhibiting the enzyme DPP-4. Their mechanism of action is of the incretin type, that inhibits the degradation of protease by DPP4, which prolongs the half-life and biological activity of GLP-1, increases the physiological secretion of insulin and suppresses the release of glucagon, with moderate effects on blood glucose reduction.[27] These molecules are indicated in monotherapy or in combination therapy in special situations, such as metformin intolerance, chronic kidney disease (GFR lower than 30 ml/minute), mild to moderate liver failure, among others.[35]

SGLT-2 inhibitors

Sodium-glucose cotransporter 2 (SGLT-2) inhibitors are involved in the first step in the reabsorption of glucose from urine, with the transport of glucose from the tubules to the peritubular capillaries through the tubular epithelial cells. Glucosuria induced by the sodium glucose cotransporter 2 inhibitor promotes mild diuresis and calorie loss, leading to modest reductions in body weight; significant reduction in the blood pressure, especially in the systolic, as well as favorable effects on arterial stiffness, possible determinants of positive outcomes for the patients with T2D.[36]

Insulin

Insulin is a drug used by more than 30% of patients with diabetes worldwide,[22] and in clinical practice it has been considered an essential component of the treatment strategy for patients who do not achieve glycemic goals with other therapies.[33]

Glargine is the most commonly used insulin worldwide due to its cardiovascular safety in people with T2D with or without previous cardiovascular events. Evidence suggests that in patients with altered fasting glucose, glucose intolerance or T2D, followed up for 7 years, the comparison of insulin glargine versus conventional therapy (lifestyle modification and/or metformin and/or sulfonylurea) did not show statistically significant differences in the composite outcomes of myocardial infarction, stroke, and cardiovascular death, or in the extended composite that included revascularization and hospitalizations for heart failure.[22,37] Meanwhile, insulin degludec is a long-acting basal insulin analog that is administered once a day. The DEVOTE clinical trial shows the cardiovascular safety of insulin degludec versus an active comparator (insulin glargine), each one added to conventional therapy.[38] The primary outcome (non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death) occurred in 8.5% of patients treated with degludec and in 9.3% of patients treated with glargine (RR 0.91; non-significant p-value), which does not demonstrate inferiority. However, regarding the secondary outcome, the patients treated with degludec experienced significantly lower rates of severe hypoglycemia compared with the glargine U100 group ($p<0.001$).[39]

GLP-1 agonists

Glucagon-like peptide 1 (GLP-1), secreted by enteroendocrine L cells after food intake, increases insulin secretion. The glucagon-like peptide 1 receptor agonists, also known as GLP-1 receptor agonists or incretin mimetics, increase insulin secretion depending on glucose concentration and generate an inhibition of glucagon secretion, with long-lasting effects on pancreatic beta cells. The expression of the GLP-1 receptor in the vascular endothelium and in the smooth muscle cells has a demonstrated favorable impact on the cardiovascular system, body weight, blood pressure, endothelial function and low-density lipoproteins.

Evidence suggests that GLP-1 agonists improve glycemic control and reduce body weight compared to placebo, with a similar gastrointestinal tolerance profile between them.

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When long-acting agents (semaglutide, dulaglutide, liraglutide, and exenatide once a week) were compared to short-acting agents (exenatide twice a day and lixisenatide), they were superior in reducing HbA1c and fasting blood glucose levels.[40] The use of liraglutide is recommended in patients with intolerance to metformin, or added to it to reduce major adverse cardiovascular events such as non-fatal infarction, non-fatal stroke and cardiovascular mortality in a population with established atherosclerotic disease and glomerular filtration rate higher than 15 cc/min.[25,30]

Discussion

The effect of a good glycemic control on clinical outcomes, specifically on the progression of diabetic kidney disease, has been the objective of multiple large-scale studies, both in type 1 and type 2 diabetic patients.

The main evidence of good glycemic control in type 1 diabetic patients is The Diabetes Control and Complications Trial (DCCT), a randomized controlled clinical trial with 1441 patients, which compared the intensive glycemic control (target HbA1c lower than 6.0%) versus the conventional glycemic control with insulin, with an average follow-up of 6.5 years. The average HbA1c was 7.3% for the group with intensive control versus 9.1% for the group with conventional control (difference of almost 2%), and demonstrated an association of intensive glycemic control with a decrease of 54% in the progression of nephropathy.[41] Later, the Epidemiology of Diabetes Interventions and Complications (EDIC) study, which continued the follow-up of the DCCT cohort (1375 patients with 4-year follow-up), also demonstrated the benefit of strict glycemic control on the microvasculature.[42]

The available data from patients with type 2 diabetes include the Kumamoto Study[43] and the UK Prospective Diabetes Study (UKPDS),[44] which confirmed the findings described and their long-term persistence. The United Kingdom Prospective Diabetes Study (UKPDS), where HbA1C in the intensive treatment group was 0.9% lower than in that with conventional therapy, concluded after 10 years of follow-up that there was a 25% reduction in microvascular complications in the intensive treatment group, and that for every 1% reduction in HbA1C, there was a 21% reduction in the risk of any primary outcome of diabetes or death, a 37% reduction in microvascular complications, and a 14% reduction in the risk of myocardial infarction.[45,46] It is important to mention that in this study the average time of diagnosis of diabetes was not longer than one year; that is, vascular damage and/or metabolic memory were not yet established, according to studies that suggest the need for very early active treatment to minimize long-term diabetic complications.[47]

Three large clinical studies with the participation of approximately 25,000 patients assessed the potential beneficial effect of intensive glycemic control in type 2 diabetic patients. The Action to Control Cardiovascular Risk in Diabetes (ACCORD),[48] Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE)[49] and Veterans Affairs Diabetes Trial (VADT)[50] studies showed that low HbA1c levels were associated with a late onset or slowing of the progression of some microvascular complications. It should be taken into account that the patients in these studies had been diagnosed with diabetes for several years, with vascular damage and metabolic memory already established. In addition, the risk of hypoglycemia and the need for polypharmacy to achieve these glycemic goals must be considered, therefore these studies support the recommendation to adjust HbA1c goals individually.

The available evidence raises doubts about the impact of metformin on vascular disease. The cardiovascular benefits of metformin come primarily from the UK Prospective Diabetes Study (UKPDS), in which 3,867 patients with newly diagnosed T2D were randomly assigned to receive sulfonylureas or insulin versus conventional therapy. The intensive therapy with metformin was assigned to 342 individuals with overweight (with more than 120% of the ideal body weight), while 411 received conventional diet measures. The analysis of this subgroup of patients showed a reduction of deaths related with diabetes, overall mortality and non-fatal myocardial infarction of 42% (p=0.017), 36% (p=0.011) and 39% (P=0.01), respectively, in the group treated with metformin. These protective effects of metformin were observed even in the 10

years of follow-up of the patients, despite achieving HbA1c goals in all treatment arms.[9]

Although the results of the UKPDS favor metformin, the statistical power of this trial is limited. In recent meta-analyzes that included the UKPDS, all outcomes, with the exception of stroke, favored metformin, but none of them reached statistical significance.[51] The clinical trials developed to date did not demonstrate the ability of metformin to modify clinically relevant vascular outcomes, and also confirmed an increase in cardiovascular risk and mortality with the addition of metformin to sulfonylureas versus sulfonylurea alone (HR 1.60; 95% CI, 1.02-2.52).[9]

Regarding the evaluation of the safety of DPP4 inhibitors and they effectiveness in patients with T2D, three clinical trials that assessed the cardiovascular outcomes were conducted: with saxagliptin (SAVOR-TIMI 53),[52,53] with alogliptin (EXAMINE)[54] and with sitagliptin (TECOS).[55] All of these determined statistical non-inferiority compared to placebo for the combined outcome of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke).[27] On the other hand, recent meta-analyses and the SAVOR-TIMI 53 clinical trial report that the use of saxagliptin increased hospitalizations for heart failure by 27% and reduced progressive albuminuria regardless of the initial kidney function.[52] Although the EXAMINE did not report significant differences in heart failure with the use of alogliptin versus placebo, *post hoc* analyses showed that the incidence of this pathology increased in patients with signs of heart failure at the time of randomization (RR 1.76, 95% CI, 1.07-2.90). The findings described have led to regulatory warnings for saxagliptin and alogliptin.[56] Among the patients with T2D and established cardiovascular disease, sitagliptin added to conventional therapy did not increase the risk of major adverse cardiovascular events, hospitalization for heart failure (even after adjusting for pre-existing heart failure), or other adverse events.[9,55]

The data described suggest that the increased risk of heart failure is not a class effect of DPP-4 inhibitors,[9,57] with further evidence of superiority of these drugs compared with sulfonylureas regarding hospital admission for heart failure. In the same way, clinical trials with DPP4 inhibitors reported no significant differences in microvascular outcomes[27]; i.e., they improve glycemic figures but have not been shown to have an impact on the outcomes. The most recent recommendations on DPP4 inhibitors consider them reasonable and safe options to achieve glycemic control,[30] preferably for patients who are not eligible for an SGLT2 inhibitor or a GLP-1 receptor agonist, as well as in all stages of chronic kidney disease including patients on dialysis (hemodialysis or peritoneal dialysis).[1]

In the EMPAREG OUTCOME5 study it was evidenced that empagliflozin (SGLT-2 inhibitors), compared with placebo, showed a significant reduction in the primary composite outcome (HR 0.86; 95% CI 0.74-0.99), as well as in cardiovascular death (HR 0.62; 95% CI 0.49-0.77), hospitalizations for heart failure (HR 0.65; 95% CI 0.50-0.85) and all-cause mortality (HR 0.68; 95% CI 0.57-0.82). This study was the first with adequate statistical power that showed a reduction in cardiovascular risk with the use of a new antidiabetic drug. In the CANVAS program, which integrated data from two clinical trials with a total of 10,142 participants with T2D and high cardiovascular risk, it was evidenced that the composite outcome of mortality from cardiovascular causes, non-fatal myocardial infarction or non-fatal stroke was less frequent in patients treated with canagliflozin than in those with placebo (HR 0.86, 95% CI 0.75 – 0.97; p<0.001 for non-inferiority; p = 0.02 for superiority).[58]

Regarding the renal impact of SGLT2 inhibitors, it was observed that the onset or progression of nephropathy was significantly reduced by 39% with empagliflozin, doubling of serum creatinine was reduced by 44%, and the combination of incidental nephropathy or progression and cardiovascular death was reduced by 39%.[59] It was also observed a possible benefit of canagliflozin with respect to the progression of albuminuria (HR 0.73, 95% CI 0.67-0.79) and in the composite outcome by a sustained reduction of 40% in the estimated glomerular filtration rate, the need for renal replacement therapy or death from renal causes (HR 0.60, 95% CI 0.47-0.77).[58] Similar results have also been observed with dapagliflozin, that is, it can

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also have nephroprotective effects (decrease in kidney outcomes). In Colombia, this drug is currently recommended for patients with an estimated GFR higher than 60 ml/min/1.73 m.[60]

The recommendations of the ADA (2018) include the use of empagliflozin in combination with metformin, in patients with T2D and established atherosclerotic cardiovascular disease, in order to reduce major adverse cardiovascular events and cardiovascular mortality, according to the characteristics of the patient.[25] Empaglifozin is currently approved for use in patients with a GFR higher than 45 cc/min. It is not recommended in type 2 diabetic patients with lower GFR.

To date, there are four studies of cardiovascular safety with GLP receptor agonists: ELIXA (with lixisenatide), LEADER (with liraglutide), SUSTAIN-6 (with semaglutide) and EXSCEL (with Exenatide). Regarding the vascular outcomes, the meta-analysis findings describe a significant reduction in the risk of death from all causes versus the control group (RR 0.888; CI 0.804-0.979; p=0.018) and in the risk of cardiovascular death (RR 0.858; CI 0.757-0.973; p=0.017). It was also reported that GLP1 agonists did not affect the risk of myocardial infarction, cerebrovascular accident, retinopathy and nephropathy (RR 0.866; CI: 0.625-1.199; p=0.385).[61]

In the EXSCEL study, which assessed the cardiovascular effects of the treatment with exenatide in patients with T2D and which included 14,752 patients, it was found a HR of 0.91 (95% CI 0.83-1.00) for the composite outcome of the occurrence of death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke. Thus, the rates of death from cardiovascular causes, fatal or non-fatal myocardial infarction, fatal or non-fatal stroke, hospitalization for heart failure and hospitalization for acute coronary syndrome, and the incidence of acute pancreatitis, pancreatic cancer, medullary carcinoma of the thyroid and serious adverse events was not different between exenatide and placebo.[62]

From the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Results (LEADER) study, the secondary renal outcomes of liraglutide compared with placebo were determined, finding a HR of 0.78 (95% CI 0.67-0.92; p = 0.003) for the composite outcome consisting of persistent macroalbuminuria of recent onset, persistent doubling of serum creatinine level, end-stage renal disease, or death from renal disease. This outcome is mainly related to the reduction in persistent macroalbuminuria, which occurred in a smaller number of participants in the group treated with liraglutide (HR 0.74, 95% CI 0.60-0.91; p = 0.004).

In the LEADER trial, which included patients with high cardiovascular risk, liraglutide significantly reduced the occurrence of major adverse cardiovascular events by 13%, cardiovascular death by 22%, and all-cause mortality by 15%, without significant effects on non-fatal myocardial infarction, non-fatal stroke and hospitalization for heart failure. The cardiovascular benefits of liraglutide were observed much earlier than in the classical trials of glycemic control in diabetes (Diabetes Control and Complications Trial [DCCT], UKPDS).

Conclusions

Among the main causes of morbidity and mortality in patients with T2D are those related to vascular damage, especially cardiovascular disease and kidney commitment. In this context, pharmacological treatment of diabetes mellitus has been focused on finding drugs that significantly reduce cardiovascular events and at the same time delay the onset of nephropathy or its progression. Thiazolidinediones, DPP4 inhibitors (alogliptin, saxagliptin, and sitagliptin), insulin glargine, and degludec have demonstrated cardiovascular safety, but no incremental cardiovascular benefit in T2D patients who are at high risk for atherosclerotic cardiovascular disease.

Large randomized controlled clinical trials have been conducted in recent years, which have reported statistically significant decrease in cardiovascular events, in general for SGLT2 inhibitors (empaglifozin, canaglifozin and dapaglifozin) and for some GLP-1 agonists (liraglutide, semaglutide and dulaglutide) in diabetic patients with atherosclerotic cardiovascular disease. The risk of hypoglycemia from these drugs is low and they have an adequate safety profile.

Finally, it is important to mention the reduction in the onset or progression of diabetic kidney disease with these drugs, even in patients with stage 3 chronic kidney disease with HbA1c higher than 7% but lower than 8%. Since the worsening of diabetic kidney disease is an important risk factor for a wide range of complications of atherosclerotic cardiovascular disease, including heart failure, the adequate use of these drugs could contribute to further closing of the prognosis gap in patients with atherosclerotic cardiovascular disease and diabetes

Thus, for patients with T2D who have atherosclerotic cardiovascular disease, it is recommended to incorporate an agent with strong evidence of cardiovascular risk reduction to the treatment with metformin, especially those with proven benefit in both major adverse cardiovascular events and cardiovascular death, after considering the characteristics and preferences of the patient on an individual basis. However, it is important to keep in mind that the fundamental axis in the management of the diabetic patient is the achievement of persistent lifestyle changes.

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Conflict of interest

Dr. Castillo reports that he has received fees from AstraZeneca, Boehringer-Ingelheim, NovoNordisk, Bayer, Pfizer, Sanofi, Abbott, Novartis, Amgen and Merck. These fees were not related to the performance of this work. Dr. Ibatá Bernal reports that she has received fees from Novartis, Astellas, AbbVie and Abbott which were not related to the performance of this work. Dr. Martínez Rojas reports that she has received grants from Novonordisk during the study; fees from Novartis, Astellas, Abbvie y Abbott, out of the work presented. Dr. Gómez has been a speaker for Novonordisk, Medtronic, Abbott, Boeringher, Astrazeneca and mSD. Dr. Rico Fontalvo, Dr. Ramírez Rincón, Dr. Melgarejo Rojas, Dr. Lopera and Dr. Rico Fontalvo declare that they have no conflict of interest.

Ethical responsibilities

Protection of people and animals

The authors declare that no experiments were performed on human beings or animals for this research.

Right of privacy and informed consent

The authors declare that patient data do not appear in this article.

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References

1. Schernthaner G, Lehmann R, Prázný M, et al. Translating recent results from the Cardiovascular Outcomes Trials into clinical practice: Recommendations from the Central and Eastern European Diabetes Expert Group (CEEDEG). *Cardiovasc Diabetol*. 2017;16(1):137. https://doi:10.1186/s12933-017-0622-7
2. Litwak L, Goh SY, Hussein Z, Malek R, Prusty V, Khamseh ME. Prevalence of diabetes complications in people with type 2 diabetes mellitus and its association with baseline characteristics in the multinational A1chieve study. *Diabetol Metab Syndr*. 2013;5(1):57. https://doi:10.1186/1758-5996-5-57
3. Gregg EW, Sattar N, Ali MK. The changing face of diabetes complications. *Lancet Diabetes Endocrinol*. 2016;4(6):537-547. https://doi:10.1016/ S2213-8587(16)30010-9
4. IDF. IDF diabetes atlas - 2017 Atlas. IDF Diabetes Atlas.
5. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373(22):2117-2128.
6. CDCP. National estimates and general information on diabetes and prediabetes in the US. *http//www caldiabetes org/content_display cfm? FontSize= Norm 562&CategoriesID= 31*. Published online 2011. http://ndep.nih.gov/media/fs_gensnapshot.pdf
7. Vrsalovi? M, Vu?ur K. Diabetes, renal dysfunction, inflammation, and anemia: the deadly quartet in peripheral artery disease. *Endocr Oncol Metab*. 2016;2(1):82-87. https://doi:10.21040/eom/2016.2.9
8. Booth GL, Kapral MK, Fung K, Tu J V. Relation between age and cardiovascular disease in men and women with diabetes compared with non-diabetic people: a population-based retrospective cohort study. *Lancet*. 2006;368(9529):29-36. https://doi:10.1016/S0140-6736(06)68967-8
9. Paneni F, Beckman JA, Creager MA, Cosentino F. Diabetes and vascular disease: pathophysiology, clinical consequences, and medical therapy: part I. *Eur Heart J*. 34(31):2436-2443.
10. Sarwar N, Gao P, Kondapally Seshasai SR, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: A collaborative meta-analysis of 102 prospective studies. *Lancet*. 2010;375(9733):2215-2222. https://doi:10.1016/S0140-6736(10)60484-9
11. Di Angelantonio E, Kaptoge S, Wormser D, et al. Association of cardiometabolic multimorbidity with mortality. *Jama*. 2015;314(1):52-60.
12. Tejada García J, Redondo Robles L. Epidemiología de la enfermedad vascular cerebral en los pacientes con diabetes. *Av en Diabetol*. 2010;26(6):397-402. https://doi:10.1016/S1134-3230(10)66003-6
13. Lehrke M, Marx N. Diabetes Mellitus and Heart Failure. *Am J Cardiol*. 2017;120(1):S37-S47. https://doi:10.1016/j.amjcard.2017.05.014
14. Vásquez EM, Burbano Á, Ibáñez CI, et al. Panel nacional de expertos sobre la atención de la cardiomiopatía diabética. *Rev la ALAD*. 2016;6(4):170-180. https://search.ebscohost.com/login.aspx?direct=true&db=ccm&AN=120221110&site=ehost-live
15. Afkarian M, Zelnick LR, Hall YN, et al. Clinical manifestations of kidney disease among US adults with diabetes, 1988-2014. *JAMA - J Am Med Assoc*. 2016;316(6):602-610. https://doi:10.1001/jama.2016.10924
16. Van Dieren S, Beulens JWJ, Van Der Schouw YT, Grobbee DE, Neal B. The global burden of diabetes and its complications: An emerging pandemic. *Eur J Cardiovasc Prev Rehabil*. 2010;17(SUPPL. 1):S3-8. https://doi:10.1097/01.hjr.0000368191.86614.5a
17. Sarafidis P, Ferro CJ, Morales E, et al. SGLT-2 inhibitors and GLP-1 receptor agonists for nephroprotection and cardioprotection in patients with diabetes mellitus and chronic kidney disease. A consensus statement by the EURECA-m and the DIABESITY working groups of the ERA-EDTA. *Nephrol Dial Transplant*. 2019;34(2):208-230. https://doi:10.1093/ndt/gfy407
18. Stratton IM, Adler AI, Neil HAW, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): Prospective observational study. *Br Med J*. 2000;321(7258):405-412. https://doi:10.1136/bmj.321.7258.405
19. Hamish M, Gohel MS, Davies AH. Peripheral arterial disease in patients with diabetes mellitus. *Br J Hosp Med*. 2008;69(10):570-574. https://doi:10.12968/hmed.2008.69.10.31316
20. Vrsalovic M, Vucur K, Vrsalovic Presecki A, Fabijanic D, Milosevic M. Impact of diabetes on mortality in peripheral artery disease: a meta-analysis. *Clin Cardiol*. 2017;40(5):287-291. https://doi:10.1002/clc.22657
21. Cosentino F, Grant PJ, Aboyans V, et al. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. *Rev Esp Cardiol*. 2020;73(5):404.e1-404.e59. https://doi:10.1016/j.recesp.2019.11.024

22. Alvarez CA, Lingvay I, Vuylsteke V, Koffarnus RL, Mcguire DK. Cardiovascular risk in diabetes mellitus: Complication of the disease or of antihyperglycemic medications. *Clin Pharmacol Ther*. 2015;98(2):145-161. https://doi:10.1002/cpt.143

23. Rodríguez-Segade S, Rodríguez J, Paz JM, Camiña F. Translating the A1C assay into estimated average glucose values. *Diabetes Care*. 2009;32(1):1473-1478. https://doi:10.2337/dc08-1214

24. Albers JW, Herman WH, Pop-Busui R, et al. Effect of prior intensive insulin treatment during the Diabetes Control and Complications Trial (DCCT) on peripheral neuropathy in type 1 diabetes during the Epidemiology of Diabetes Interventions and Complications (EDIC) study. *Diabetes Care*. 2010;33(5):1090-1096. https://doi:10.2337/dc09-1941

25. 1. Improving care and promoting health in populations: Standards of medical care in diabetesd2019. *Diabetes Care*. 2019;42(Supplement 1):S7-S12. https://doi:10.2337/dc19-S001

26. Conlin PR, Colburn J, Aron D, Pries RM, Tschanz MP, Pogach L. Synopsis of the 2017 U.S. Department of veterans affairs/ U.S. Department of defense clinical practice guideline: Management of type 2 diabetes mellitus. *Ann Intern Med*. 2017;167(9):655-663. https://doi:10.7326/M17-1362

27. Standl E, Schnell O, McGuire DK, Ceriello A, Rydén L. Integration of recent evidence into management of patients with atherosclerotic cardiovascular disease and type 2 diabetes. *Lancet Diabetes Endocrinol*. 2017;5(5):391-402. https://doi:10.1016/S2213-8587(17)30033-5

28. Rana OA, Byrne CD, Greaves K. Intensive glucose control and hypoglycaemia: A new cardiovascular risk factor? *Heart*. 2014;100(1):21-27. https://doi:10.1136/heartjnl-2013-303871

29. Wright RJ, Frier BM. Vascular disease and diabetes: Is hypoglycaemia an aggravating factor? *Diabetes Metab Res Rev*. 2008;24(5):353-363. https://doi:10.1002/dmrr.865

30. Bertoluci MC, Moreira RO, Faludi A, et al. Brazilian guidelines on prevention of cardiovascular disease in patients with diabetes: A position statement from the Brazilian Diabetes Society (SBD), the Brazilian Cardiology Society (SBC) and the Brazilian Endocrinology and Metabolism Society (SBEM). *Diabetol Metab Syndr*. 2017;9(1):53. https://doi:10.1186/s13098-017-0251-z

31. Graham I, Ata D, Borch-Johnsen K, et al. European Guidelines on Cardiovascular Disease Prevention in Clinical Practice (Ending). Fourth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice. *Ration Pharmacother Cardiol*. 2008;4(4):90-107. https://doi:10.20996/1819-6446-2008-4-4-90-107

32. Fox CS, Golden SH, Anderson C, et al. Update on prevention of cardiovascular disease in adults with type 2 diabetes mellitus in light of recent evidence: A scientific statement from the American Heart Association and the American diabetes association. *Diabetes Care*. 2015;38(9):1777-1803. https://doi:10.2337/dci15-0012

33. Inzucchi SE, Lipska KJ, Mayo H, Bailey CJ, McGuire DK. Metformin in patientswith type 2 diabetes and kidney disease a systematic review. *JAMA - J Am Med Assoc*. 2014;312(24):2668-2675. https://doi:10.1001/jama.2014.15298

34. Carlos A. Tiazolidinedionas. Beneficios y riesgos reales. *Rev Endocrinol y Nutr Abril-Junio*. 2002;10(2):69-76. http://scielo.sld.cu/scielo.php?script=sci_arttext&pid=S0864-21251997000600014

35. Agudelo-Zapata Y, Burgos-Cárdenas ÁJ, Díaz-Martínez ÁJ, Pinilla-Roa AE. Dipeptidil dipeptidase-IV inhibidors: From the theory to the practice. *Rev Fac Med*. 2015;63(2):259-270. https://doi:10.15446/revfacmed.v63n2.48820

36. Arocha Rodulfo JI, Amair P, Marantes D, Navas Blanco T. El papel del riñón en la homeostasis de la glucosa y drogas de acción renal en el tratamiento de la diabetes mellitus tipo 2^ies. *Med interna*. 2016;32(2):78-88. [%22es%22, %22es%22]

37. Gerstein HC, Bosch J, Dagenais GR, et al. Basal insulin and cardiovascular and other outcomes in dysglycemia. *N Engl J Med*. 2012;367(4):319-328. https://doi:10.1056/NEJMoa1203858

38. Marso SP, McGuire DK, Zinman B, et al. Design of DEVOTE (Trial Comparing Cardiovascular Safety of Insulin Degludec vs Insulin Glargine in Patients With Type 2 Diabetes at High Risk of Cardiovascular Events) – DEVOTE 1. *Am Heart J*. 2016;179:175-183. https://doi:10.1016/j.ahj.2016.06.004

39. Marso SP, Mcguire DK, Zinman B, et al. Efficacy and safety of degludec versus Glargine in Type 2 Diabetes. *N Engl J Med*. 2017;377(8):723-732. https://doi:10.1056/NEJMoa1615692

40. Htike ZZ, Zaccardi F, Papamargaritis D, Webb DR, Khunti K, Davies MJ. Efficacy and safety of glucagon-like peptide-1 receptor agonists in type 2 diabetes: A systematic review and mixed-treatment comparison analysis. *Diabetes, Obes Metab*. 2017;19(4):524-536. https://doi:10.1111/dom.12849

41. The Effect of Intensive Treatment of Diabetes on the Development and Progression of Long-Term Complications in Insulin- Dependent Diabetes Mellitus. *N Engl J Med*. 1993;329(14):977-986. https://doi:10.1056/NEJM199309303291401

42. Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy. *Am J Ophthalmol*. 2000;129(5):704-705. https://doi:10.1016/s0002-9394(00)00453-0

43. Ohkubo Y, Kishikawa H, Araki E, et al. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. *Diabetes Res Clin Pract*. 1995;28(2):103-117. https://doi:10.1016/0168-8227(95)01064-K

44. Lund SS, Rossing P, Vaag AA. Follow-up of intensive glucose control in type 2 diabetes [1]. *N Engl J Med*. 2009;360(4):416-418. https://doi:10.1056/NEJMc082275

45. Turner R. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet*. 1998;352(9131):854-865. https://doi:10.1016/S0140-6736(98)07037-8

46. Turner R. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet*. 1998;352(9131):837-853. https://doi:10.1016/S0140-6736(98)07019-6

47. Ceriello A. La "memoria metabólica" inducida por la hiperglucemia: el nuevo reto en la prevención de la enfermedad cardiovascular en la diabetes. *Rev Española Cardiol Supl*. 2008;8(3):12C-18C. https://doi:10.1016/s1131-3587(08)73550-7

48. Ismail-Beigi F, Craven T, Banerji MA. Erratum: Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: An analysis of the ACCORD randomised trial (The Lancet (2010) 376 (419-430)). *Lancet*. 2010;376(9751):1466. https://doi:10.1016/S0140-6736(10)61995-2

49. Intensive Blood Glucose Control and Vascular Outcomes in Patients with Type 2 Diabetes. *J Vasc Surg*. 2008;48(3):770. https://doi:10.1016/j.jvs.2008.07.045

50. Duckworth W, Abraira C, Moritz T, et al. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med*. 2009;360(2):129-139. https://doi:10.1056/NEJMoa0808431

51. Griffin SJ, Leaver JK, Irving GJ. Impact of metformin on cardiovascular disease: a meta-analysis of randomised trials among people with type 2 diabetes. *Diabetologia*. 2017;60(9):1620-1629. https://doi:10.1007/s00125-017-4337-9

52. Kalra S, Gupta Y, Baruah MP, Gupta A. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes and moderate or severe renal impairment: Observations from the SAVOR-TIMI 53 Trial. Diabetes care 2015;38:696-705. *Diabetes Care*. 2015;38(6):e88-e89. https://doi:10.2337/dc15-0006

53. Scirica BM, Bhatt DL, Braunwald E, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med*. 2013;369(14):1317-1326. https://doi:10.1056/NEJMoa1307684

54. Zannad F, Cannon CP, Cushman WC, et al. Heart failure and mortality outcomes in patients with type 2 diabetes taking alogliptin versus placebo in EXAMINE: A multicentre, randomised, double-blind trial. *Lancet*. 2015;385(9982):2067-2076. https://doi:10.1016/S0140-6736(14)62225-X

55. Cornel JH, Bakris GL, Stevens SR, et al. Effect of sitagliptin on kidney function and respective cardiovascular outcomes in type 2 diabetes: Outcomes from TECOS. *Diabetes Care*. 2016;39(12):2304-2310. https://doi:10.2337/dc16-1415

56. Sattar N, Petrie MC, Zinman B, Januzzi JL. Novel Diabetes Drugs and the Cardiovascular Specialist. *J Am Coll Cardiol*. 2017;69(21):2646-2656. https://doi:10.1016/j.jacc.2017.04.014

57. Kankanala SR, Syed R, Gong Q, Ren B, Rao X, Zhong J. Cardiovascular safety of dipeptidyl peptidase-4 inhibitors: Recent evidence on heart failure. *Am J Transl Res*. 2016;8(5):2450-2458.

58. Guthrie R. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *Postgrad Med*. 2018;130(2):149-153. https://doi:10.1080/00325481.2018.1423852

59. Saad M, Mahmoud AN, Elgendy IY, et al. Cardiovascular outcomes with sodium–glucose cotransporter-2 inhibitors in patients with type II diabetes mellitus: A meta-analysis of placebo-controlled randomized trials. *Int J Cardiol*. 2017;228:352-358. https://doi:10.1016/ j.ijcard.2016.11.181

60. Hinnen D. Glucuretic effects and renal safety of dapagliflozin in patients with type 2 diabetes. *Ther Adv Endocrinol Metab*. 2015;6(3):92-102. https://doi:10.1177/2042018815575273

61. Gargiulo P, Savarese G, D'Amore C, et al. Efficacy and safety of glucagon-like peptide-1 agonists on macrovascular and microvascular events in type 2 diabetes mellitus: A meta-analysis. *Nutr Metab Cardiovasc Dis*. 2017;27(12):1081-1088. https://doi:10.1016/ j.numecd.2017.09.006

62. Wong C, Fisher M. Inconclusive effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. *Pract Diabetes*. 2017;34(9):302-303. https://doi:10.1002/pdi.2140