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Cardiovascular effects of sodium-glucose co-transporter 2 inhibitor empagliflozin in type 2 diabetes mellitus patients: Beyond glycemic control

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ABSTRACT

Cardiovascular disease is the most frequent cause of death in type 2 diabetes mellitus, and type 2 diabetes mellitus *per se* is a cardiovascular disease equivalent. This is because patients with type 2 diabetes mellitus commonly have comorbidities that power cardiovascular risk. These include obesity, arterial hypertension, and dyslipidemia among others.
Therefore, the effective management of type 2 diabetes mellitus should focus not only on glycemic control, but also on the control of these comorbid conditions. The sodium-glucose co-transporter 2 inhibitors not only control hyperglycemia, but also reduce cardiovascular risk. This is due to their unique mechanism of action, which is independent of the pancreatic β cell and insulin. They function by inhibiting glucose renal absorption; as a consequence there is an increase in the volume of glucose excreted in urine. Empagliflozin is a drug pertaining to this new therapeutic group.
The efficacy of empagliflozin as a hypoglycemic agent and its potential for reducing cardiovascular risk is assessed in this article. We review the effects of empagliflozin on

RESUMEN

La enfermedad cardiovascular es la causa más frecuente de muerte en la diabetes *mellitus* tipo 2 (T2D), y la T2D *per se* es un equivalente de enfermedad cardiovascular debido a que los pacientes con T2D frecuentemente tienen comorbilidades que pueden intensificar el riesgo cardiovascular. Estas incluyen a la obesidad, hipertensión arterial y la dislipidemia, entre otras.
Es por esto que el manejo efectivo de la T2D no debe enfocarse solamente en el control glucémico, sino también en el control de estas comorbilidades. Los inhibidores del co-transportador de sodio-glucosa tipo 2 (SGLT2i), además de controlar la hiperglucemia, también reducen el riesgo cardiovascular. Esto se debe a su mecanismo de acción único, el cual es independiente de la célula β pancreática y la insulina. Funcionan mediante la inhibición de la reabsorción renal de glucosa; como consecuencia de ello, existe un incremento en la cantidad de glucosa en la orina. La empagliflozina es un medicamento que pertenece a este nuevo grupo terapéutico.

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cardiovascular risk factors commonly found in patients with type 2 diabetes mellitus and we discuss the results of the recently published EMPA REG study, which assessed the cardiovascular safety of this drug. (REV MEX ENDOCRINOL METAB NUTR. 2016;3:72-81)

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Key words: Atherosclerosis. Type 2 diabetes mellitus. T2DM. Empagliflozin. Glycated hemoglobin. HbA1c. Sodium-glucose co-transporter 2 inhibitor. SGLT2i. QT interval. Arterial stiffness. Systolic/diastolic blood pressure.

En este artículo se evalúa la eficacia de la empagliflozina como un agente hipoglicemiante y su potencial para reducir el riesgo cardiovascular. Revisamos los efectos de la empagliflozina sobre los factores de riesgo cardiovascular encontrados frecuentemente en los pacientes con T2D y discutimos los resultados del estudio EMPAREG recientemente publicado que analiza la seguridad cardiovascular de este medicamento.

Palabras clave: Ateroesclerosis. Diabetes mellitus tipo 2. Empagliflozina. Hemoglobina glucosilada. Inhibidores del co-transportador sodio glucosa. Intervalo QT. Rigidez arterial. Tensión arterial sistólica/diastólica

INTRODUCTION

Hyperglycemia, dyslipidemia and cardiovascular risk

The Third Report of the Expert Panel of the National Cholesterol Education Program (NCEP-ATP-III) emphasizes a clinical approach for preventing cardiovascular disease (CVD). The primary objective of treatment is to reduce plasma cholesterol concentrations, specifically low-density lipoprotein cholesterol (LDLc). Epidemiological studies conducted in different populations show that values of LDLc > 100 mg/dl, along with other cardiovascular risk factors or already established CVD, promote coronary heart disease[1].

In the Framingham Heart Study, Multiple Risk Factor Intervention Trial, and the Lipid Research Clinics Study a direct relationship between LDLc > 100 mg/dl and the first occurrence of coronary artery disease in men and women was confirmed. This relationship remains for subsequent coronary events in patients with established coronary disease[1].

According to the ATP-III experts, factors negatively influencing cardiovascular risk include smoking, high arterial blood pressure, low concentrations of high-density lipoprotein cholesterol (HDLc), a previous history of premature coronary disease, advanced age, and presence of type 2 diabetes mellitus (T2DM)[1].

In this context, T2DM is *per se* a CVD equivalent, not just a conventional cardiovascular risk factor[1]. Additionally, CVD is the most frequent cause of death in patients with T2DM; in different studies it has been concluded that the presence of T2DM significantly increases (2- to 4-fold) CVD risk compared to non-diabetic patients[2].

Dyslipidemia is highly prevalent in T2DM patients. A multivariate analysis of the United Kingdom Prospective Diabetes Study (UKPDS) showed that the presence of a dyslipidemia characterized by elevated levels of LDLc and low levels of HDLc is a strong, independent predictor for CVD. This has been confirmed in other studies in which therapeutic strategies aimed at reducing LDLc concentrations reduced the risk of major cardiovascular events in T2DM patients[2].

Given the interdependence of hyperglycemia, dyslipidemia, and cardiovascular risk in T2DM patients, it is clear that appropriate glycemic control contributes to achieving lipid targets and to reducing CVD risk. The International Diabetes Federation (IDF) guidelines recommend lifestyle modifications and pharmacological treatment with sequential addition of hypoglycemic agents in order to achieve glycated hemoglobin (HbA1c) of < 6.5% or

(according to other consensus) < 7.0%[3], which in practical terms corresponds to an average fasting glycemia of 150 mg/dl ("acceptable" risk for diabetes complications)[4].

In this respect, the guidelines of the American Diabetes Association (ADA) establish that the HbA1c target of < 7.0% is reasonable for most adults, except for pregnant women, whilst the HbA1c target of < 6.5% may be considered for adults with recent-onset diabetes, long life expectancy, and no CVD or other complications, provided that the latter goal is reached without hypoglycemia or other adverse event risk[5].

The ADA guidelines also establish that an HbA1c < 8.0% may be appropriate for patients with a history of severe hypoglycemia, low life expectancy, macrovascular or microvascular complications, other comorbidities, and long-term diabetes since achieving an HbA1c target between 6.5 and 7.0% in this population without hypoglycemia may be difficult; usually, the use of multiple hypoglycemic agents such as insulin in these stages of the disease is required[5].

Stratification of cardiovascular risk and non-pharmacological and pharmacological interventions

The European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) use the following criteria for the stratification of cardiovascular risk; arterial blood pressure (BP) and the presence or absence of other cardiovascular risk factors, including T2DM, dyslipidemia, and obesity. In the most recent ESH and ESC consensus guidelines (2013), elevated BP is defined as a systolic blood pressure value > 140 mmHg and a diastolic BP value > 90 mmHg[6].

The ESH and ESC recommend changes in lifestyle as an initial strategy, focusing principally on arterial blood pressure control. This includes restricting the use of tobacco, salt, and alcohol, together with dietary changes and regular exercise to reduce body weight. In addition, the guidelines stipulate specific values for hyperglycemia and dyslipidemia to be considered in the overall risk stratification for CVD: fasting plasma glucose of 126 mg/dl in two consecutive measurements and/or HbA1c > 7% and/or post-load plasma glucose of 198 mg/dl; total cholesterol of 190 mg/dl and/or LDLc of 115 mg/dl and/or HDLc of 40 mg/dl (men) or 46 mg/dl (women) and/or triglycerides of 150 mg/dl[6]. These same guidelines support the recommendations issued by the European Association for the Study of Diabetes (ADA/EASD) for the management of hyperglycemia.

As for the American College of Cardiology (ACC) and the American Heart Association (AHA) guidelines, also issued in 2013, the focus is on reducing atherosclerotic CVD risk by targeting dyslipidemia. The use of statins at varying potencies according to the degree of CV risk (treatment with low, moderate, and high potency statins)[7].

Despite the validity of recommendations from the ESH, ESC, ACC, and AHA, it is evident that the reduction of cardiovascular risk also requires glycemia control and not only the management of arterial BP, reduction in body weight, and improvement of dyslipidemia.

Inhibition of sodium-glucose co-transporter 2 inhibitors and reduction of cardiovascular risk

The inhibition of sodium-glucose co-transporter 2 (SGLT2) is a novel way to reduce plasma glucose concentrations. The mechanism of action does not depend on the β pancreatic cell or insulin. Inhibiting the SGLT2 partially removes excess glucose from the body by inhibiting its renal absorption and promoting an increase in the volume of glucose-containing urine (VGCU)[8,9].

Sodium-glucose co-transporter 2 inhibitors (SGLT2i) are agents that have an ideal profile to reduce CVD risk in diabetic patients. Whether in monotherapy or combined with other hypoglycemic agents, they help to effectively control the principal factors promoting cardiovascular risk, i.e. hyperglycemia, arterial hypertension, obesity, and a possible reduction in arterial stiffness without prolongation of the QT

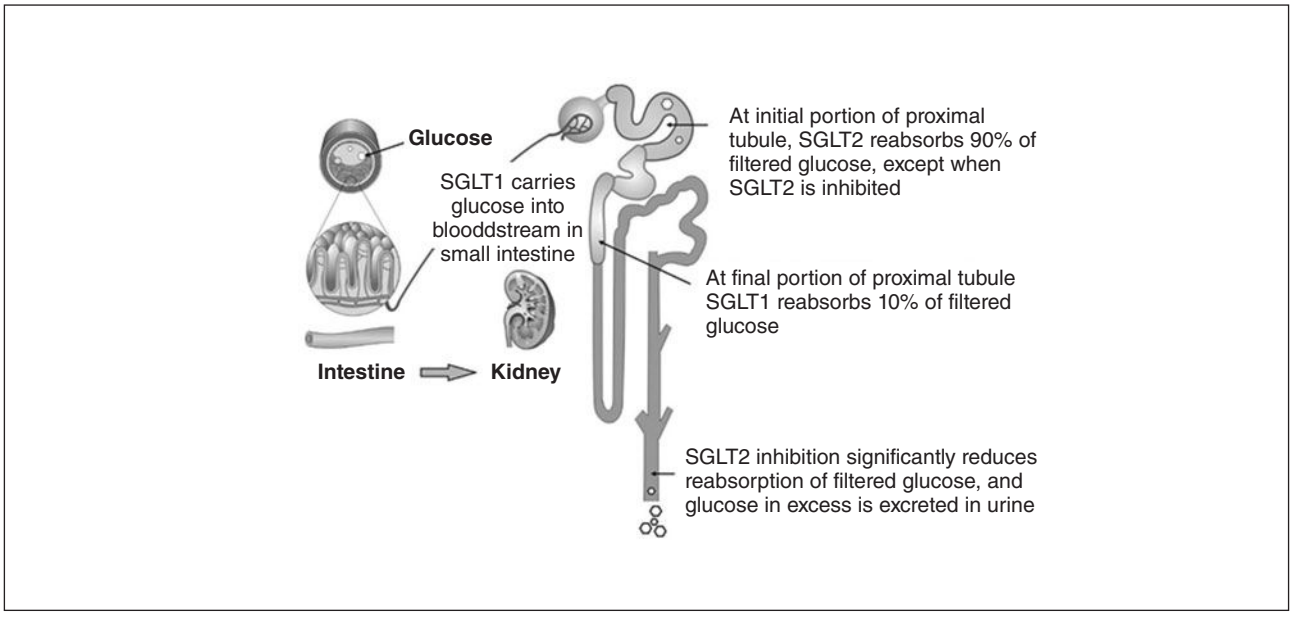

Figure 1. Glucose lowering mechanism of sodium-glucose co-transporter 2 inhibitors[11,17].
SGLT: sodium-glucose co-transporter.

segment (according to studies conducted in type 1 diabetes patients). Long-term treatment with SGLT2i may also improve β pancreatic cell function and insulin sensitivity[10-15].

In T2DM patients, each 1% reduction in HbA1c translates to a 37% reduction in CVD risk, a 43% reduction in peripheral vascular disease, a 14% reduction in myocardial infarction, a 12% reduction in stroke, and a 16% reduction in cardiac failure[16].

As a result, it is important to use agents that effectively reduce HbA1c, without adversely affecting other risk factors, or even better, modifying them such that there is a reduction in cardiovascular risk. Currently, the SGLT2i empagliflozin stands out among these agents: phase II and III studies have shown favorable effects on glucose homeostasis (reduction of HbA1c values), arterial blood pressure, and body weight either in monotherapy, as an add-on agent with other pharmacological combinations, and in special populations such as adults with T2DM and arterial hypertension, or in patients with renal impairment (Grade 2 or 3)[11].

Sodium-glucose co-transporter 2 function in glucose homeostasis

The kidney plays a fundamental role in glucose homeostasis; in particular, glucose reabsorption from the glomerular filtrate and renal gluconeogenesis[11,17].

In a healthy adult, the kidneys filter the entire blood volume approximately 50 times each day. Therefore, 180 l/day of plasma are filtered with an average glucose concentration of 100 mg/dl, which, in healthy persons, is equivalent to filtering 180 g of glucose per day. This is enough to preserve plasma glucose concentrations at normal levels (approximately 100 mg/dl). Thus, practically all filtered glucose is reabsorbed in the renal proximal tubules, resulting in an absence of glucose in urine[11,17].

This reabsorption is possible due to the activity of sodium-dependent transmembrane proteins called sodium-glucose co-transporters (SGLT), in particular: SGLT2 (responsible for 90% of glucose renal reabsorption), and SGLT1 (responsible for the reabsorption of the remaining 10%). An understanding of this process explains the glucose-lowering effects of SGLT2i (Fig. 1)[11,17].

Table 1. Pharmacokinetics and pharmacodynamics of sodium-glucose co-transporter 2 inhibitor empagliflozin[8,9,18]

In healthy volunteers	Quick absorption: peak concentrations (C_{max}) occur within 1.25 to 2.50 hours post-dose. Plasma concentrations decrease in a biphasic manner; the mean elimination half-life ($t_{1/2}$) is 7.76 to 11.7 hours. Exposition increases arecrease tion from the glomerular filtrate and renal gluconeogenesis dose-dependent; the clearance (140-172 ml/min) is dose independent. Average 24 hour VGCU after the administration of 100 mg of drug is 74.3 g. This is dose dependent.
In T2DM patients	C_{max} occurs within 1.5-2.0 hours post-dose. $t_{1/2}$ is between 13.2 and 18.0 hours. With single or multiple doses (0.5 to 800 mg), the exposure to drug increases in a dose-dependent way; steady state occurs on the sixth day of treatment.
In special groups	Drug pharmacology does not change with mild-to-moderate hepatic or renal impairment and for those with terminal renal impairment. Empagliflozin does not induce clinically relevant drug interactions in patients treated with warfarin.

T2DM: type 2 diabetes mellitus; VGCU: volume of glucose-containing urine.

EMPAGLIFLOZIN

Mechanism of action

Empagliflozin produces a potent and selective inhibition of SGLT2, 2,500-fold that for SGLT1. It is an oral hypoglycemic agent that is effective in inhibiting glucose renal reabsorption, resulting in a noticeable increase in VGCU[8,9].

The pharmacokinetics and pharmacodynamics of empagliflozin are summarized in table 1[8,9,18].

Effects on glucose homeostasis

In animal models

The duration of the glucose lowering effect and the preservation of β cell function have been investigated in diabetic and obese Zucker rats in 4-8 week studies, using comparators such as liraglutide, glibenclamide, and empagliflozin. Empagliflozin and liraglutide showed efficacy for both endpoints, whereas glibenclamide only had a glucose lowering effect. Empagliflozin and liraglutide inhibited the progressive decrease in insulin concentrations[19].

Even though the therapeutic target of empagliflozin is not the pancreatic β cell, preclinical experiments (with Zucker rats) have shown that it is effective in preserving β cell mass. In addition, unlike glibenclamide and liraglutide, empagliflozin is able to maintain glucose homeostasis for longer periods of time (due to its β cell independent mechanism of action)[19].

In healthy volunteers

Compared to placebo and in a dose-dependent manner, empagliflozin increases VGCU without significant effects on total 24-hour urine volume. In addition, dose-dependent VGCU increases are related to urinary excretion ≥ 90 g/day for glucose[8,11].

Although VGCU increases proportionally to empagliflozin dose within 72 hours, this increase reaches a plateau with the administration of 100 mg of drug. Empagliflozin doses ≥ 10 mg inhibit filtered glucose absorption by 40%, whilst the administration of even higher doses causes inhibition ranging from 40 to 60%[11].

In type 2 diabetes mellitus patients (Table 2)

Practically all doses of empagliflozin assessed in the studies (2.5 to 100 mg), increase VGCU and reduce plasma glucose concentrations[20].

Table 2. Empagliflozin: effects on glucose homeostasis (reduction in HbA1c) in phase II and III studies[11,20]

Phase I studies				
Baseline HbA1c values	HbA1c reduction with empagliflozin (5-25 mg)	HbA1c reduction with empagliflozin (1-50 mg)	HbA1c reduction with empagliflozin (5-50 mg)	HbA1c reduction with empagliflozin (10-25 mg)
7.8 ± 0.8 to 7.9 ± 0.8	–0.4 to –0.6%			
7.8 ± 0.7 to 7.9 ± 0.7		–0.1 to –0.5%		
7.9 ± 0.1 to 8.0 ± 0.1			–0.4 ± 0.1 to –0.6 ± 0.1	
8.3 ± 0.1				–0.6 ± 0.1 (10 mg) –0.7 ± 0.1 (25 mg)

Phase III studies		
Monotherapy with single daily doses of empagliflozin vs. sitagliptin in T2DM diagnosed patients without previous pharmacological treatment		
HbA1c reduction with empagliflozin (10 mg)	HbA1c reduction with empagliflozin (25 mg)	HbA1c reduction with sitagliptin (100 mg)
–0.66%	–0.78%	–0.66%

Add-on treatment to previous monotherapy or pharmacological combination		
Previous monotherapy or combination	HbA1c reduction when adding empagliflozin (10 mg)	HbA1c reduction when adding empagliflozin (25 mg)
Metformin	–0.70 ± 0.05%	–0.77 ± 0.05%
Metformin + sulphonylurea	–0.82 ± 0.05%	–0.77 ± 0.05%
Metformin + pioglitazone	–0.59 ± 0.07%	–0.72 ± 0.07%

Special populations		
Type of population	HbA1c reduction with empagliflozin (10 mg)	HbA1c reduction with empagliflozin (25 mg)
Adults with T2DM and arterial hypertension	–0.59 ± 0.04	–0.62 ± 0.04
Adults with T2DM and renal impairment Grade 2	–0.46%	–0.63%
Adults with T2DM and renal impairment Grade 3		–0.37%

HbA1c: glycated hemoglobin; T2DM: type 2 diabetes mellitus.

Over 28-days, empagliflozin reduces glycemia parameters (–35.28 to –45.72 mg/dl; $p < 0.01$ vs. placebo) and fasting plasma glucose (–28.08 to –42.66 mg/dl; $p < 0.01$ vs. placebo) in a dose-dependent fashion (1, 5, 10, and 25 mg). These effects have been observed when using empagliflozin in monotherapy or in combination with metformin; for patients treated with insulin, use of empagliflozin not only improves glycemic control but also reduces the insulin dose[11,18].

Table 3. Degree of weight loss corresponding to differing doses of empagliflozin[11-13]

Dose of empagliflozin	Loss associated in body weight
5 to 25 mg	−1.8 to −2.0 kg
1 to 50 mg	−1.6 to −2.9 kg
5 to 50 mg	−2.5 ± 0.2 to −3.1 ± 0.2 kg
10 to 25 mg	−2.2 ± 0.5 to −2.0 ± 0.5 kg

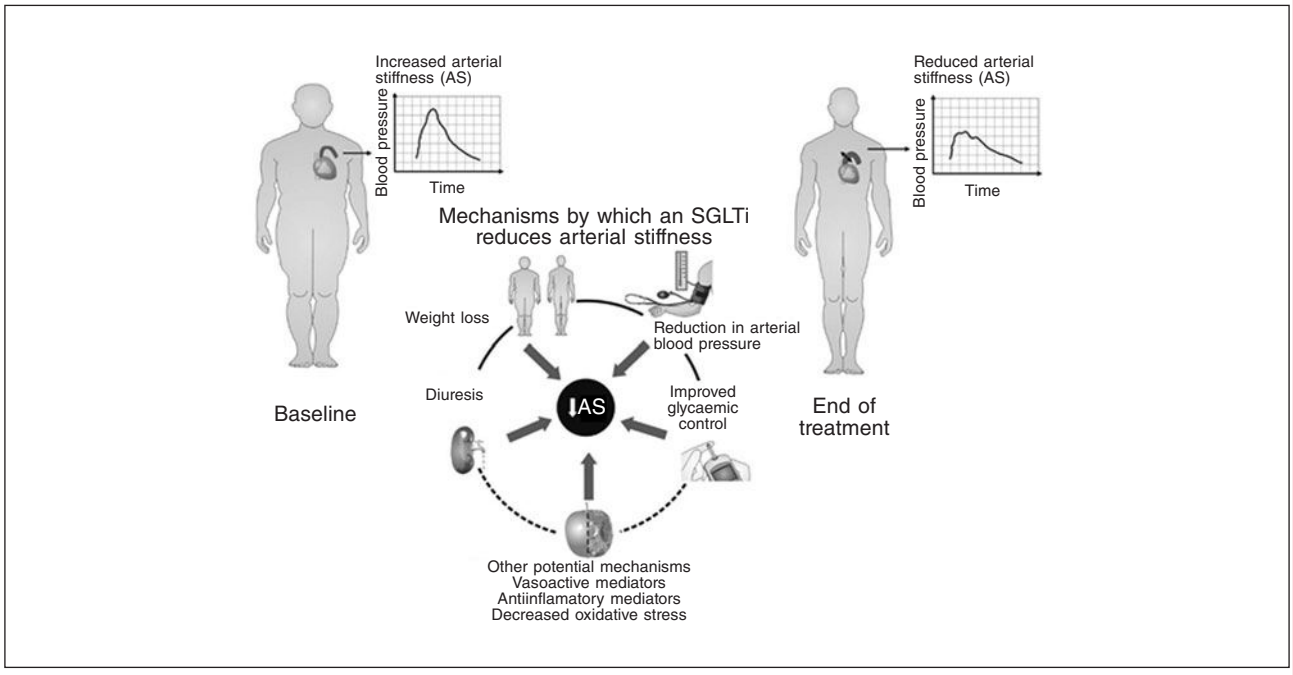

Figure 2. Physiological mechanisms involved in the reduction of arterial stiffness with the use of sodium-glucose co-transporter 2 inhibitors[10]. AS: arterial stiffness; SGLT2i: sodium-glucose co-transporter 2 inhibitor.

TREATMENT WITH EMPAGLIFLOZIN AND REDUCTION OF CARDIOVASCULAR RISK

Weight loss

The use of different doses of empagliflozin is directly related to the degree of weight loss (Table 3)[11].

Reduction in arterial blood pressure

Empagliflozin 10 and 25 mg administered over 12 weeks reduces systolic BP by 4-5 mmHg. The antihypertensive effects of empagliflozin are more significant in patients with a baseline systolic BP > 140 mmHg[11].

Reduction in arterial stiffness and effects on heart rate (Fig. 2)

Forty normotensive T1D patients took part in the following study. Measurement of arterial BP, arterial stiffness, heart rate, and circulating adrenergic mediators were conducted at baseline and following eight weeks of treatment with empagliflozin (25 mg once daily). An interesting aspect of this study was that the results of these parameters in patients with

treatment-induced euglycemia (fasting plasma glucose 72-108 mg/dl) were compared to the results obtained in subjects with hyperglycemia despite treatment with empagliflozin (fasting plasma glucose 162-198 mg/dl)[10].

In the T1DM patients who achieved euglycemia with empagliflozin, there was a reduction in the levels of cardiovascular risk parameters: systolic BP (from 111 ± 9 to 109 ± 9 mmHg; p = 0.02) and an improvement in arterial stiffness at the following locations; radial (from −52 ± 16 to −57 ± 17%; p = 0.0001), carotid (from 1.3 ± 17.0 to −5.7 ± 17.0%; p < 0.0001), and aortic (from 0.1 ± 13.4 to −6.2 ± 14.3%; p < 0.0001)[10].

An improvement in arterial stiffness also occurred in the T1DM patients who were hyperglycemic, but this was not accompanied by changes in arterial BP. The carotid-radial pulse decreased significantly in both the euglycemia and hyperglycemia (p ≤ 0.0001) groups, but carotid/femoral pulse wave velocity only decreased in the cases with hyperglycemia (from 5.7 ± 1.1 to 5.2 ± 0.9 m/s; p = 0.0017)[10].

There was no difference between the euglycemia and hyperglycemia groups with respect to variability in heart rate and noradrenaline and adrenaline concentrations[10].

No prolongation of the QT interval

In healthy volunteers, empagliflozin 25 mg (therapeutic dose) and 200 mg (supra-therapeutic) are well tolerated and do not prolong the QT interval[14].

In a randomized, double blind, placebo-controlled study, 30 volunteers (16 men and 14 women with a mean age of 34.5 years [range: 18-52]) were randomized to receive either a single empagliflozin dose (25 or 200 mg), placebo (negative control), or moxifloxacin 400 mg (positive control). Moxifloxacin is a fluoroquinolone that favors a prolonged QT interval[14].

At baseline and within 24 hours post-dose, three 12-lead ECG assessments were conducted. A QT interval of 10 ms was considered a harmless and safe change. Within 1-4 hours post-dose, both empagliflozin doses resulted in QT intervals that were within the safety margin compared to placebo: 0.6 ms (CI_{90}: −0.7 to 1.9) with 25 mg, and −0.2 ms (CI_{90}: −1.4 to 0.9) with 200 mg. In contrast, the effects of a single dose of moxifloxacin exceeded the 10 ms QT interval safety margin compared to placebo: the QT interval was prolonged to 12.4 ms (CI_{90}: 10.7 to 14.1) within 2-4 hours post-dose[14].

All the volunteers appropriately tolerated both empagliflozin doses, and even the incidence of adverse events (primarily mild nasopharyngitis) was higher for placebo (27.6%) than for empagliflozin-based active treatment (23.3%)[14].

Cardioprotective potential

As discussed previously, both in the *in vitro*/preclinical studies and in the phase II and III clinical trials, empagliflozin has shown efficacy with regards to glycemic control, weight loss, and reduction in arterial BP in diabetic patients, without affecting heart rate or extending the QT interval.

The EMPA-REG-OUTCOME study was designed to determine the cardiovascular safety of empagliflozin in T2DM patients with established CVD. The study also provided an opportunity to explore a potential cardioprotective role for empagliflozin[21].

The recruitment period for the EMPA-REG-OUTCOME study was from September 2010 to April 2013. This was a randomized, double blind, placebo-controlled trial that included over 7,000 patients attending 52 centers (41% in Europe, 20% in North America, and 19% in Asia). Subjects were assigned to either empagliflozin (10 or 25 mg) or placebo[21].

This study included two groups of subjects: those who were without pharmacological treatment for diabetes for at least 12 weeks prior to study entry (HbA1c ≥ 7.0 and ≤ 9.0%), and patients who were already taking hypoglycemic agents for at least 12 weeks prior to study entry (HbA1c ≥ 7.0 and ≤ 10.0%). The baseline characteristics of the participants included: a mean age (63 ± 9 years), a mean body mass index (BMI: 30.6 ± 5.3 kg/m^2), hyperglycemia (HbA1c:

8.1 ± 0.8%), and a mean estimated glomerular filtration rate (eGFR: 74 ± 21 ml/min/1.73 m^2)[21].

The study included patients with recognized cardiovascular risk factors: 94% received regular treatment with antihypertensive drugs, 13% were smokers and 49% former smokers, 57% were long-term diabetics (> 10 years), and 99% had a previous history of CVD (47% with a previous myocardial infarction, 11% with coronary disease in a vessel and 47% in multiple vessels, 25% had undergone revascularization, 23% had a history of stroke, and 21% had a history of peripheral occlusive arterial disease)[21]. Subjects were well treated with respect to lipid-lowering agents and anti-hypertensive agents[22].

The primary endpoint was the composite of either death from a cardiovascular cause (outcome research), the occurrence of a non-fatal myocardial infarction or stroke, or hospitalization due to angina pectoris. According to the study design, the study would continue until ≥ 691 primary endpoints were confirmed[21].

After a median of 3.1 years the study ended with a median duration of treatment of 2.6 years. The primary outcome occurred in 10.5% in the pooled empagliflozin group and 12.1% in the placebo group (hazard ratio in the empagliflozin group: 0.86; 95.02% CI: 0.74-0.99; p = 0.04 for superiority)[22]. The primary outcome occurred in a significantly lower percentage of subjects taking empagliflozin.

In the empagliflozin group, there were significantly lower rates of death from cardiovascular causes (3.7 vs. 5.9% in the placebo group; 38% relative risk reduction), hospitalization for heart failure (2.7 and 4.1%, respectively; 35% relative risk reduction), and death from any cause (5.7 and 8.3%, respectively; 32% relative risk reduction)[22].

Interestingly, the reduction in risk associated with cardiovascular outcomes and death from any cause was evident early on in the trial (within six months) and this benefit was maintained throughout the study period. With respect to glycemic control, the mean glycated hemoglobin was 7.81% in the empagliflozin group and 8.16% in the placebo group[22]. There was an increased rate of genital infection in the empagliflozin patients, but no increase in other adverse events.

The mechanisms associated with the cardiovascular benefits of empagliflozin are probably multifactorial and as yet unknown. We can speculate that an improvement in arterial stiffness, decreased uric acid levels, a reduction in body weight, improved glycemic control and dyslipidemia, and a reduction in arterial hypertension all contribute to the cardioprotective process. However, possible novel cardiorenal mechanisms must also be investigated in the future. Finally, we do not know if this is a general class effect and we must remember that these findings are only applicable to T2DM subjects at high cardiovascular risk.

The clinical impact of this trial is important. Firstly it establishes the cardiovascular safety of empagliflozin in T2DM patients with CVD. Secondly, initiating empagliflozin in such patients not only reduces the risk for diabetes complications (by improving glycemic control), but also theoretically reduces cardiovascular mortality, thus extending patient life.

CONCLUSIONS

Type 2 diabetes mellitus is a major cardiovascular risk factor as well as the main cause of death in T2DM patients.

The presence of T2DM increases 2- to 4-fold the risk of CVD: each 1% increase in HbA1c translates into a 38% increase in developing CVD.

In T2DM, not only is appropriate glycemia control mandatory, but also the control of additional cardiovascular risk factors, including obesity, arterial hypertension, and dyslipidemia.

The SGLT2i empagliflozin has demonstrated efficacy in glycemic control, weight loss, and a reduction in blood pressure, without altering heart rate or prolonging the QT interval.

The EMPA-REG-OUTCOME study was designed to determine the cardiovascular safety of empagliflozin in patients with T2DM who were at high cardiovascular risk.

Empagliflozin, when compared to placebo, showed a significantly lower rate for the primary cardiovascular composite endpoint. It was associated with a 38% relative risk reduction for cardiovascular death, a 35% relative risk reduction for hospitalization for heart failure, and 32% relative risk reduction for death from any cause.

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