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REVIEW ARTICLE

SGLT2 Inhibitors and Cardiovascular Outcomes: Do They Differ or There is a Class Effect? New Insights from the EMPA-REG OUTCOME trial and the CVD-REAL Study

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Abstract: A new group of hypoglycemic drugs has been used to treat diabetes type 2. This group is active sodium glucose co-transporter (SGLT2) or SGLT2 inhibitors. It has been shown that besides the treatment of diabetes, this drug class is responsible for the mildness of the cardiovascular events shown in patients with diabetes type 2. However, there is an intriguing question regarding the range of SGLT2 inhibitors and if there is a difference between them or if there is a class effect among their results. EMPA-REG OUTCOME trial and the CVD-study are used to answer this question. Additional information from the DECLARE-TIMI 58 and Dapa-HF trials is studied.

Keywords: SGLT2 inhibitors, T2DM, diabetes type 2 mellitus, EMPA-REG OUTCOME trial, CVD-REAL study, class effect, cardiovascular events.

1. INTRODUCTION

There are drugs which seem to be similar in their clinical effects. Therefore, they are frequently exchangeable during treatments. The drug class effect concept is characterized by three concepts. We could say that there is a drug class effect if a group of drugs has similar chemical structure, similar mechanism of action or similar pharmacological effects [1].

One group of drugs that could be characterized as a class effect is the blood glucose co-transporter (SGLT2) or SGLT2 inhibitors. This group of drugs has a hypoglycemic action against hyperglycemia, by increasing the blood glucose ejections into the urine through the kidney. This mechanism of reaction categorizes SGLT2 inhibitors into antidiabetic drugs and makes them suitable for the treatment of diabetes type 2. A number of pharmaceutical substances are classified into the SGLT2 inhibitors class, such as empagliflozin, canagliflozin, dapagliflozin [2]. Diabetes is not the only disease that can be treated through SGLT2 inhibitors, since cardiovascular (CV) disease is the main cause of mortality in patients with diabetes mellitus type 2 (T2DM) and SGLT2 inhibitors have an effect on it too [3].

SGLT2 protein is located in the kidneys. It is a glucose transporter protein in humans and it is responsible for the reabsorption of glucose by the kidney. SGLT2 inhibitors inhibit the SGLT2 protein and therefore lower blood glucose levels by blocking glucose resorption in the kidney, due to an increase in renal urinary glucose (glycosuria). Further glucose control can be accomplished [3].

Empagliflozin, being one of the SGLT2 inhibitors, is responsible for the inhibition of the renal sodium-glucose cotransporter-2 (SGLT-2 inhibitor) [4]. There has been a study about the daily dosage of empagliflozin in patients with diabetes type 2 mellitus (T2DM) and whether it reduces CV mortality in patients with high-risk CV events, compared to placebo treatment. This is the EMPA-REG OUTCOME trial (Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes trial). More specifically, it has been

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tested whether the daily dosage of empagliflozin of 10 or 25 mg reduces CV mortality, nonfatal MI, or nonfatal strokes. These results were compared to the results from the placebo treatment.

The EMPA-REG OUTCOME study is not the only study for the use of SGLT2 inhibitors against cardiovascular events in patients with T2DM. The CVD-REAL study is another useful multinational cohort study [5]. However, according to this study, no placebo treatment was used. This study deals with patients with type 2 diabetes mellitus who are being treated with SGLT-2 inhibitor or another glucose-lowering drug. The main goal of this study is to compare the percentage of cardiovascular diseases in patients who recently started SGLT-2 inhibitors with the percentage of those who recently started other glucose-lowering drugs [5]. SGLT2 inhibitors significantly improve blood pressure, weight loss and glycaemic levels. However, a question has been raised whether there is a class effect or not [6]. Diabetes was treated with insulin and SFUs until metformin was used in 1995. However, the drugs used did not help with the cardiovascular diseases. In 2008, the US FDA suggested that the drugs produced for T2DM should mention that they do not increase the risk of cardiovascular diseases.

The SGLT-2 inhibitor's mechanism of action is to increase the urinary glucose excretion causing loss of weight. The mechanisms of cardiovascular protection by SGLT2 inhibitors can be seen in Fig. (**1**). Besides SGLT-2 inhibitors though there are also other types of drugs that threat T2DM and help with the prevention of cardiovascular events at the same time. The GLP-1 receptor agonists increase the insulin release and decrease the glucagon amount also causing loss of weight. The DPP-4 inhibitors have the same mechanism of action with GLP-1 receptor agonists with a neutral effect on weight loss. All the three drugs categories mentioned above show a low risk of hypoglycemia. Moreover, these agents could be combined together as the proper treatment. Drugs belonging to the class of DPP-4 inhibitors are gemigliptin, anagliptin, teneligliptin, alogliptin, trelagliptin, omarigliptin, evogiptin, dutogliptin and retagliptin.

2. MATERIALS AND METHODS

During the EMPA-REG OUTCOME trial, all the participants were randomized and treated with empagliflozin (10 or 25mg) or placebo. Then, the group that received placebo was compared with the groups that were treated with empagliflozin.

Empagliflozin and other SGLT2 drugs have been tested against not only placebo but other glucose-lowering drugs, such as canagliflozin. Both empagliflozin and canagliflozin prevent deaths caused by cardiovascular diseases and the population tested showed a high risk of cardiovascular disease. In order to define the percentages of cardiovascular mortality in patients with T2DM, new users of SGLT2 inhibitors have been studied against new users of other glucose-lowering drugs (Table **1**) [7].

The CVD-REAL Nordic study took place for the period of 2012 until 31 Dec 2015. Patients from Denmark, Norway, and Sweden were tested and observed. The aim of this study was the clarification of the levels of cardiovascular mortality and other cardiovascular diseases in patients with T2DM. All participants of the study were prescribed for glucose-lowering drugs and they were divided into two categories, to the new users of SGLT2 inhibitors and the new users of other glucose-lowering drugs. According to the protocol,

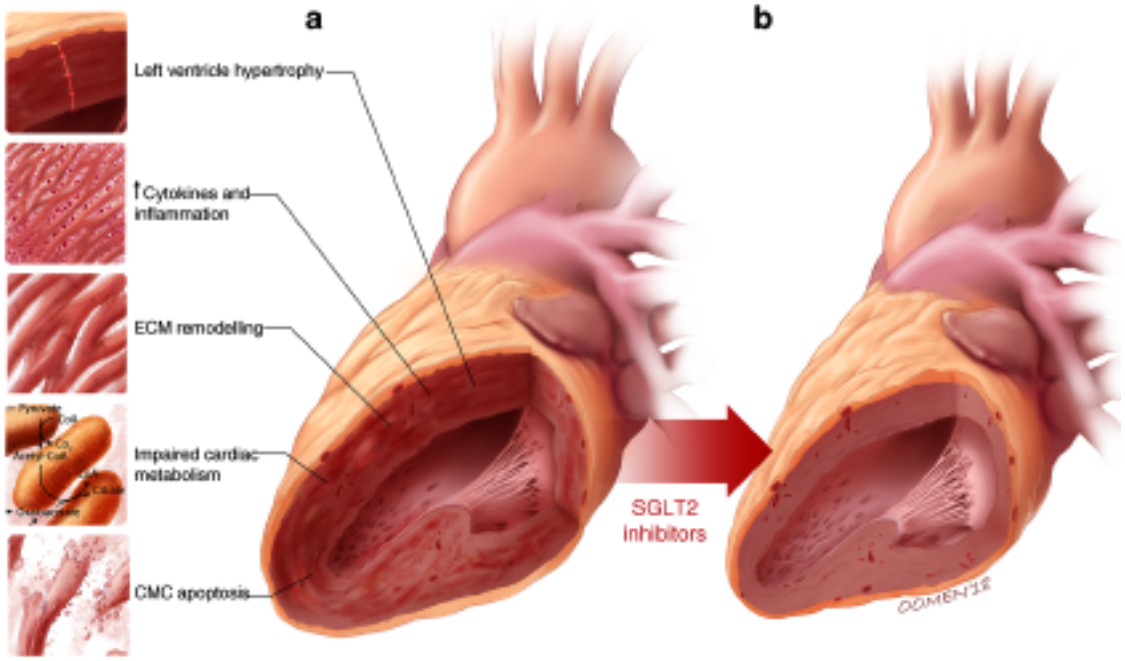

Fig. (1). Diabetes-associated ventricular remodelling (**a**) is characterised by left ventricular hypertrophy, inflammation, increased extracellular matrix (ECM) production, impaired cardiac metabolism and cardiomyocyte (CMC) apoptosis. SGLT2 inhibitors may offer salutary effects on several of the fundamental molecular and cellular pathways involved in the development and natural history of cardiac failure in diabetes (as illustrated by a healthy heart in **b**). © G. Oomen 2018. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

three users of any other glucose-lowering drug should match with one new user of SGLT2 inhibitor. These matches were accomplished by using the propensity scores Table **2** [7].

There are also other studies for the relationship between the glucose-lowering drugs and the cardiovascular diseases which are present in patients with T2DM. Canagliflozin and dapagliflozin are another two SGLT2 inhibitors and they have been tested through the CANagliflozin cardiovascular Assessment Study (CANVAS). Through studies like CANVAS could be specified if it is a class effect or not [8]. However, patients with diabetes participated differ significantly from those in the EMPA-REG OUTCOME study. A prior CV event was present at a percentage of 60–70% of patients in CANVAS. The rest of the patients also had a CV risk factor profile and they were categorized according to that. The hemodynamic actions of empagliflozin are responsible for their effects on CV events. Due to that reason, someone would expect that other drugs of this class will show similar effects on CV cases.

The DECLARE-TIMI 58 was a randomized, double-blind, multinational, placebo-controlled, phase 3 trial of dapagliflozin in patients with type 2 diabetes and established atherosclerotic cardiovascular disease or multiple risk factors for atherosclerotic cardiovascular disease [9]. The official title of the trial is "Dapagliflozin Effect on Cardiovascular Events A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Effect of Dapagliflozin 10 mg Once Daily on the Incidence of Cardiovascular Death, Myocardial Infarction or Ischemic Stroke in Patients With Type 2 Diabetes". It was sponsored by AstraZeneca pharmaceutical company and the collaborators were Bristol-Myers Squibb, The TIMI Study Group and the Hadassah Medical Organization. It was an interventional clinical trial with an enrollment of 17,160 randomized participants 40 years old or older. All of them were patients with non-insulin dependent diabetes mellitus type 2 and they suffer from cardiovascular disease or they show at least two risk factors for cardiovascular disease. Its main aim was to test whether the chronic use of dapagliflozin in patients with type 2 diabetes mellitus has positive effects on cardiovascular diseases. According to the results of the research, treatment with dapagliflozin did not result in a higher or lower rate of major adverse cardiovascular events than placebo but did result in a lower rate of cardiovascular death or hospitalization for heart failure, a finding that reflects a lower rate of hospitalization for heart failure [9].

An ongoing trial testing the effects of dapagliflozin on heart diseases is the Dapa-HF trial. More specifically the main subject of this study is the prevention of cardiovascular (CV) death or reduction of heart failure (HF) events after dapagliflozin treatment in patients with Chronic Heart Failure With Reduced Ejection Fraction (HFrEF) [10]. It is also sponsored by AstraZeneca. Dapagliflozin (10mg or 5 mg daily oral consumption) is compared with placebo effect on cardiovascular diseases. It is currently at the phaseIII. A total of 4,500 participants are randomized and tested. The trial began on February the 8th of 2017 and it is estimated to be accomplished by July 17th 2019.

These three studies could assist in the definition of the existence of a class effect. However, there were used different selection criteria and a smaller amount of participants, compared to the EMPA-REG OUTCOME trial [11]. All the SGLT2 inhibitors show similar hemodynamic effects, but due to the fact that the trials mentioned above have differences in their sample, it seems that it is difficult to observe whether there are beneficial effects of canagliflozin and dapagliflozin on the reduction of CV mortality [11, 12].

The VERTIS CV study, according to the U.S. National Library of Medicine, is a trial for *"Cardiovascular Outcomes Following Ertugliflozin Treatment in Type 2 Diabetes Mellitus Participants with Vascular Disease"* and it started on November of 2013 and estimated to be accomplished by October of 2019. It is a placebo controlled trial with 8000 participants. Ertugliflozin is another SGLT-2 inhibitor. During this trial, patients were treated with 15mg or 5 mg daily oral dosage of ertugliflozin or placebo and they were observed for 6.1 years. The primary outcome is the time to first occurrence of major adverse cardiovascular events. The secondary outcome measures are many, such as the time to first occurrence of cardiovascular death or hospitalization for heart failure and the time to occurrence of cardiovascular death. For all the outcomes the time frame is 6.1 years.

3. EXPERIMENTAL

The EMPA-REG study lasted for 3.1 years and a daily empagliflozin dosage of 10 or 25 mg was received by the participants. During EMPA-REG OUTCOME trial, 7,020 patients with type 2 diabetes who were at high risk of CV events and who were under glucose-lowering therapy (HbA1c $\geq$7.0% and $\leq$10.0%) or drug-naïve (HbA1c $\geq$7.0% and $\leq$ 9.0%) were studied [13]. According to the protocol, they were randomized (1:1:1) and received treatment of empagliflozin. More specifically they received empagliflozin 10 mg, empagliflozin 25 mg, or placebo treatment. The main outcomes to be studied were if empagliflozin shows beneficial results over the CV diseases compared with placebo. The trial continued until $\geq$691 confirmed primary outcome events have supervened providing 90% accuracy of the limit of the highest dosage assuming equal risks between placebo and empagliflozin [13, 14].

During the CVD-REAL study, data from 309,056 patients were collected and were divided into two groups of 154,528 patients each group. Patients who were treated with canagliflozin were observed the most (53%), followed by dapagliflozin (42%) and empagliflozin (5%) patients. There was an overall 39% lower risk of heart failure hospitalization ($p < 0.001$), 51% reduction in total death rate ($p < 0.001$), and 46% reduction of heart failure hospitalization or death ($p < 0.001$). In the US, canagliflozin was used more often (76%) but dapagliflozin was mostly used in Europe (92%). However, similar results were obtained across different countries [15-18]. The mean age of the patients was 61 years [16].

The VERTIS clinical trial is still in progress and it was a 52-week, double-blind, multicentre, randomized, parallel-group study. The phase A of the trial was a period of a placebo treatment for 26 weeks. Phase B of the trial took place on the second part of the trial, for another 26 weeks in 461 patients, males and females, above 18 years old with inadequate glycaemic control (glycated haemoglobin [HbA1c]

concentration 7.0% to 10.5% [53-91 mmol/mol], inclusive). (a) There is a combination of two substances which is a composite one drug which was approved in 2015 by the U.S. FDA. These substances are empaglidlozin plus linagliptin (Glyxambi; Boehringer Ingelheim/Eli Lilly) tablets. Their purpose is to help with the glycaemic regulation in adults with T2DM. This tablet combines two drug categories for the treatment of T2DM, which are the SGLT2 inhibitors (empagliflozin) and DDP-4 (linagiptin). The dosage combination is 10mg or 25 mg empagliflozin and 5mg of linagliptin. (b) The approval of glyxambi was a result of a phase 3 clinical trial which was compared with the efficacy and the safety of glyxambi with the individual drugs (empagliflozin or linagliptin). The patients were adults with T2DM. They were also receiving metformin. (c) The first two weeks 686 patients were treated with placebo and the disease was in control (HbA1c levels, 7.0%-10.5%). After that period of time, they were randomized to different groups.

4. RESULTS

According to the EMPA-REG OUTCOME trial, reduced events of cardiovascular death were obtained to the patients who were receiving empagliflozin (10.5% *vs*. 12.1%; p=0.04; NNT 62), as well as a reduction in all-cause mortality (5.7% *vs*. 8.3%; p<0.001; NNT 38) and CV mortality (3.7% *vs*. 5.9%; p<0.001; NNT 45). Data of this study were published in 2015 and help to extract the conclusion that the drug was generally well tolerated [19]. During this trial, empagliflozin managed to reduce cardiovascular death and hospitalization due to heart failure in patients with type 2 diabetes and high cardiovascular risk. Patients with and without baseline heart failure had more benefits through this treatment [20]. Among patients who were treated with empagliflozin, a lower percentage (265/4687 patients [5.7%]) suffered from heart failure hospitalization or cardiovascular death in comparison with patients who were treated with placebo (198/2333 patients [8.5%]) (hazard ratio, HR: 0.66 [95% confidence interval, 95% CI: 0.55-0.79; P, 0.001]). Among all patients, 126 from the empagliflozin group, went through at least one heart failure hospitalization, 43 patients had 111 remittent events (either heart failure or cardiovascular death) [20]. Regarding the placebo group, 95 patients had at least one heart failure hospitalization and 43 patients had 115 remittent events. In general, a smaller ratio of patients who received empagliflozin treatment died due to cardiovascular issues, in comparison with the patients who received placebos (17 [13.5%] *vs*. 23 [24.2%]). A 34% reduction in heart failure and cardiovascular deaths was achieved through empagliflozin treatment [21-23]. Cox regression models were used to analyze the empagliflozin *vs.* placebo results [23, 24].

Changes appeared in the hematocrit and hemoglobin when compared between the patients who received empagliflozin and those who receive placebo. The results of the EMPA-REG OUTCOME trial are those changes between the two groups of patients occurred, such as in hematocrit (51.8%), hemoglobin (48.9%) and smaller effects (maximum 29.3%) were observed for uric acid, fasting plasma glucose, and HbA1c. These results led to the conclusion that the most important factors about the CV deaths are the changes caused in plasma volume by empagliflozin. Especially when compared with the changes in plasma caused by placebo [23].

Between Sept 2010 and April 2013, 592 clinical sites randomized and treated 7034 patients (41% from Europe, 20% from North America, and 19% from Asia). At baseline, the mean age was 63 ± 9 years, BMI 30.6 ± 5.3 kg/m^2, HbA1c 8.1 ± 0.8%, and eGFR 74 ± 21 ml/min/1.73 m^2. The study is expected to report in 2015.

In general, the use of SGLT2 inhibitors reduced the risk of cardiovascular mortality, major adverse cardiovascular events, and hospitalization due to heart failure. However, no considerable variations were observed regarding non-fatal myocardial infarction, non-fatal stroke and atrial fibrillation no considerable variations between the use of SGLT2 inhibitors and other glucose-lowering drugs. It has been shown that SGLT2 inhibitors are responsible for a reduced risk of hypoglycemia compared with other glucose-lowering drugs and there were no differences in the levels of cardiovascular mortality [24, 25].

Glucose, weight and blood pressure is lowered by SGLT2 inhibitors. However, they have mixed effects on lipids, showing an increase in LDL-cholesterol and HDL-cholesterol [26]. This is the reason why it was extremely difficult to predict the results of SGLT2 inhibitors on cardiovascular outcomes. When empagliflozin treatment was compared with placebo treatment results, a few reductions were observed, such as in HbA1c (by ~0.3-0.5%), weight (by ~2 kg) and systolic blood pressure (by ~3 mmHg) but no satisfactory increase in the heart rate wasnoted. As expected, there were also minor rises in LDL-cholesterol and HDL-cholesterol levels. Stroke events were non-significantly increased (HR 1.18 [95% CI 0.89, 1.56]) despite the blood pressure reduction and the stable levels of myocardial infarction [26]. On the other hand, results from other pre-specified outcomes showed a different. Empagliflozin significantly lowered the ratio of death from cardiovascular causes by 38% and heart failure hospitalization by 35% [26].

The results of the EMPA-REG trial indicate, in general, that empagliflozin is superior to placebo in improving glycemic control and reducing cardiovascular events in patients with type 2 diabetes. It also appears to have a salutary effect on renal outcomes and a significant mortality benefit. Unlike canagliflozin, there was no safety signal, regarding increased amputations, even among patients with established peripheral artery disease. These findings are really important because they suggest that agents, such as liraglutide and empagliflozin that have proven cardiovascular benefits may need to be considered as the second-line therapy in similar high-risk patients.

The main results of the EMPA-REG OUTCOME trial are presented in Table **1** below.

During the CVD-REAL study, decreased risk of cardiovascular mortality was observed with the use of SGLT2 inhibitors, when compared with other glucose-lowering drugs, with (HR 0.53 [95% CI 0·40-0.71]), major adverse cardiovascular events (0·78 [0.69-0·87]), and hospital events for heart failure (0.70 [0.61-0.81]; p<0.0001 for all). Moreover, reduced risk of severe hypoglycemia was observed with the

Table 1. Results from the EMPA-OUTREG trial as mentioned in Fitchett D, Zinman B, Wanner C, *et al.* Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: Results of the EMPA-REG OUTCOME®trial. European Heart Journal. 2016; 37(19): 1526-1534.

Outcomes	Placebo	Empagliflozin	p-value
Heart Failure Hospitalization or Cardiovascular Death	8.5%	5.7%	<0.001
Hospitalization for or Death from Heart Failure	4.5%	2.8%	<0.001
Hospitalization for Heart Failure	4.1%	2.7%	0.002
Reported Heart-Failure	6.1%	4.4%	0.001
Reported Serious Heart Failure	5.8%	4.1%	0.001
All-Cause Hospitalization	39.6%	36.8 %	0.003

Table 2. Results from the CVD-REAL Nordic Study as shown in Birkeland K, Jørgensen M, Carstensen B, *et al.* Cardiovascular mortality and morbidity in patients with type 2 diabetes following initiation of sodium-glucose cotransporter-2 inhibitors versus other glucose-lowering drugs (CVD-REAL Nordic): A multinational observational analysis. The Lancet Diabetes & Endocrinology. 2017; 5(9): 709-717.

-	SGLT2 Inhibitors (Events)	Other Glucose-Lowering Drugs (Events)	p Value for Heterogeneity Between Countries
Cardiovascular Mortality	56	340	0.076
Major Adverse Cardiovascular Event	339	1349	0.099
Non-Fatal Myocardial Infarction	161	574	0.105
Non-Fatal Stroke	144	514	0.965
Hospitalization for Heart Failure	224	984	0.428
All-Cause Mortality	289	1768	0.02
Atrial Fibrillation	328	1063	0.247
Severe Hypoglycemia	181	736	0.056

use of SGLT2 inhibitors (HR 0.76 [0·65-0.90]; p = 0.001) [27].

The latest results of the study in March 2018 showed that treatment with SGLT-2i (empagliflozin, ipragliflozin, canagliflozin, tofogliflozin or luseogliflozin) was associated with a 49% lower risk of ACD, 36% of hHF, 19% of MI and 32% of stroke ($p \leq 0.001$ for all) compared to other T2D medicines. There was also a 40% lower risk of the composite endpoint of hHF or ACD ($p<0.001$) [28].

The results of the VERTIS clinical trial (Table **3**) [29] showed that at week 26, the placebo-adjusted least squares mean HbA1c changes from baseline. Results are presented below.

For the empagliflozin/linagliptin combination, the time for the first results was the 24th week. After 24 weeks of treatment, a significant improvement in HbA_{1c} levels was observed ($p <.001$) and also in the fasting glucose levels. The results were compared with the therapy of individual drugs, only empagliflozin and linagliptin. The effects of the drug combination on body weight were a little bit complexed. When compared with linagliptin alone, it showed a great reduction in weight. However, no differences were observed when it was compared with the empagliflozin treatment (Table **4**) [30, 31]. Results of the trial are shown below.

5. DISCUSSION

All the SGLT2 inhibitors show similar effects on glucose levels, body weight loss and blood pressure. They are also responsible for the reduction of HbA1c and show a good safety profile. In addition, according to the EMPA-REG OUTCOME study results, cardiovascular mortality is decreased by 38% when empagliflozin is the chosen treatment for diabetes in high-risk T2DM patients with cardiovascular disease. This is the reason why empagliflozin is suggested as the proper treatment, over any other SGLT2 inhibitors. However, there are no sufficient data to support the use of one SGLT2 inhibitor over the other, for patients with T2DM who are in early stages of the disease and do not have a CV disease history [32].

On the other hand, the CVD-REAL study represents real-world data and it shows class effect rather than drug effect of SGLT2 inhibitors on cardiovascular diseases. The results with SGLT2 against placebo were tested through another

Table 3. Summary of changes in key secondary efficacy endpoints as mentioned in Terra S, Focht K, Davies M, *et al*. Phase III, efficacy and safety study of ertugliflozin monotherapy in people with type 2 diabetes mellitus inadequately controlled with diet and exercise alone. Diabetes, Obesity and Metabolism. 2017; 19(5): 721-72.

Treatment	Baseline	-	Week 26	-	Change from Baseline at Week 26	-	-
-	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	LS Mean (95% CI)
Placebo	153	8.11 (0.919)	89	7.76 (1.020)	153	-0.09 (0.901)	0.20 (0.02, 0.37)
Ertugliflozin 5mg	155	8.16 (0.876)	133	7.31 (0.856)	156	-0.80 (0.830)	-0.79 (-0.95, -0.63)
Ertugliflozin 15mg	151	8.35 (1.115)	124	7.28 (1.012)	151	-1.04 (1.044)	-0.96 (-1.12, -0.80)

Table 4. Results from comparing empagliflozin plus linagliptin *versus* each drug alone as add-on therapy in patients inadequately controlled with metformin by Raedler L. in Glyxambi (Empagliflozin/Linagliptin): A dual-acting oral medication approved for the treatment of patients with type 2 diabetes. American Health and Drug Benefits. 2015; 8: 171-175.

Efficacy Parameter	Empagliflozin/ Linagliptin 10mg/5mg	Empagliflozin/ Linagliptin 25mg/5mg	Empagliflozin 10mg	Empagliflozin 25mg	Linagliptin 5mg
HbA_{1c} Level	-	-	-	-	-
Patients, N	135	133	137	139	128
Baseline, Mean, %	8.0	7.9	8.0	8.0	8.0
Change in HbA1c from Baseline, Adjusted Mean, %	-1.1	-1.2	-0.7	-0.6	-0.7
Comparison *vs.* Empagliflozin 25mg or 10mg, Adjusted Mean, %	-0.4 (95% CI, -0.6 to -0.2)	-0.6 (95% CI, -0.7 to -0.4)	-	-	-
Comparison *vs.* Linagliptin 5mg, Adjusted Mean, %	-0.4 (95% CI, -0.6 to -0.2)	-0.6 (95% CI, -0.7 to -0.3)	-	-	-
Fasting Plasma Glucose	-	-	-	-	-
Patients, N	133	131	136	137	125
Baseline, Mean, mg/dL	157	155	162	160	156
Change from Baseline, Adjusted Mean, mg/dL	-33	-36	-21	-21	-13
Comparison *vs.* Empagliflozin 25mg or 10mg, Adjusted Mean, mg/dL	-12 (95% CI, -18 to -5)	-15 (95% CI, -22 to -9)	-	-	-
Comparison *vs.* Linagliptin 5mg, Adjusted Mean, mg/dL	-20 (95% CI, -27 to -13)	-23 (95% CI, -29 to -16)	-	-	-
Body Weight	-	-	-	-	-
Patients, N	135	134	137	140	128
Baseline, Mean, kg	87	85	86	88	85
Percent change in Weight from Baseline	-3.1	-3.4	-3.0	-3.3	-0.7
Comparison *vs.* Empagliflozin 25mg or 10 mg, Adjusted Mean, kg	0.0 (95% CI, -0.9 to 0.8)	0.1 (95% CI, -0.8 to 0.9)	-	-	-
Comparison *vs.* Linagliptin 5mg, Adjusted Mean, kg	-2.4 (95% CI, -3.3 to -1.5)	-2.7 (95% CI, -3.6 to -1.8)	-	-	-

meta-analysis and no clear evidence was demonstrated regarding the fact that the cardiovascular outcomes are different according to the various types of the class [33]. However, as mentioned above, another meta-analysis including only placebo-controlled randomized clinical trials proved that empagliflozin was the main drug with beneficial effects

against cardiovascular mortality. More specifically, the EMPA-REG outcome trial proved that empagliflozin is the most effective SGLT2 inhibitor among others. However, a sensitivity analysis, as part of a meta-analysis, excluding the EMPA-REG Outcome Trial revealed potential harm with SGLT-2 inhibitors on the results of cardiovascular mortality compared with placebo (OR 1.88, 95% CI 0.93-3.80, p=0.08, I2=0%) [34]. Ongoing randomized controlled clinical trials on multiple drug types in this group should provide further insight into the safety and efficacy of SGLT-2 inhibitors [33].

According to the VERTIS trial, the treatment of ertugliflozin of 5 and 15 mg for 26 weeks shows positive effects on glycaemic control and body weight reduction, factors which affect the cardiovascular diseases. Regarding the combination of empagliflozin and linagliptin, this treatment helps with the control of glucose and HbA1c levels when compared with patients receiving monotherapy of empagliflozin and linagliptin.

CONCLUSION

In general, through EMPA-REG OUTCOME trial, it has been shown that empagliflozin is responsible for the reduction of the risk of cardiovascular (CV) death and heart failure hospitalizations (HFH) in patients with type 2 diabetes (T2D). Empagliflozin systematically improved heart failure (HF) outcomes both in patients at low or high HF risk. Moreover, the CVD-REAL study proved that SGLT2 inhibitors show better effects on the prevention of cardiovascular diseases, compared with other glucose-lowering drugs and especially ertuglifozin and the combination of empagliflozin and linagliptin are beneficial for the patients. According to our findings, SGLT-2 inhibitors are not characterized as a class effect because empagliflozin seems to show significantly more positive effects than the other SGLT-2 inhibitors. However, further study must be done in order to clarify with higher accuracy if there is a class effect or not.

Even though it seems that different types of SGLT-2 inhibitors have a different effect, the authors of this article do not suggest that since the patients' characteristics and the design of the trials differ. Therefore, we suggest that a direct comparative study of the different SGLT 2 inhibitors be conducted in order to find out whether they have differential effects on cardiovascular outcomes in patients with type 2 diabetes mellitus.

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CONFLICT OF INTEREST

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Declared none.

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