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Cardiovascular Protection by Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitor: How to Optimize the Agent for Patients?

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ABSTRACT

Sodium-glucose co-transporter 2 (SGLT2) inhibitor such as empagliflozin and canagliflozin have been shown to decrease atherosclerotic cardiovascular morbidity and mortality in patients with type 2 diabetes and overt cardiovascular disease (CVD). In the primary analysis, dapagliflozin did not appear to reduce atherosclerotic cardiovascular morbidity or cardiovascular mortality. However, it decreased cardiovascular outcomes in a sub-analysis of the primary trial. The cardiovascular trials to date have been carried out in very high-risk populations to increase the hazard rate for major CVD events and complete the studies in a relatively brief period of time. Compared with the empagliflozin and canagliflozin trials, the dapagliflozin trial had a lower fraction of participants with established CVD and a greater proportion of patients with multiple risk factors for CVD (multiple risk factors in 60 percent compared with 0 and 34 percent in the empagliflozin and canagliflozin trials, respectively). This difference in patient population may explain, in part, the differences in atherosclerotic CVD outcomes. However, the ertugliflozin cardiovascular trial only included patients with established CVD and did not show superior benefit in the composite outcome (cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke). In patients with type 2 diabetes and heart failure, all SGLT2 inhibitors have shown salutary effects.

INTRODUCTION

Current management of type 2 diabetes (T2DM) is aimed for increasing insulin availability (either through direct insulin administration or through drugs that promote insulin secretion), increasing insulin sensitivity, delaying delivery and absorption of carbohydrates from the gastrointestinal tract, or increasing urinary glucose excretion. Sodium-glucose co-transporter 2 (SGLT2) inhibitors are drugs that reduce blood glucose by increasing urinary glucose excretion. Sodium-glucose co-transporter 2 inhibitors is a relatively new antidiabetic drug, targeting the kidneys. This drug has a unique mechanism of action, particularly increasing glucosuria, osmotic diuresis and natriuresis, thereby improving glucose control with minimal risk of hypoglycaemia and providing additional positive effects of weight loss and lowering blood pressure. Multiple outcome studies with canagliflozin, dapagliflozin or empagliflozin, reported statistically significant reductions in major cardiovascular events, hospitalizations for heart failure and worsening of advanced renal disease in patients with T2DM who already had atherosclerotic cardiovascular disease, multiple cardiovascular risk factors, albuminuria mild to moderate chronic kidney disease or heart failure. The current guidelines propose a new paradigm in the management of T2DM, namely giving a preferential site to SGLT2 inhibitors, after metformin, in patients with atherosclerotic cardiovascular disease, heart failure and progressive renal disease. Ongoing studies might expand the therapeutic potential of SGLT2 inhibitors in patients with, as well as without T2DM. This review provides an update on current knowledge about SGLT2 inhibitors moving from their use as glucose-lowering drugs to their new position as cardiovascular and renal protective drugs.[1]

DISCUSSION

In a meta-analysis of three large studies of CVD outcomes (empagliflozin, canagliflozin, dapagliflozin), SGLT2 inhibitors compared with placebo were shown to reduce the risk of major adverse cardiovascular events (MACE) (86.9 versus 99.6 events per 1000 patient-years, hazard ratio [HR] 0.89, 95% CI 0.83–0.96) and the combined outcome of CV death or hospitalization due to heart failure (48.2 versus 65.6 events per 1000 patient-years, HR 0.77, 95% CI 0.71-0.84). The clinical benefit of SGLT2 inhibitors in reducing the risk of major cardiovascular events (myocardial infarction, stroke, cardiovascular death) is limited to patients with atherosclerotic CVD, not to those with multiple CVD risk factors.[2,3] In contrast to the findings

for adverse MACE, meta-analyses demonstrated a reduction in heart failure hospitalizations with the use of SGLT2 inhibitors regardless of the presence of atherosclerotic CVD or heart failure. In a subsequent meta-analysis of five studies comparing SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, sotagliflozin) with placebo in people with type 2 diabetes and CVD, SGLT2 inhibitors reduced the risk of cardiovascular death (72 versus 86 per 1000 people; odds ratio [OR] 0.82, 95% CI 0.70-0.95) and heart failure hospitalization (78 versus 116 per 1000 people, OR 0.65, 95% CI 0.59-0.71).[4] SGLT2 inhibitors did not reduce the risk of fatal or nonfatal myocardial infarction (54 versus 56 per 1000 people; OR 0.97, 95% CI 0.84-1.12) or stroke (34 versus 31 per 1000 people; OR 1.12.95 %CI 0.92-1.36). Until large, prospective, randomized studies are conducted, it is not known whether empagliflozin, canagliflozin, or other SGLT2 inhibitors will have a similar CVD effect in the majority of people with type 2 diabetes who do not have overt CVD.

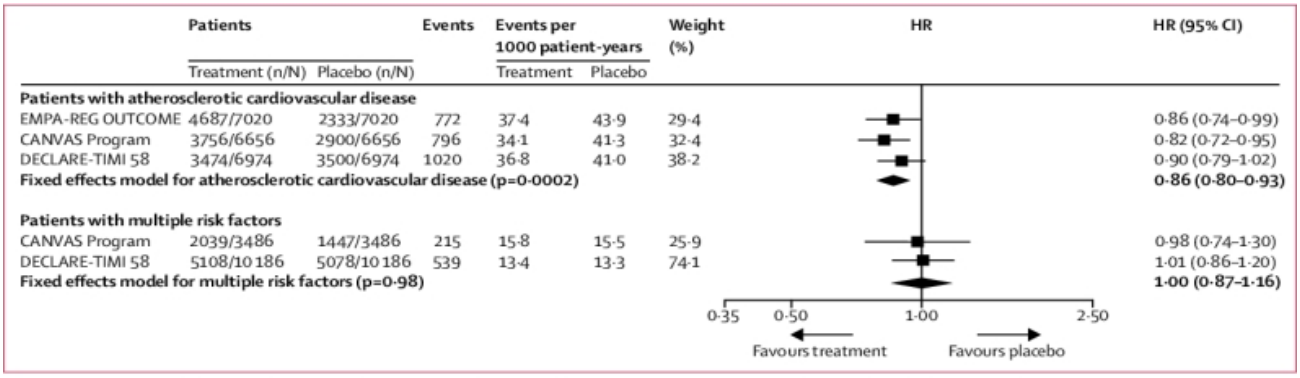

Figure 1: Meta-analysis of SGLT2i trials on the composite of myocardial infarction, stroke, and cardiovascular death (major adverse cardiovascular events) stratified by the presence of established atherosclerotic cardiovascular disease. No heterogeneity was found in terms of between-study variance in the subgroups (atherosclerotic cardiovascular disease: Q statistic=0·94, p=0·63, I^2=0%; multiple risk factors: Q statistic=0·03, p=0·86, I^2=0%). Tests for subgroup differences were based on F tests in a random effect meta-regression estimated using restricted maximum likelihood and Hartung Knapp adjustment. The p value for subgroup differences was 0·0501. HR=hazard ratio. SGLT2i=sodium-glucose cotransporter-2 inhibitors.[2]

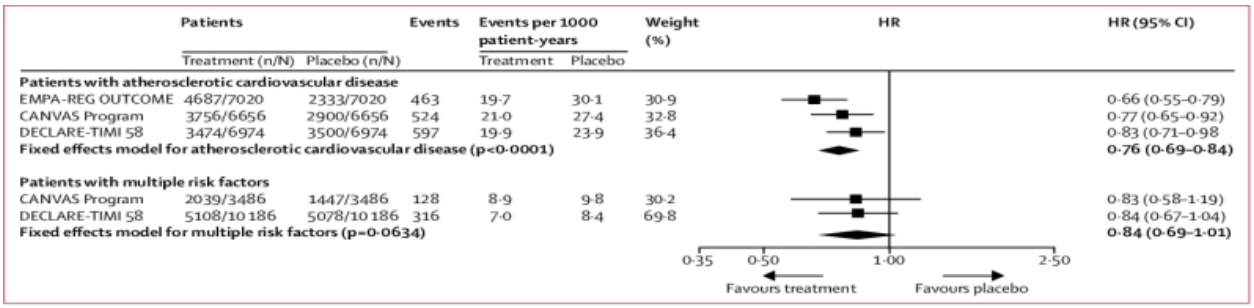

Figure 2: Meta-analysis of SGLT2i trials on hospitalisation for heart failure and cardiovascular death stratified by the presence of established atherosclerotic cardiovascular disease. Atherosclerotic cardiovascular disease: Q statistic=3·49, p=0·17, I^2=42·7%; multiple risk factors: Q statistic=0·00, p=0·96, I^2=0%. The p value for subgroup differences was 0·41. Tests for subgroup differences were based on F tests in a random effect meta-regression estimated using restricted maximum likelihood and Hartung Knapp adjustment. HR=hazard ratio. SGLT2i=sodium-glucose cotransporter-2 inhibitors.[2]

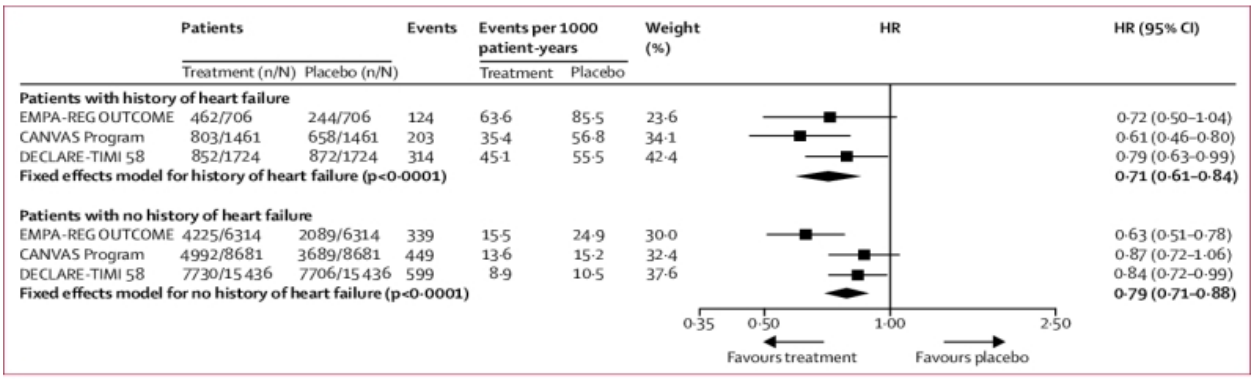

Figure 3: Meta-analysis of SGLT2i trials on hospitalisation for heart failure and cardiovascular death stratified by history of heart failure. History of heart failure: Q statistic=2·02, p=0·37, I^2=0·8%; no history of heart failure: Q statistic=5·89, p=0·0527, I^2=66%. The p value for subgroup differences was 0·51. Tests for subgroup differences were based on F tests in a random effect meta-regression estimated using restricted maximum likelihood and Hartung Knapp adjustment. HR=hazard ratio. SGLT2i=sodium-glucose cotransporter-2 inhibitors.2

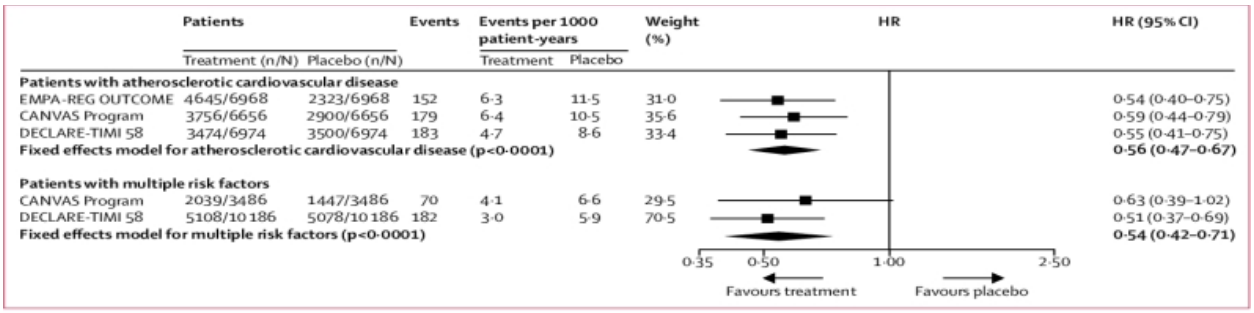

Figure 4: Meta-analysis of SGLT2i trials on the composite of renal worsening, end-stage renal disease, or renal death stratified by the presence of established atherosclerotic cardiovascular disease. Atherosclerotic cardiovascular disease: Q statistic=0·19, p=0·91, I^2=0%; multiple risk factors: Q statistic=0·52, p=0·47, I^2=0% The p value for subgroup differences was 0·71. Tests for subgroup differences were based on F tests in a random effect meta-regression estimated using restricted maximum likelihood and Hartung Knapp adjustment. HR=hazard ratio. SGLT2i=sodium-glucose cotransporter-2 inhibitors.2

In a study designed specifically to evaluate cardiovascular morbidity and mortality in patients with type 2 diabetes and cardiovascular disease, 7028 patients with type 2 diabetes (mean A1C of about 8 percent) and CVD were randomized to empagliflozin (10 or 25 mg) or placebo once a day.[5] The majority of patients were taking metformin, antihypertensives, and lipid-lowering drugs (both groups were evenly distributed) to control blood glucose, blood pressure, and cholesterol. About 48 percent of the patients in each group were taking insulin. After three years, the main outcome (combined cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) occurred less in patients given empagliflozin than in placebo (10.5 versus 12.1 percent; HR pooled analysis 0.86, 95% CI 0.74- 0.99). The findings were supported by a significant reduction in the risk of death from cardiovascular causes (3.7 versus 5.9 percent with placebo; HR 0.62, 95% CI 0.49-0.77). There was no significant difference in the occurrence of the individual components of nonfatal myocardial infarction (4.5 versus 5.2 percent with placebo) or nonfatal stroke (3.2 versus 2.6 percent). Similar findings were found in the individual empagliflozin dose groups. Hospitalization rates for heart failure were lower in the empagliflozin group (2.7 versus 4.1 percent in the placebo group). Compared with patients taking placebo, patients taking empagliflozin had lower A1C levels (mean A1C 7.8 versus 8.2 percent) and reductions in body weight, waist circumference, systolic and diastolic blood pressure (without an increase in heart rate), and uric acid. There was a slight increase in low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol in patients taking empagliflozin. In patients with heart failure with low ejection fraction (HFrEF), with or without diabetes, empagliflozin has been shown to reduce cardiovascular mortality and worsening of heart failure.[6]

In two studies designed to assess the effects of canagliflozin on cardiovascular, renal, and safety outcomes in patients with type 2 diabetes and high cardiovascular risk, 10,142 patients (mean A1C of about 8.2 percent) were randomly assigned to either canagliflozin or placebo.[7] The majority of patients took metformin, antihypertensives, and lipid-lowering agents (both groups were evenly distributed) to manage blood glucose, blood pressure, and cholesterol. About 50 percent of the patients in each group were taking insulin. After a mean follow-up of 3.6 years, the primary outcome, combined cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke, occurred in fewer patients in the canagliflozin group (26.9 versus 31.5

patients per 1000 patient-years, HR 0.86, 95% CI 0.75-0.97). The reduction in occurrence of individual components of the composite outcome in those randomized, to canagliflozin (11.6 versus 12.8, 9.7 versus 11.6, and 7.1 versus 8.4 patients per 1000 patient-years) was not significantly significant. statistics. Hospitalization rates for heart failure were lower in the canagliflozin group (5.5 versus 8.7 patients per 1000 patient-years in the placebo group, HR 0.67, 95% CI 0.52–0.87). Compared with patients taking placebo, patients taking canagliflozin had lower A1C levels (mean difference -0.58 percent) and decreased body weight and systolic and diastolic blood pressure. In a subsequent study designed to evaluate renal outcome in patients with type 2 diabetes and nephropathy (mean eGFR 56.2 mL/min/1.73 m2, median urinary albumin-creatinine ratio 927 [mg/g]), there was a reduction in similar in cardiovascular events.[8]

In a study designed to assess the effects of dapagliflozin on cardiovascular and renal outcomes, 17,160 patients with type 2 diabetes (mean A1C of about 8.3 percent) who had or were at risk of CVD were randomized to receive dapagliflozin (10 mg) or placebo once daily.[9] The majority of patients took metformin, antihypertensives, and lipid-lowering drugs (evenly distributed in both groups) to manage blood glucose, blood pressure, and cholesterol. About 40 percent of the patients in each group were taking insulin. After a median follow-up of 4.2 years, the first major outcome (combined cardiovascular death, nonfatal myocardial infarction, or nonfatal ischemic stroke) occurred in 8.8 and 9.4 percent of patients taking dapagliflozin and placebo (HR 0.93, 95). %CI 0.84-1.03). There was a significant reduction in the second primary outcome (combined cardiovascular death or hospitalization for heart failure), particularly in terms of a significant reduction in hospitalizations for heart failure (6.2 versus 8.5 percent with placebo, HR 0.73, 95% CI 0.61-0.88). There was no difference between the two groups in death from any cause (6.2 versus 6.6 percent in the placebo group, HR 0.93, 95% CI 0.82 to 1.04). The dapagliflozin study involved a large number of participants with cardiovascular disease or multiple risk factors at baseline, randomized to dapagliflozin or placebo, to perform a sub-analysis in both groups.[10] Dapagliflozin reduced two major cardiovascular outcomes in participants with a previous myocardial infarction (15.2 versus 17.8 percent [HR 0.84, 95% CI 0.72–0.99]), but not in those without a previous myocardial infarction (7 .1 versus 7.1 percent [HR 1.00, 95% CI 0.88 to 1.13]). In a subsequent exploratory analysis, dapagliflozin also reduced the incidence of atrial fibrillation/atrial flutter.[11] In patients with or without diabetes, dapagliflozin has been shown to reduce all-cause mortality and worsening heart failure in adults with heart failure with a reduced ejection fraction (HFrEF) with a New York Heart Association class II, III, or IV functional class.[12] Dapagliflozin in the treatment of HFrEF is reviewed separately. In a trial designed to evaluate the lack of non-inferiority in the composite cardiovascular outcome, 8246 individuals with type 2 diabetes (mean A1C 8.2 percent) and common CVD were randomized to receive ertugliflozin (5 or 15 mg) or placebo once daily.[13] The majority of participants were taking metformin (76 percent), and about 47 percent of the patients were taking insulin. After a mean follow-up of 3.5 years, ertugliflozin treatment was not superior to placebo in the primary composite end point of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke (11.9 percent in each group [HR 0.97, 95% CI 0.85] -1.11]). There was a significant reduction in hospitalizations for heart failure (2.5 versus 3.6 percent with placebo [HR 0.7, 95% CI 0.54–0.90]). The findings of this study need to be kept in perspective. The relatively large cardiovascular benefit of empagliflozin and canagliflozin in a population at very high risk with CVD. In addition, the absolute risk reduction is approximately 10 to 15 cases per 1000 patient-years and the benefit in patients taking canagliflozin is particularly, followed by an increased risk of amputation. The difference in glycemia between the treatment groups was minimal, indicating that the extra-glycaemic effect of the drug was responsible for the CVD outcome. The benefit of SGLT2 inhibitors on the outcome of heart failure appears to be a class of effects.

CONCLUSION

Sodium-glucose cotransporter type 2 inhibitor (SGLT2is) improves glucose control through direct and indirect mechanisms, with little risk of hypoglycaemia, and exerts other positive effects on body weight, blood pressure. An SGLT2 inhibitor added to standard care reduces the incidence of major cardiovascular events (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke) in patients with type 2 diabetes mellitus (T2DM) at high cardiovascular risk. SGLT2 inhibitors reduce the risk of hospitalization for heart failure and worsening end-stage renal disease in patients with T2DM who are at high cardiovascular risk, and are independent effects of improving glucose control. SGLT2 inhibitors are now considered preferential to metformin, in patients with T2DM and atherosclerotic cardiovascular disease (as alternatives to peptide 1 receptor agonists such as glucagon), heart failure or chronic kidney disease. SGLT2is can be associated with several side effects, including genital infection, volume depletion, and diabetic ketoacidosis.

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