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Sodium-glucose co-transporter-2 drugs: are we sure they are useful only in the treatment of diabetes?

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The sodium-glucose co-transporter-2 (SGLT2) inhibitors are a new class of oral anti-diabetic drugs acting through the inhibition of renal reabsorbtion of glucose. Three important randomized clinical trial in diabetic patients receiving SGLT2 inhibitors (vs. placebo), demonstrated a significant reduction of major adverse cardiovascular events, but only in patients with known atherosclerotic disease, and a clear-cut and early reduction in hospital admissions for heart failure in patients in primary as well as secondary prevention settings. This latter information prompted the design of a recent study the DAPA-HF (Dapagliflozin And Prevention Of Adverse-outcomes In Heart Failure) trial, comparing dapagliflozin vs. placebo, and showing a significant reduction of clinical relevant episodes of heart failure in patients with reduced left ventricular ejection fraction, regardless the presence of diabetes mellitus. The mechanism by which the SGLT2 inhibitors exert their anti-heart failure action is not well understood but appears to be independent from its hypoglycaemic action. These results, along with the scarcity of adverse side effects of the drug, render dapagliflozin a new tool in the treatment of heart failure.

Introduction

Type 2 diabetes mellitus represents an important risk factor for cardiovascular events, responsible for a high incidence of morbidity and mortality in affected subjects.[1] Glyco-metabolic control is certainly a factor capable of improving this aspect although, recently, several studies have shown the age and in particular the type of drug used play a key role in this regard. In fact, an excessive intensification of the hypoglycaemic therapy aimed at obtaining optimal glycaemic control was found to be counterproductive in elderly patients with long disease duration and multiple cardiovascular complications leading to an increased morbidity and mortality linked to frequent hypoglycaemic episodes. In this category of patients, therefore, a less stringent therapeutic goal than desirable in less fragile subjects is indicated.[1]

Similarly, various evidences have shown that the type of hypoglycaemic drug used represents a further variable in the stratification of the cardiovascular risk of the diabetic population. Over the years, numerous anti-diabetic drugs have been developed that can reduce blood sugar through various mechanisms. A large meta-analysis conducted in 2016 showed that there was no difference in the incidence of mortality and cardiovascular morbidity considering different categories of drugs, including sulphonylureas, thiazolinidedions, metformin, dipethyl peptidase IV inhibitors, and basic insulin.[2] Vice versa the LEADER 3 and EMPA-REG 4 studies clearly demonstrated a possible beneficial effect on the cardiovascular outcomes of liraglutide and empagliflozin.

Mechanism of action of drugs SGLT-2

The kidney has an important role in glucose homeostasis as it determines its reabsorption at the level of the proximal

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glomerular tubule through the action of sodium-glucose co-transporter (SGLT) SGLT1, the lesser share, and SGLT2, constituting the preponderant share. In physiological conditions, the kidney's reabsorption of glucose exceeds the amount of glucose filtered from the plasma with the consequent absence of glycosuria. When blood sugar exceeds the kidney's ability to reabsorb glucose, the latter is lost in the urine. In diabetic patients, a greater expression of SGLT2 is observed in the renal tubules with consequent increase in glucose reabsorption, contributing to the maintenance of a hyperglycaemic condition.[4]

SGLT2 inhibitors (SGLT2i) represent a new class of oral anti-diabetic drugs indicated in type 2 diabetes mellitus, which includes dapagliflozin, canagliflozin, and empagliflozin. The hypoglycaemic action of these molecules is expressed through the inhibition of renal glucose reabsorption, even up to over 50%, with a consequent increase in its excretion in the urine. By acting only on the kidney with a mechanism independent of the presence of insulin but directly proportional to the glycaemic values, these molecules are associated with a low risk of hypoglycaemia and remain effective even in conditions of high insulin resistance.[5]

SGLT2 and cardiovascular events in patients with type 2 diabetes mellitus

In 2015, the EMPA-REG OUTCOME[6] study was published which assessed the incidence of cardiovascular events in 7020 patients with type 2 diabetes mellitus and known cardiovascular disease treated with empagliflozin vs. placebo and followed on average for over 3 years, finding a significant reduction of the composite endpoint of cardiovascular mortality, myocardial infarction and stroke [major adverse cardiovascular events (MACE)] [empagliflozin 10.5% vs. placebo 12.1%—hazard ratio (HR) 0.86]. This result was mainly derived from a conspicuous reduction in cardiovascular mortality (3.7% vs. 5.9%—HR 0.62) in the absence of differences related to myocardial infarction and stroke. Empagliflozin also resulted in a significant reduction in total mortality (5.7% vs. 8.3%—HR 0.68) and hospitalizations for heart failure (2.7% vs. 4.1%—HR 0.65), with a persistence of efficacy even in patients with renal dysfunction. Even in the presence of an increase in genital infections, the drug was not burdened by further significant adverse events, rather correlating with a lower progression of renal failure.

Similar benefits have been found in the CANVAS programme (Canagliflozin cardiovascular assessment study)[7] born from the union of two twin studies (CANVAS and CANVAS-Renal) that tested canagliflozin overall in 10 142 diabetic patients with high cardiovascular risk, 65.6% with known cardiovascular disease, compared to placebo. In the follow-up of over 3.5 years, the primary composite endpoint of MACE (cardiovascular mortality, myocardial infarction, and stroke) was assessed, detecting a significant benefit in patients treated with canagliflozin compared to placebo (2.7% vs. 3.1% per year—HR 0.86). The analysis by subgroups revealed how the positive effect of the drug in reducing MACE was confined to patients with known cardiovascular disease, without achieving significance in subjects in primary prevention. In addition, patients treated with canagliflozin experienced a lower incidence of hospitalizations for heart failure (0.5% vs. 0.9% per year—HR 0.67), less progression of albuminuria (HR 0.73), and worsening of kidney function (HR 0.60). On the contrary, there was a slight increase in the risk of necessitating lower limbs amputations (0.63% vs. 0.34% per year) in the treated patients.

More recently, the DECLARE-TIMI 58[8] trial was published, which assessed the effect of dapagliflozin vs. placebo on the incidence of major events in a population of 17 160 diabetic patients, which compared to previous studies included a smaller proportion of subjects with known cardiovascular disease (40.5%) and a higher percentage of subjects carrying only multiple cardiovascular risk factors (59.5%). During the median follow-up of 4.2 years, the primary composite endpoint of MACE (cardiovascular mortality, myocardial infarction, and stroke) showed no significant differences (dapagliflozin 8.8% vs. placebo 9.4%, $P = 0.17$), while the other primary composite endpoint consisting of cardiovascular mortality and heart failure hospitalizations showed a significant advantage in favour of active therapy (dapagliflozin 4.9% vs. placebo 5.8%, HR 0.83), driven exclusively by the reduction of hospitalizations for decompensation (HR 0.73), despite the absence of a previous history of heart failure in the majority of patients enrolled. There were no differences in terms of total mortality (dapagliflozin 6.2% vs. placebo 6.6%), while dapagliflozin was associated with a reduced incidence of renal complications (dapagliflozin 4.3% vs. placebo 5.6%) and a slight increase in the risk of diabetic ketoacidosis (0.3 vs. 0.01%—$P = 0.02$) and genital infections, the main cause of therapy withdrawal (dapagliflozin 0.9% vs. placebo 0.1%).

A recent meta-analysis of the data of these three trials published by Zelniker *et al.*[9] has cumulatively re-evaluated the over 34 000 diabetic patients enrolled, confirming a significant reduction in the cumulative risk of MACE, equal to 11%, in patients treated with SGLT2i compared to placebo. This result has remained entirely confined to patients with known atherosclerotic disease (MACE reduction of 14%), without achieving statistical significance in subjects in primary prevention with multiple cardiovascular risk factors. The composite endpoint of cardiovascular death and hospitalization for heart failure was also significantly reduced in patients treated with SGLT2i (−23% vs. placebo), a consequence of a preponderant share of the reduction of hospitalizations for heart failure (−30% vs. placebo). This figure appears particularly significant in consideration of the low prevalence of patients diagnosed with heart failure at the time of enrolment, equal to 10-15% of the total. Significant was also the absence of differences in the reduction of hospitalizations for heart failure according to the presence or absence of known atherosclerotic disease. The SGLT2i drugs also confirmed a robust protective effect on renal function, with a 45% reduction in the composite endpoint of worsening renal function, end-stage renal failure, or death from renal causes compared to placebo, which can be superimposed both in patients in primary and secondary cardiovascular prevention.

The reno-protective effect of SGLT2i was more pronounced in patients with preserved baseline renal function, while on the contrary the reduction of hospitalizations for heart failure was more evident in patients with more advanced renal dysfunction. The authors conclude by suggesting the use of SGLT2i drugs in all diabetic patients mainly to prevent hospitalizations for heart failure and the progression of renal failure and, in addition, in subjects on secondary cardiovascular prevention, to reduce MACE.

Two *post hoc* analyses of the DECLARE-TIMI 58[10] and CANVAS[11] studies, albeit with the limitations of retrospective investigations, assessed the incidence of hospitalizations for heart failure according to the left ventricular systolic function detected at enrolment, finding a greater benefit in patients with lower ejection fraction.

To investigate the effectiveness of SGLT2i drugs in the real world Pasternak *et al.*[12] analysed a large Scandinavian registry obtaining a cohort study involving over 40 000 diabetic patients about to start anti-diabetic therapy, half of whom were treated for the first time with SGLT2i (mostly dapagliflozin) and the other half with dipeptidyl peptidase 4 (DPP4).

Patients in secondary cardiovascular prevention represented a minority, equal to 19% of the total. During the 18-month follow-up, patients treated with SGLT2i had a significantly lower incidence of heart failure hospitalizations than in the control group (SGLT2i 0.47% per year vs. DPP4 0.71% per year, HR 0.66), while there were no significant differences in the cumulative incidence of MACE (SGLT2i 1.7% per year vs. DPP4 1.8% per year—HR 0.94). Similar results were found in another population registry that assessed 300 000 patients treated with SGLT2 or other oral hypoglycaemic agents in six different countries (the USA, Norway, Denmark, Sweden, Germany, and the UK).[13]

These results also confirmed in the real world the beneficial effect on the reduction of hospitalizations for heart failure by SGLT2i drugs and the absence of a substantial effect on MACE in a population mainly in primary cardiovascular prevention.

Initially, the use of these drugs was limited by warnings from both the Food and Drug Administration and the European Medicine Agency derived primarily from case reports of important adverse events, including diabetic ketoacidosis, urinary tract infections, acute renal failure, fractured bones, and increased risk of lower limb amputations.[14,15] More recently, Donnan *et al.*[16] published a meta-analysis of the data available in 60 082 diabetic patients treated with SGLT2i. The comparison with placebo showed a significant protective effect by SGLT2i against acute renal failure (RR 0.59) without significant differences regarding diabetic ketoacidosis, urinary tract infections, or bone fractures. With regard to the incidence of amputation, the available data are limited, having been evaluated only in three studies and being different from placebo only in CANVAS against canagliflozin (6.3 vs. 3.4/1000 pcs/year).

SGLT2 and heart failure treatment in patients without diabetes mellitus

As previously reported in the three main studies[6–8] that investigated the cardiovascular prognosis in diabetic patients treated with SGLT2i, a common and significant reduction in hospitalizations for heart failure was observed, around 30%, although involving patients who were not affected by this condition at the time of enrolment. Noteworthy was the rapidity of the onset of the effect from the moment of randomization, suggesting the mechanisms of action other than the mere prevention of complications of diabetes mellitus.

On this basis the DAPA-HF study,[17] a double-blind randomized multicentre trial, was designed to evaluate the efficacy in the reduction of hospitalizations for heart failure and cardiovascular death of dapagliflozin 10 mg per day vs. placebo in patients with heart failure [New York Heart Association (NYHA) II–IV] and left ventricular ejection fraction <40%, regardless of whether or not diabetes mellitus was present. There were 4744 patients already enrolled in full standard medical treatment randomized 1:1 to receive dapagliflozin or placebo and followed on average for over 18 months. In this interval, there was a significant reduction of the composite primary endpoint consisting of worsening heart failure (intended as a new hospitalization for heart failure or urgent visit with subsequent administration of intravenous therapy for this indication) and death from cardiovascular causes (dapagliflozin 16, 3% vs. placebo 21.2%—HR 0.74), with an overall number of patients to be treated to avoid an event equal to 21. This result was driven at a greater share by the reduction in hospitalizations for heart failure (dapagliflozin 9, 7% vs. placebo 11.5%—HR 70) but remained significant for all components of the endpoint. The benefits began to appear already a few weeks after the start of therapy and the curves continued to diverge over the following months. It should be noted that the proportion of diabetic patients in the study was 41% of the total, and there were no differences in outcomes between diabetic and non-diabetic subjects.

Among secondary endpoints, total mortality was significantly reduced with dapagliflozin compared to placebo (11.6 vs. 13.9%—HR 0.83) and active therapy resulted in a significant improvement in symptoms, assessed through a specific score (Kansas City Cardiomyopathy Questionnaire).

The subgroups analysis has demonstrated the persistence of a significant reduction in the primary endpoint even in patients already receiving sacubitril-valsartan (HR 0.75). A lower benefit was observed in patients with a more advanced functional class (NYHA III–IV) (HR 0.63 vs. 0.9); however, this result was not in line with the substantial benefit found with dapagliflozin in the analysis for subgroups in patients with reduced left ventricular function, higher atrial natriuretic peptides, previous hospitalizations for heart failure, and worse kidney function.

As regards safety, there were no differences in terms of volume depletion (dapagliflozin 1.2% vs. placebo 1.7%—$P = 0.23$), while dapagliflozin showed a lower incidence of worsening renal function (1.6% vs. 2.7%—$P = 0.009$). The drug was overall well tolerated with an incidence of withdrawal <5%, equal to placebo, and episodes of significant hypoglycaemia were very rare (0.2% in both groups) and limited to diabetic patients.

In the accompanying editorial,[18] it is reported that the benefit found in patients receiving dapagliflozin has proven

Table 1 Randomized clinical trials with SGLT2 inhibitors and cardiovascular events

Trial	Comparison	No. of pts	Age	T2DM (%)	Known CVD	Follow-up (median)	MACE (%/year)	Total mortality (%/year)	HFhospitalization (%/year)
EMPA-REG OUTCOME[6]	Empagliflozin vs. placebo	7020	63	100	100%	3.1 years	3.74 vs. 4.39 (HR 0.86)	1.94 vs. 2.86 (HR 0.68)	0.94 vs. 1.45 (HR 0.65)
CANVAS[7]	Canagliflozin vs. placebo	10142	63	100	65.6%	2.4 years	2.69 vs. 3.15 (HR 0.86)	1.73 vs. 1.95 (HR 0.87)	0.55 vs. 0.87 (HR 0.67)
DECLARE-TIMI 58[8]	Dapagliflozin vs. placebo	17160	64	100	40.5%	4.2 years	2.26 vs. 2.42 (HR 0.93)	1.51 vs. 1.64 (HR 0.93)	0.62 vs. 0.85 (HR 0.73)
DAPA-HF[17]	Dapagliflozin vs. placebo	4744	66	41.8	56%	1.5 years	NA	7.9 vs. 9.5 (HR 0.83)	6.9 vs. 9.8 (HR 0.70)

CVD, cardiovascular disease; HF, heart failure; HR, hazard ratio; MACE, major advance cardiac events; Pts, patients; T2DM, type 2 diabetes mellitus.

to be additive to the standard therapy of heart failure and is substantially comparable to that obtained with sacubitril-valsartan. However, it is underlined how the baseline blood pressure and heart rate data still left room for the standard therapy titration which could have attenuated the extent of the results obtained. It also highlights the lack of data transferable to clinical practice in patients with advanced heart failure (NYHA III–IV) or in those with concomitant intake of sacubitril-valsartan due to the low number, in the trial, of subjects with these characteristics. *Table 1* compares the characteristics and results of the main comparison trials between SGLT2i and placebo in the evaluation of cardiovascular events.

In the wake of these results, other trials have been designed to better investigate the effects of dapagliflozid in the prevention of heart failure. A study similar to DAPA-HF, the EMPEROR-Reduced[19] will evaluate the incidence of cardiovascular death and hospitalizations for heart failure in approximately 3600 patients with heart failure and reduced left ventricular ejection fraction (<40%), half of whom are non-diabetic randomized double blind to receive empagliflozin vs. placebo. Two other planned studies (EMPEROR-Preserved with empagliflozin and DELIVER with dapaliglozin) will, instead, evaluate the effects on the prognosis in >10 000 patients diagnosed with heart failure with preserved systolic function.

Mechanisms of benefit of SGLT2i on heart failure

The reduction in the incidence of heart failure in patients treated with SGLT2i was uniformly present in all randomized trials, both in diabetic and non-diabetic patients and was confirmed by registry studies.

The mechanism by which the anti-decompensation action of these drugs is carried out has not yet been well understood. In diabetic patients, a secondary effect was initially hypothesized to the improvement of glycaemic control; however, the substantial overlap of the results of the DAPA-HF study in diabetic and non-diabetic patients seems to exclude this mechanism.

The most accredited theory of the anti-decompensation efficacy of SGLT2i is based on the reduction of water retention, a consequence of a greater excretion of sodium. In a recent comment to the DAPA-HF study, Packer *et al.*[20] however questioned this mechanism, underlining that in patients treated with dapagliflozin there is only a marginal reduction (10–15%) of the values of atrial natriuretic peptide, a typical effect of the diuretic therapy, and how the increase in diuresis obtained with the increase in diuretic therapy has never been related to an increase in survival in heart failure. Packer *et al.* suggested a likely different action through increasing the efficiency and vitality of cardiomyocytes and reducing apoptosis.[21] A direct inhibition action by the drugs SGLT2i exerted on the sodium-hydrogen exchanger channels 1 (sodium-hydrogen exchanger-1) present on cardiomyocytes has been hypothesized.[22] These channels are increased in both diabetes mellitus and heart failure and are associated with an increase in intracellular calcium, correlated in preclinical studies of dysfunction and death of cardiomyocytes. There are also several preclinical studies that demonstrate a direct action of this category of drugs on the modulation of cardiac energy metabolism, the inhibition of inflammatory cytokines and oxidative stress, all factors implicated in the increase of myocardial fibrosis, a crucial element in the pathogenesis of heart failure, especially in patients with preserved systolic function.[18,23] Finally, a further recent line of research is based on the direct effect of SGLT2i drugs in reducing epicardial fat and its production of inflammatory cytokines, directly implicated in the development of myocardial fibrosis and of the left atrial appendge.[20]

To better investigate the real mechanism of action of dapagliflozin, the DAPA-MECH study program (DEFINE-HF,

PRESERVED-HF, DAPASALT, DAPAMAAST, DAPACARD, DIAMOND) is underway, aimed at the study of the mechanisms of the cardiovascular and renal effects of this drug.

Conclusions

According to the current indications of the diabetic guidelines, SGLT2i appear together with other anti-diabetic drugs as second-line therapy after metformin. The significant reduction of MACE in diabetic patients in secondary cardiovascular prevention and the evident reduction of hospitalizations for heart failure in all diabetic patients, even in primary prevention, make these drugs particularly attractive in patients with this pathology. The DAPA-HF study clears dapagliflozin from the mere treatment of diabetes mellitus, demonstrating significant efficacy in reducing mortality, total and cardiovascular, and especially hospitalizations for heart failure in all patients with reduced left ventricular function. These results, in association with the scarce side effects detected, make dapagliflozin a new weapon available in the treatment of heart failure. New ongoing studies will define with more certainty the mechanisms through which the anti-decompensation action of SGLT2i drugs is carried out and will evaluate their effectiveness in patients with heart failure associated with preserved left ventricular systolic function.

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