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ANMCO POSITION PAPER: on administration of type 2 sodium-glucose co-transporter inhibitors to prevent heart failure in diabetic patients and to treat heart failure patients with and without diabetes

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This ANMCO (Associazione Nazionale Medici Cardiologi Ospedalieri) position paper aims to analyse the complex action of sodium-glucose co-transporter 2 inhibitors at the level of the kidney and cardiovascular system, focusing on the effect that these molecules have shown in the prevention and treatment of heart failure in diabetic and non-diabetic subjects. The goal was pursued by comparing the data generated with pathophysiology studies and with multicentre controlled studies in large populations. In accordance with the analysis carried out in the document, the following recommendations are issued: (i) canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin are molecules recommended for the prevention of heart failure hospitalizations in type 2 diabetic subjects; (ii) canagliflozin and dapagliflozin are recommended for the prevention of heart failure hospitalizations in type 2 diabetic subjects with severe chronic kidney disease, dapagliflozin proved to be safe and effective also in diabetic subjects; and (iii) dapagliflozin and empagliflozin are recommended to reduce the combined risk of heart failure and cardiovascular death in diabetic and non-diabetic subjects with heart failure and reduced ejection fraction.

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The kidney gluco-metabolic organ implications in cardiovascular physiology, the role of glucose and sodium co-transporters 2 and 1 (SGLT2, SGLT1)

Scientific research has shown that the kidney is capable of carrying out gluconeogenesis and that renal glucose production accounts for 20% of systemically produced glucose.[1]

The data indicate that renal gluconeogenesis plays a key role in maintaining glycaemic homeostasis in the body by using glucose as metabolic fuel and by reabsorbing filtered glucose through the sodium-glucose co-transponders (sodium-glucose co-transponders 1-2) SGLT1 and SGLT2 located in the thick portion of the proximal tubule. In euglycaemic subjects, the reabsorption of glucose from the renal filtrate is about 125 mg/min which corresponds approximately to one-third of the renal maximum capacity for glucose tubular transport system (TmG).[2]

The SGLT2 enzyme, located more proximal to Bowman's capsule, has a higher transport capacity and reabsorbs 80-90% of the filtered glucose by associating the reabsorption of only one Na^+ molecule for each glucose molecule.

The enzyme SGLT1, located in the tubule in a more distal position than SGLT2, has a higher affinity for glucose and a lower transport capacity. It associates the reabsorption of one molecule of glucose with that of two molecules of Na^+ (*Figure 1A*). Importantly, the reabsorption of glucose by the complex of SGLT 1 and 2 is closely linked to that of Na^+ and determines the reabsorption of about 5% of the sodium globally reabsorbed in the renal tubule[3] (*Figure 1B*).

The Na^+ concentration reaching the juxtaglomerular apparatus (dense macula) provides the signal of the state of kidney perfusion through the mechanism known as 'tubule-glomerular feedback'.[2-4]

The system constituted by the co-transporters SGLT2 and SGLT1 can markedly increase the reabsorption of filtered glucose and implement the complete recovery of filtered glucose up to the threshold value of glycaemia of 180 mg/dL. Only beyond this value, glycosuria appears to represent in many cases the first and late diagnostic parameter of diabetes.

Therefore, there is a time window between the elevated blood glucose value and the appearance of glycosuria which can be prolonged by the increase of the spillover threshold of glucose in the urine of diabetic patients. This effect is a consequence of the SGLT1 and SGLT2 system-related induction which increases the recovery of glucose from the filtrate (an increase of TmG) and of Na^+ which is involved in this reabsorption mechanism. The net effect of this mechanism delays the onset of glycosuria and reduces the concentration of Na^+ reaching the dense macula (juxtaglomerular apparatus)[3] (*Figure 2A*).

Consequences of increased sodium and glucose reabsorption in the glomerular filtrate

In diabetic patients with poorly controlled blood glucose values, the low concentration of Na^+ reaching the juxtaglomerular apparatus (dense macula) defines the signal of reduced kidney perfusion through the mechanism known as tubule-glomerular feedback[2-4] activating the production of angiotensin II, hence the constriction of the adjacent efferent arteriole and dilation of the afferent arteriole secondary also to the release of local neurohormonal factors (*Figure 2B*). The result of the changes in intra-renal haemodynamics is an increase in intraglomerular pressure and in glomerular filtration rate which determine the progressive glomerular damage in diabetic patients, up to the appearance of albumin in the urine expressed by the progressive alteration of the albumin-creatinine ratio (urine albumin-creatinine ratio, UACR),[5] an indicator of mesangial damage.

The renal effects of treatment with SGLT2 enzyme inhibitors

Treatment with SGLT2 inhibitors reduces TmG and results in the loss of glucose and Na^+ in the glomerular filtrate which leads to increased Na^+ concentration in the filtrate reaching the juxtaglomerular apparatus. The increased Na^+ concentration restores afferent arteriole tone by re-establishing the signal of adequate renal perfusion (*via* tubule-glomerular feedback) and defuses the increase in renin secretion and angiotensin II production. The pharmacological effect of these molecules decreases intraglomerular pressure and reduces filtration rate, factors that contribute to the impairment of renal function and subsequently to the integrity of the glomerulus[5] (*Figure 2C*).

As mentioned above, this action is followed by a relative decrease in the glomerular filtrate ('dipping') which, in the longer term, is partially or fully recovered depending on pre-existing renal conditions and improvement in cardiovascular and renal haemodynamics.[3,6]

The impact of the action of SGLT2 inhibitors on renal function, pathophysiological implications, and clinical consequences are uniformly present in diabetic patients with and without chronic kidney disease as well as in patients with other established cardiovascular conditions, as will be analysed below.

The class effects of SGLT2 inhibitors on renal function are important because the decrease in intraglomerular pressure is a major contributor to the improvement in cardiovascular endpoints considered in all studies conducted.[7] In contrast to inhibitors of the renin-angiotensin system that induce predominant vasodilation of the efferent arteriole, SGLT2 inhibitors restore tone (vasoconstriction) of the afferent arteriole with reactivation of the described tubule-glomerular feedback mechanism. The mechanism of action both of SGLT2 inhibitors and renin-angiotensin system inhibitors reduce intraglomerular filtration pressure by independent and complementary mechanisms.[3]

Of note, the hypoglycaemic effect induced by the SGLT2 inhibition activates the production of glucagon by renal hepatic reflex which restores the glycaemic level, limiting the possible onset of hypoglycaemia which can be significant only in insulin-dependent patients.[2]

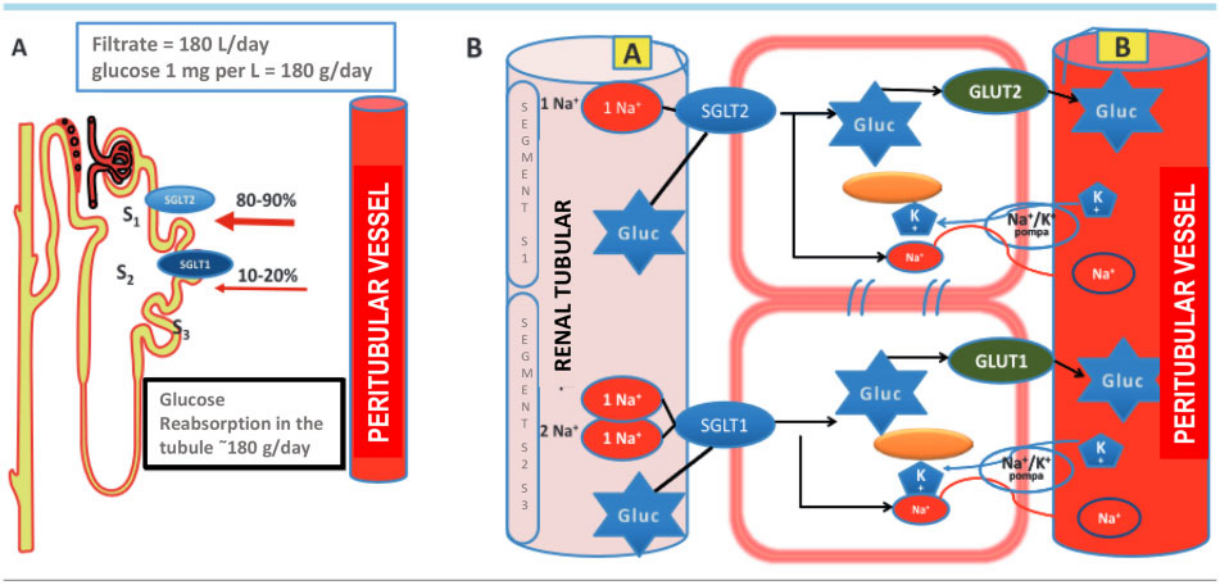

Figure 1 (*A*) The kidney is an organ that promotes glucose sparing. In healthy adult humans, the kidney filters about 180 g daily. The filtered glucose is prematurely reabsorbed in toto (180 g/day) and glycosuria does not appear. The mechanism that allows the kidney to recover the glucose present in the glomerular filtrate is based on the coupled and integrated function of glucose and Na+ transport from the peritubular vessel to the renal tubule. This mechanism benefits from the action of the sodium-glucose co-transporter type 2 (SGLT2) located in the tubule just below Bowman's capsule in segment S1, associated with the sodium-glucose co-transporter type 1 (SGLT1) located in the underlying segment S2-S3. Eighty percent to 90% of the filtered glucose is reabsorbed by the SGLT2 enzyme and the remaining portion by the SGLT1 enzyme. (*B*) Glucose sparing in the kidney occurs via reabsorption in the proximal tubule. The action of the SGLT2-SGLT1 co-transporters is complementary, aimed at preventing glucose loss with urine. The reabsorption capacity of the co-transporters is higher than the activity they normally perform. In particular, the presence of a higher concentration of glucose in the filtrate leads to an increase in the activity of the co-transporter SGLT1, which has a high affinity for glucose, leading to an increase in the threshold of glycosuria. The figure shows how the coupling of SGLT2 and SGLT1 with the reciprocal glucose transporter GLUT2 and GLUT1, compose a single mechanism, functional to the complete recovery of glucose present in the filtrate. This mechanism is coupled to Na+ recovery, maintaining a glucose to Na+ ratio of 1:1 for SGLT2 and 1:2 for SGLT1. Energy for reabsorption of molecules is provided by the Na+/K+ ATPase-dependent pump that is located in the basolateral membrane of the tubule. Reproduced with permission from Gronda *et al.*[4]

Analysis of populations and cardiovascular outcomes in controlled trials conducted with SGLT2 inhibitors in type 2 diabetic patients

Large studies conducted with FDA-approved SGLT2 inhibitors (dapagliflozin, empagliflozin, canagliflozin, and ertugliflozin) in patients with diabetes were designed to prove their cardiovascular safety. Accordingly, for each of the molecules approved for diabetes therapy, a large study conducted in patients with type 2 diabetes (T2D) with intermediate- to high-grade cardiovascular risk is available, having as primary endpoint the incidence of major cardiovascular events.[8–11] These studies arise from safety regulatory requirements and have peculiar characteristics whereby the enrolled populations are represented mainly[9,10] or exclusively[8,11] by patients with previous major cardiovascular events or with prevalent and multiple risk factors.

The objective of these investigations was to verify the safety of the drugs in patients who had the highest potential cardiovascular risk, therefore, they did not represent the treatment population in the real world where there are low-risk diabetic subjects. Moreover, the study population size was calculated to obtain a sufficient number of events to conclude the trial in a relatively short time (generally less than 3 years). To achieve quickly enough the objective required by the regulatory authorities, the main outcome chosen was the composite outcome defined by major adverse cardiovascular events (based on non-fatal myocardial infarction, non-fatal stroke, and cardiovascular mortality). This composite indicator does not allow to adequately discriminate the effects of a drug on single components of cardiovascular risk. Since the goal was to assess cardiovascular safety, these studies added both treatment and placebo to the usual hypoglycaemic therapy that was modifiable by the investigators to maintain the best glycaemic control of the patients. This strategy eliminated or reduced the possible effects of the investigated drugs on glycaemia. Finally, since the studies were primarily designed to demonstrate the safety, and not the efficacy of the therapy, the primary endpoint was of non-superiority.[8–10] In a single case, a primary efficacy endpoint (therefore, superiority) was included, following an amendment to the original protocol[11] after the positive results were achieved by a molecule of the same class.

In diabetics, the design of studies set on the safety of SGLT2i has resulted, at least in part, an underestimation of the true efficacy on cardiovascular events.[12] The relatively short duration of these studies may have been insufficient for the finding of the full cardiovascular benefits of a class of drugs acting on complex renal and metabolic mechanisms. Also, when calculated for a primary endpoint of non-inferiority, study sizes may have been too small to document superiority.

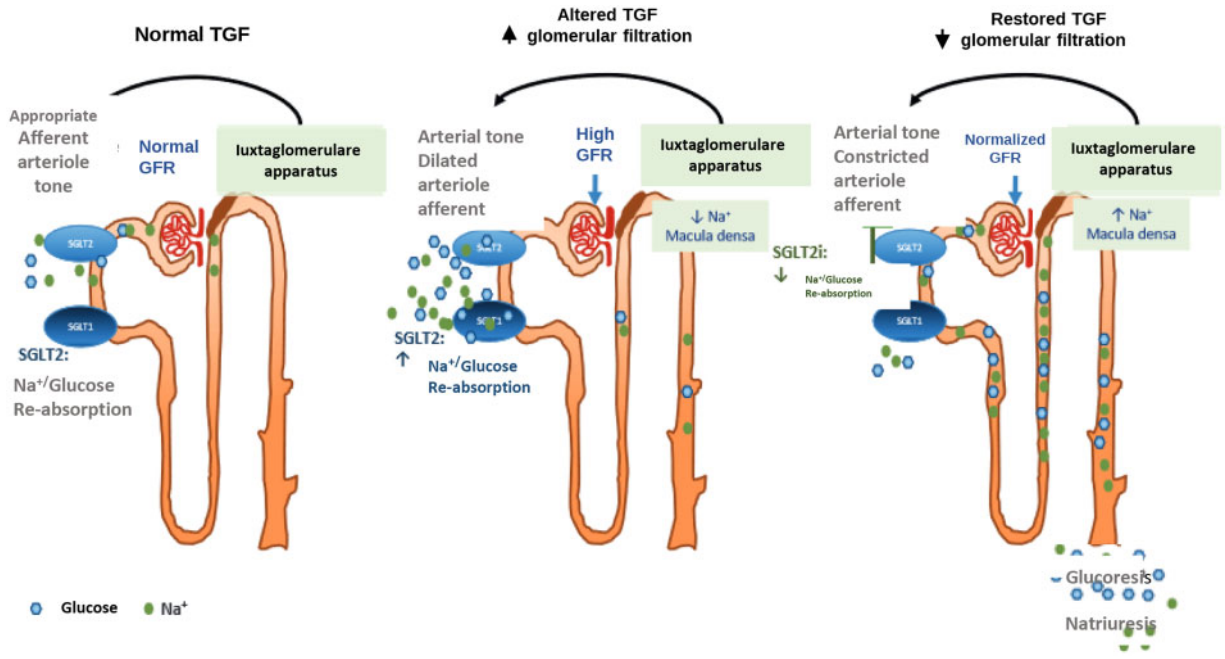

Figure 2 Effect of the action of type 2 sodium-glucose co-transporters (SGLT2) on filtered glucose in the normal and diabetic subject and of SGLT2 inhibition on nephron physiology. (*A*) Normally glucose in the tubule is entirely reabsorbed along with a proportion of the sodium present. Under normal conditions only the sodium reaches the juxtaglomerular apparatus, which depending on the concentration of the ion in the filtrate maintains the appropriate intraglomerular gradient for filtrate production. The mechanism is known as tubulo-glomerular feedback (TGF). (*B*) In the diabetic with poorly controlled blood glucose, the amount of glucose increases in the glomerular filtrate. Due to the action of SGLT2 and SGLT1, the coupled reabsorption of glucose and Na+ in the proximal tubule increases. The increase in Na+ reabsorption, which normally represents 5% of the sodium reabsorbed in the tubule, increases up to 15%. This significantly reduces its concentration in the filtrate that reaches the juxtaglomerular apparatus. In this location, the detection of the decreased electrolyte concentration simulates and amplifies the signal of reduced perfusion of the kidney, leading to the increase of renin that activates the neurormonal axis and the formation of angiotensin II. Angiotensin II induces predominant vasoconstriction of the efferent arteriole. In addition, the afferent arteriole is affected by the vasodilating action produced by other local substances (nitric oxide, adenosine, and prostanoids). These changes result in increased intraglomerular pressure and filtrate production, factors that damage the complex and delicate structure of the glomerulus. (*C*) Treatment with an SGLT2 inhibitor prevents the reabsorption of most of the glucose and Na+ present in the filtrate, increasing the concentration of glucose and Na+, which, eliminated with the urine, reaches the juxtaglomerular apparatus. The re-established Na+ concentration in the filtrate is detected by the juxtaglomerular apparatus which, through the restored tubulo-glomerular feedback, inhibits renin increment and angiotensin II production, restoring filtration pressure and abolishing hyperfiltration in the glomerulus. In context, SGLT1 increases its Na+ and glucose reabsorption activity by relatively reducing the glucose and electrolyte elimination that results from SGLT2 inhibition. This allows us to explain why a lower than expected proportion of Na+ and glucose is found in the urine. Reproduced with permission from Gronda *et al.*[4]

However, the results on cardiovascular outcomes of the trials conducted with SGLT2 inhibitors in diabetes have been much higher than expected: in the trials conducted with empagliflozin and canagliflozin, a significant reduction in the incidence of major cardiovascular events was observed,[8,9] as well as for the primary endpoints of these trials, defined as a composite of non-fatal heart attack, non-fatal stroke, and cardiovascular mortality. In the trial with dapagliflozin, a similar trend was seen, although statistical significance was not reached.[10]

Moreover, in the empagliflozin trial, a very high reduction in cardiovascular mortality was found associated with a reduction of more than 30% in overall mortality.[8] Jointly analysing the cardiovascular trials conducted with SGLT2 inhibitors in patients with diabetes concerning the components of the main composite endpoint, a reduction in the risk of myocardial infarction, cardiovascular mortality, and incidence of hospitalization for heart failure was observed, whereas the effects on the incidence of stroke did not seem relevant.[7,13] In all four studies, however, the most striking finding concerns the magnitude of the reduction in the predefined secondary endpoint of incidence of hospitalization for heart failure[8–11] (*Table 1*).

The effect on major cardiovascular events, driven primarily by effects on myocardial infarction, appears less homogeneous, with significant reductions in some studies,[7,13] but not in others.[12,17] The differences could depend on the characteristics of the individual studies, in particular, the characteristics of the patients recruited, rather than on different effects among the molecules of the class: in fact, the reduction in major cardiovascular events is less evident the lower the cardiovascular risk of the population studied[7,12] and is very small or absent in patients without previous events,[13] differently represented in the populations of the individual studies. In particular, in studies with dapagliflozin[10] and, to a lesser extent with canagliflozin,[9] a subpopulation with multiple risk factors, without prior cardiovascular events, was included and had a lower risk than secondary prevention populations.

The existence of differences in cardiovascular effects among the various SGLT2 inhibitors, in the absence of direct comparisons between molecules, is a much-debated

Table 1 Effect of type 2 sodium-glucose co-transporter inhibitors in diabetic patients with different cardiovascular risk profile and comparison with the effect of ACE inhibitors

	Study entry criteria	HR (CROs)	HR (SC)
SGLT2i			
EMPA-REG OUTCOME[8] (empagliflozin)	Secondary prevention 100%	0.72	0.65
CANVAS Program[9] (canagliflozin)	Primary prevention 34% + Secondary prevention 66%	0.61	0.67
DECLARE-TIMI 58[10] (dapagliflozin)	Primary prevention 61% + Secondary prevention 39%	0.79	0.73
CREDENCE[14] (canagliflozin)	Chronic renal failure with albuminuria	0.66	0.61
ACE-inhibitors			
Captopril[15]	Diabetic nephropathy	0.64 (dialysis/renal transplantation)	-
Ramipril[16]	High cardiovascular risk (diabetes 38%)	-	0.77

Table shows the relative risk reduction data for the CRO outcome (which includes: doubling of creatinine value, renal dialysis or transplantation, death from renal cardiovascular causes) and hospitalization for heart failure achieved in trials conducted, for registration purposes, with empagliflozin, canagliflozin, and dapagliflozin in diabetic subjects with a diverse cardiovascular risk profile.[8–10,14] For comparison, data from two studies conducted with captopril in subjects with diabetic nephropathy (composite outcome limited to dialysis or renal transplantation) and with ramipril in subjects with high cardiovascular risk of whom two of five were diabetic for the composite outcome of cardiovascular death or hospitalization for heart failure are reported below.[15,16]

CROs, composite outcome of renal adverse events; HR, hazard ratio; SC, heart failure; SGLT2i, sodium-glucose co-transporter type 2 inhibitors.

issue. It is, however, necessary to note that, although the pharmacological effect is homogeneous in the class of drugs, they have different half-lives and have been investigated in variable clinical settings performing different study designs and statistical assumptions. The availability of large studies aimed at finding outcomes in clinical conditions ranging from diabetes in patients with only cardiovascular risk factors to renal failure and heart failure in subjects with and without diabetes has resized hypothetical differences between molecules for cardiovascular mortality which appears moderately reduced in studies conducted with empagliflozin, dapagliflozin, and canagliflozin, without relevant heterogeneity of the class.[17] Some caution may concern ertugliflozin for which a single large study did not provide significant results on mortality and major cardiovascular events, but only on hospitalizations for heart failure.[11]

Analysis of the renal action of SGLT2 inhibitors and their effects in renal failure in diabetic patients

Although in all studies conducted in diabetics with empagliflozin, dapagliflozin, and canagliflozin administration of SGLT2 inhibitors, the reduction in renal outcomes was always associated with the reduction in heart failure hospitalizations, the meta-analysis by Zelniker *et al.*[13] highlighted the peculiar distribution of efficacy regarding the outcomes investigated by the trials.

In the meta-analysis,[13] study populations were stratified according to an increasing glomerular filtrate value (<60, 60 < 90, >90 mL/min per m^2). This showed that the effect of SGLT2 inhibitors on the composite renal endpoint (defined as worsening renal function, need for renal replacement therapy, or death from renal causes) was statistically greater in patients with better-preserved renal function than in patients with more impaired function. The *P*-value for the trend towards reduced events in the subgroups was 0.0258. In contrast, the reduction in heart failure hospitalizations was shown to increase about the greater degree of pre-existing renal dysfunction. In the analysis, the *P*-value for the trend towards reduced events in the subgroups was 0.0073.

The relationship between the extent of renal damage and prevalent prevention of decompensation recurrence also emerges in the study conducted with ertugliflozin.[11] In the study population of 8246 T2D patients, approximately one quarter were heart failure carriers with different phenotypes and almost as many had estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2, ertugliflozin significantly reduced the risk of heart failure hospitalization in subjects with eGFR <60 mL/min/1.73 m^2 [hazard ratio (HR) 0.50; 95% confidence interval (CI) 0.33–0.76], with albuminuria, or who were already taking loop diuretics (*P* for interaction equal to 0.04; 0.02; 0.01, respectively) with albuminuria or who were already taking diuretics and loop diuretics (*P* for interaction respectively = 0.04; 0.04; 0.02; 0.01). Furthermore, the significant reduction in hospitalizations for heart failure was present only in subjects with ejection fraction <45% (HR 0.48; 95% CI 0.30–0.76) or with previous heart failure (HR 0.63; 95% CI 0.44–0.90). Besides, a significant reduction in heart failure hospitalizations was present only in patients with previous heart failure (HR 0.63; 95% CI 0.44–0.90).[15]

Overall, the renal benefit induced by SGLT2 inhibitors mirrored the reduction in heart failure hospitalizations and was comparable to what was obtained on the same fronts by the introduction of angiotensin-converting enzyme inhibitors (ACEi)[14,16] (*Table 1*).

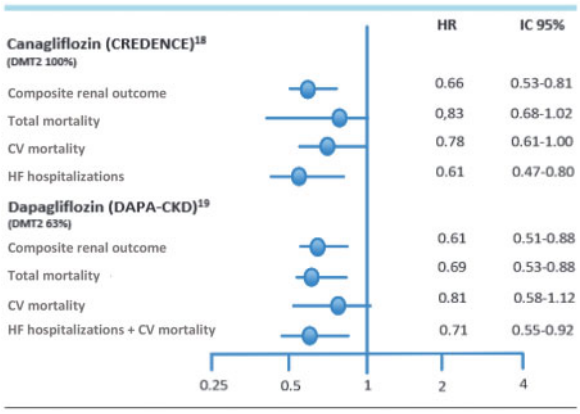

Figure 3 Results of studies conducted with sodium-glucose co-transporter type 2 (SGLT2i) inhibitors in diabetic and non-diabetic subjects with chronic renal failure for the primary renal outcome. In studies conducted in patients with chronic renal failure characterized by low glomerular filtration (lower limit eGFR $\geq$25 mL/min/1.73 m^2) also in association with albuminuric nephropathy, administration of canagliflozin and dapagliflozin resulted in an unequivocal early benefit on all outcomes predicted in the research design, mandating early closure of the two studies.

Analysis of the action of SGLT2 inhibitors based on studies conducted for the primary renal outcome

Glomerular hyperfiltration is a frequent pathological phenomenon in diabetic patients. This condition is defined by the presence of a glomerular filtrate $\geq$135 mL/min/1.73 m^2. It constitutes the marker of intraglomerular hypertension that determines the onset and progression of diabetic nephropathy which is characterized by increased basement membrane permeability to albumin.

SGLT2 inhibition induces glucoresis and, at the same time, natriuresis, which determines the reactivation of tubule-glomerular feedback contributing to the reduction of hypertension and hyperfiltration in the glomerulus, preventing consequent damage.

The effect of SGLT2 inhibitors on albuminuria has been investigated by the secondary outcome in all controlled studies conducted for cardiovascular safety and efficacy in diabetics. In all studies, these molecules demonstrated an effective reduction of albuminuria in the treatment arm.

Considering the relevance of the topic, two studies were designed with the efficacy of SGLT2 inhibitors in reducing renal outcomes in overt nephropathy as the primary objective (*Figure 3*).

A first study conducted with canagliflozin[18] enrolled diabetic patients with eGFR between 30 and <90 mL/min/1.73 m^2 and macroalbuminuria UACR between >300 and <5000 mg/g. The subpopulation with filtrate between <45 and 20 mL/min/1.73 m^2 was included in the study, and the enrolled patients could present with normal-, micro-, or macroalbuminuria to provide the broadest spectrum of outcomes for efficacy against diabetic nephropathy. The test population had a much higher risk of renal disease progression than patients enrolled in the previous cardiovascular safety and efficacy studies.

The second study was conducted with dapagliflozin[19] and enrolled patients with macroalbuminuria and eGFR between 25 and <75 mL/min/1.73 m^2. A subgroup of non-diabetic patients, corresponding to 30% of enrolled subjects, was predefined in this study. The purpose of this choice was to ascertain the efficacy of SGLT2 inhibition, regardless of diabetic status.

The study conducted with canagliflozin was stopped early because of the unequivocal benefit documented by the interim analysis. Published data confirmed the significant 30% (HR 0.70; CI 95%: 0.59–0.82) reduction in the primary composite renal endpoint, in the absence of any observed heterogeneity based on the pre-existing renal picture. In association with the renal benefit, a 39% reduction of failure hospitalizations was observed,[18] similar to previous studies.

The study conducted with dapagliflozin in 4304 patients with chronic renal failure, of whom 33.5% were non-diabetic, was also discontinued at the time of the interim analysis because of the clear superiority of the treatment over placebo. The drug was shown to reduce the incidence of the composite renal outcome by 44% compared with placebo treatment, with highly significant statistical significance (HR 0.56; 95% CI: 0.45–0.68), regardless of the degree of filtrate reduction or the extent of pre-existing albuminuria. Together, the combined outcome of death from cardiovascular causes or hospitalization for heart failure (HR 0.71 95% CI: 0.55–0.92) and overall mortality (HR 0.69; 95% CI: 0.53–0.88) were significantly reduced. In enrolled patients, the efficacy of dapagliflozin was similar in both the presence and absence of T2D, and the drug's safety profile was confirmed in both conditions. In this context, data from the study conducted with sotaglifozin, the only molecule that simultaneously inhibits SGLT2 and SGLT1, are also relevant. The drug was investigated in a controlled study that enrolled 10,584 type 2 diabetics and with eGFR between 25 and 60 mL/min/1.73 m^2.[20] The investigation was discontinued after 16 months because of issues that arose in the follow-up following the SARS COV 2 outbreak. As a result, the research design was modified and the composite outcome of cardiovascular mortality, hospitalization, or urgent visit for heart failure was constituted as the primary outcome.

In the treated arm of the study, there was a highly significant reduction in the primary composite outcome (HR 0.74; 95% CI: 0.63–0.88), but also in the secondary outcome related to exacerbation of heart failure (HR 0.77; 95% CI: 0.66–0.91). The short study duration associated with the early efficacy of Na^+ and glucose co-transporters in reducing the incidence of heart failure strengthened the evidence of the rapid benefit induced by these molecules.

Analysis of studies conducted in symptomatic, reduced ejection fraction heart failure

Although originally designed for the treatment of hyperglycaemia in T2D, SGLT2 inhibitors have been unanimously shown in diabetics to improve renal outcomes and, at the same time, the incidence of heart failure. This finding

motivated the extension of clinical research with two SGLT2 inhibitors in patients with heart failure with reduced ejection fraction, carriers and non-carriers of T2D in the DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) that enrolled 4744 patients (58% non-diabetic)[21] and the EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction) that enrolled 3730 subjects (50.2% non-diabetics), respectively.[22] Although the two studies shared the enrolment criterion of ejection fraction <40%, their respective designs were based on populations with different severity. *Table 2* reports for comparison the selection criteria, the salient characteristics of the enrolled populations and the prominent results achieved in the DAPA-HF[21] and EMPEROR-Reduced[22] studies.

In the study conducted with empagliflozin, the N-terminal pro-brain natriuretic peptide (NT-proBNP) threshold value for enrolment included a higher value in the presence of ejection fraction greater than 30%, whereas in the study conducted with dapagliflozin, the value was set at 600 pg/mL (or ≥400 pg/mL in patients with the previous hospitalization for decompensation in the previous 6 months). Moreover, in the study conducted with empagliflozin, enrolment contemplated the presence of eGFR ≥30 mL/min/1.73 m^2 compared with the value of eGFR ≥20 mL/min/1.73 m^2 indicated in the study conducted with dapagliflozin. By far the lowest filtrate value among those allowed for enrolment in studies conducted with SGLT2 inhibitors.

The different compositions of the two case histories may account for the partial difference in the results obtained in the two studies.

Concerning the consistency of the results, it can be observed that the event/year rate for the composite outcome of cardiovascular death or hospitalization for heart failure was 21% in the study with empagliflozin and 15% in that conducted with dapagliflozin. Both studies presented homogeneous results for the reduction in the composite outcome of cardiovascular death or hospitalization for heart failure and the isolated outcome of hospitalization for decompensation by 25% and 30%, respectively.

Based on the published data, to prevent an event in the study with dapagliflozin would require treating 21 patients over a median of 18 months and, in the study with empagliflozin, 19 patients over a median of 16 months of follow-up.

The analysis of the published data showed that cardiovascular mortality was significantly reduced in the study with dapagliflozin (HR 0.82; 95% CI: 0.69–0.98) and with it the overall mortality (HR 0.83; 95% CI: 0.71–0.97), while it was only numerically (not significantly) lower in the study with empagliflozin (HR 0.92; 95% CI: 0.75–1.12).

The difference in results could, in good part, result from the higher frequency of hospitalizations for decompensation present in the more severe case series of the study conducted with empagliflozin in the context of the short follow-up in which the two studies were carried out.

Regarding renal outcomes, both molecules achieved a similar effect in reducing glomerular filtrate loss in a manner, however, the composite renal outcome was reduced only in the study with empagliflozin. The cause could be due to the enrolment of patients with more advanced renal failure in the study with empagliflozin, which included a 40% drop in filtrate in the composite renal outcome, compared with the study with dapagliflozin in which the composite outcome included a 50% drop in filtrate.

Of note, the clinical benefit achieved in the treatment of heart failure by both molecules was present in patients subjects treated and untreated with anti-aldosterone drugs, untethering the action of SGLT2 inhibitors from interaction with other natriuretic drugs predicted in the guidelines. Besides, in both studies the reduction in NT-proBNP value was modest: minus 20% after dapagliflozin at 32 weeks and minus 5% after empagliflozin at 58 weeks.

In both studies, the tolerability of SGLT2 inhibitors was excellent in patients with heart failure, with no significant discontinuation of treatment for hypovolaemia- or hypoglycaemia-related effects.

A separate mention deserves the study conducted with sotaglifozin in a population of T2D patients who had a recent episode of acute heart failure, regardless of ejection fraction value.[23] In the study, 1222 patients were enrolled and randomized to treatment with sotagliflozin (608) or placebo (614).

The first dose of drug or placebo was administered before hospital discharge in 48.8% and after discharge in 51.2%, with a median of 2 days.

In the median 9-month follow-up, the combined primary endpoint for cardiovascular death or hospitalization or urgent visit for heart failure (first and subsequent events) was assessed. The trial, which was terminated early by the sponsor because of lack of funds, nevertheless proved that sotagliflozin administration resulted in the significant reduction of the primary endpoint (51.0% vs. 76.3%; HR: 0.67; 95% CI: 0.52–0.85; $P < 0.001$) although the differences for cardiovascular mortality (10.6 vs. 12.5; HR: 0.84; 95% CI: 0.58–1.22) and all-cause mortality (13.5% vs. 16.3; HR 0.82; 95% CI: 0.59–1.14) were not significant. The data obtained in such a small follow-up appear to reinforce the class action of SGLT2 inhibitors in heart failure.[23]

Pharmacological effects of SGLT2 inhibitors and clinical consequences in association with sacubitril-valsartan

The ‘dipping’ effect of the partial drop in glomerular filtration initially induced with the administration of SGLT2i inhibitors has been a cause of apprehension for the use of these molecules in diabetic patients with risk factors or with manifest cardiovascular disease. Successive studies have dispelled doubts and fears regarding potential, persistent negative consequences on glomerular filtration and have shown to preserve it better in the long term, with significant improvement in cardiovascular prognosis. The robustness of the results supported, in studies conducted on reduced ejection fraction heart failure, the enrolment of patients treated with sacubitril-valsartan (known as ARNI, angiotensin receptor neprilysin inhibitor) molecule that improved the prognosis of reduced ejection fraction heart failure, however, associating a progressive reduction in the glomerular filtrate.[24] This effect could have generated perplexity regarding the association of the two classes of drugs

Table 2 Comparison of the design and populations of the DAPA-HF and EMPEROR-Reduced studies

	DAPA-HF ($n = 4744$)	EMPEROR-Reduced ($n = 3730$)
Age (years, median)/follow-up (months)	66.5/≈18	66.5/≈16
Inclusion criteria	• FEVS ≤40% e NT-proBNP ≥600 pg/mL (without FA) o ≥ 900 pg/mL (with FA) • FEVS ≤40% e HHF in the last 12 months and NT-proBNP ≥400 pg/mL (without FA) o ≥ 900 pg/mL (with FA) • eGFR ≥0 mL/min/1.73 m^2	• FEVS ≤30% e NT-proBNP ≥600 pg/mL (without FA) e ≥ 1200 pg/mL (with AF) • FEVS 31-35% e NT-proBNP ≥1000 pg/mL (without FA) e ≥ 2000 pg/mL (with FA) • FEVS 36-40% e NT-proBNP ≥2500 pg/mL (without FA) e ≥ 5000 pg/mL (with FA) • FEVS ≤40% e HHF in the last 12 months e NT-proBNP ≥600 pg/mL (without FA) e ≥ 1200 pg/mL (with FA) • eGFR ≥20 mL/min/1.73 m^2
FEVS (%)	30.9	27.2
NT-proBNP (pg/mL, median)	1446	1926
Diabetes (%)	41.8	49.8
eGFR, mL/min/1.73 m^2 (%)	65.5	62.2
Atrial fibrillation (%)	38.0	37.8
ACE inhibitor or sartan without ARNI (%)	82.8	68.9
Beta-blocker (%)	96.2	94.7
Antialdosteronic (%)	70.6	72.6
ARNI (%)	10.9	20.7
Implantable defibrillator (%)	26.1	31.8
Cardiac resynchronization therapy (%)	6.9	11.9
Clinical outcomes of studies (HR, 95% CI)	Dapagliflozin vs. placebo	Empagliflozin vs. placebo
Primary outcome[a]	0.74 (0.65-0.85) $P < 0.001$	0.75 (0.65-0.86) $P < 0.001$
CV death or hospitalization for decompensation	0.75 (0.65-0.85)	0.75 (0.65-0.86)
Hospitalization for decompensation	0.70 (0.59-0.83)	0.69 (0.59-0.81)
CV death	0.82 (0.69-0.98)	0.92 (0.75-1.12)
Overall mortality	0.83 (0.71-0.97)	0.92 (0.77-1.10)
Average eGFR drop (mL/min/1.73 m^2) per year	1.78	1.73
Composite renal outcome[b] (HR, 95% CI)	0.71 (0.44-1.16)	0.50 (0.32-0.77)
Variation in biomarkers[c]	Dapagliflozin vs. placebo (32 weeks)	Empagliflozin vs. placebo (52 weeks)
HbA1c (diabetics) (%)	−0.24	−0.16
Haematocrit (%)	+2.41	+2.36
Body weight (kg)	−0.87	−0.82
NT-proBNP (variation %) (pg/mL)	−5 (32 weeks)	−20 (52 weeks)
Haematocrit (%)	+2.41	+2.36
Systolic blood pressure (mmHg)	−1.27	−0.7

For continuous variables, mean values are shown.

ACE, angiotensin-converting enzyme; AF, atrial fibrillation; ARNI, angiotensin receptor inhibitor and neprilysin; CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; e, and; FEVS, left ventricular ejection fraction; HbA1c, glycated haemoglobin; HR, hazard ratio; NT-proBNP, N-terminal fragment of B-type natriuretic propeptide; o, or.

[a]In the EMPEROR-Reduced study, the primary outcome was the composite of CV death or hospitalization for worsening heart failure. In the DAPA-HF study, the primary outcome was the composite of CV death or worsening heart failure.

[b]In the EMPEROR-Reduced study, the composite renal outcome was a combination of the need for dialysis or renal transplantation or a ≥40% reduction in eGFR. In the DAPA-HF study, the composite renal outcome was the combination of ≥50% reduction in eGFR for ≥28 days or the occurrence of end-stage renal disease (defined as eGFR <15 mL/min/173 m^2 for ≥28 days or need for dialysis or renal transplantation) or death from renal or any cause. Absolute risk reductions are reported as a function of both baseline and relative risk reductions.

[c]Average changes for absolute values.

in patients with heart failure in particular associated with advanced renal failure.

Surprisingly, the association of dapagliflozin and empagliflozin with ARNI generated an additive benefit on cardiovascular mortality and hospitalizations for decompensation in patients with heart failure, with no statistically significant interaction between the two drug classes in the study with empagliflozin.[25] Moreover, the relative risk reduction for the combined outcome of cardiovascular death or hospitalization for heart failure in the two trials with SGLT2 inhibitors was not less than that generated by ARNI in the comparison with valsartan in the PARADIGM-HF trial[26] (*Table 2*), amplifying the benefit of the drug combination. On the other hand, the most striking finding seems to be presented in the study with empagliflozin. In the study, the simultaneous administration of ARNI and the SGLT2

inhibitor achieved a tendentially greater reduction in the relative risk for adverse renal events (HR 0.39; 95% CI 0.11–1.45 vs. HR; 95% CI 0.32–0.81).[25] It is noteworthy the EMPEROR-reduced study did not report a significant drop in NT-proBNP even in this subgroup of patients in whom SGLT2i was associated with ARNI. It seems reasonable the hypothesis the association of the two molecules, by amplifying the fall in filtration pressure, may greatly affect the glomerular hyperfiltration, representing a key mechanism to lead to the lower incidence of renal events, closely related to the prevalent heart failure adverse events.

We recognize we did not analyze the manifold action on a number of pleiotropic effects linked to SGLT2 inhibition in current manuscript. All those effects may have contributed to the enhance the drug action beyond the well-established benefit provided by HF therapies addressed in current guidelines.[27]

Safety profile and risk-benefit ratio in the administration of SGLT2i

SGLT2 inhibitors represent a pharmacological class with a high safety profile as addressed by the incidence of prevalent adverse events in large controlled studies performed in diabetic and non-diabetic patient.[8–11,14,18–21] In most of the trials conducted in diabetic patients, an infection of the external genitalia was frequently observed as an adverse effect, whereas a similar percentage of urinary tract infections was observed as a placebo.

In the CANVAS study, a higher percentage of amputations and fractures were observed in patients treated with Canaglifozin, albeit minimal in terms of absolute difference. The same trend, however, was not observed in the CREDENCE study in which Canaglifozin was also tested against placebo, nor in the other main trials.

In DAPA-HF, a trend towards a higher incidence, not significant, of volume depletion was observed. In this regard, it should be recalled that DAPA-HF and EMPEROR-reduced excluded patients with a history of hypotension and systolic blood pressure below 100 and 95 mmHg, respectively, at enrolment. Also, a sub-analysis of the DAPA-HF analysed the relationship between the occurrence of hypotension and loop diuretic therapy.[28] Compared with placebo, dapagliflozin reduced the risk of the primary endpoint both in patients without treatment with a loop diuretic and in those with a daily dose of furosemide less than or greater than 40 mg/day. The frequency of fluid depletion was higher among diuretic-treated patients at enrolment and, in particular, among those taking the furosemide dose >40 mg/day. In contrast, in patients not treated with a loop diuretic, dapagliflozin intake was associated with lower fluid depletion. Overall, dapagliflozin intake was shown to be safe, regardless of association with a loop diuretic.

Regarding hypoglycaemia, no significant differences were observed in the treated group as compared to placebo in both DAPA-HF- and EMPEROR-reduced diabetic and non-diabetic patients.

In the study with sotaglifozin, a non-selective SGLT2 and SGLT1 inhibitor, which enrolled diabetic patients with recent exacerbation for heart failure,[23] severe hypoglycaemia was significantly more frequent in the treated group (1.5% vs. 0.3%) and diarrhoea was observed more frequently, as compared to placebo (6.1% vs. 3.4%). These data should be reviewed for comparison with results generated by trials in patients with a recent episode of acute heart failure, now being treated with selective SGLT2 inhibitors. Finally, in all studies conducted with SGLT2i, no significant change in plasma electrolytes was observed. SGLT2i appear to be a drug class whose benefits outweigh the risks in diabetic and non-diabetic patients with chronic renal failure and/or reduced ejection fraction heart failure.

In all studies, side effects attributable to SGLT2i therapy were similar when compared with placebo. The totality of the data reinforces the safety and therefore the rationale for the use of these molecules in clinical practice.

Recommendations for the effective implementation of evidence-based therapy in the treatment of heart failure

In the current guidelines, dedicated to the treatment of heart failure, the prescription of different classes of drugs is recommended according to the chronological order derived from the temporal sequence of the publication of large controlled studies produced in the past three decades.

This approach is accompanied by the indication to achieve, for each drug class, the administration of the maximum dose indicated in the studies or the maximum tolerated by the patient as well as involves a prolonged phase of titration of therapies that reduces the extent of the benefit that could be drawn from them. Besides, the long titration phase of the drugs favours under-dosing in long-term treatment. This aspect has gained particular relevance with the publication of studies conducted with ARNI[26] and with SGLT2i in patients with heart failure with reduced ejection fraction.[21,22] The results of these investigations have changed the composition of the classes of drugs effective for the treatment of HFrEF. In particular, the Angiotensin-Neprilysin Inhibition in Acute Decompensated Heart Failure study allowed to accredit the introduction of sacubitril-valsartan therapy in patients hospitalized for acute heart failure, avoiding the transition to treatment with ACEi or angiotensin receptor blockers (ARBs).[29] Cardiology now has robust evidence of the efficacy of four different classes of molecules: ARNI and SGLT2i which complement the already established beta-blockers and anti-aldosterone drugs. This wide availability complicates the strategy to be adopted for the appropriate treatment of patients with HFrEF. The most logical decision-making sequence, however, can be inferred by observing the magnitude of the maximum benefit achieved by the drug class on the expected outcomes and the temporal latency between the initiation of treatment and the curve spread of the treated arm from the control arm of the studies. In this regard, it is surprising to observe how the efficacy produced by the different drugs induces the divarication of the curve of the treatment from that of the placebo of only 2–4 weeks

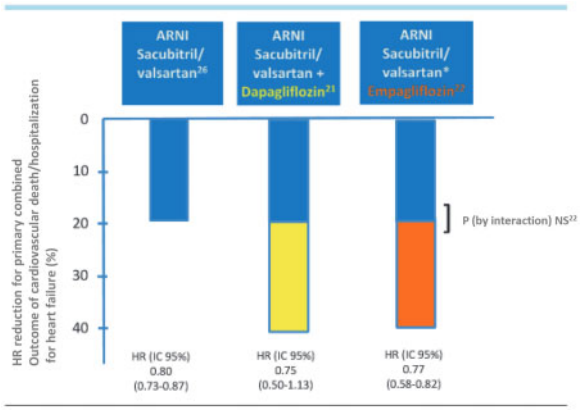

Figure 4 Superior efficacy of the combination of sacubitril/valsartan and sodium-glucose co-transporter type 2 (SGLT2i) inhibitors.
The figure illustrates the additive benefit for reduction in the primary composite outcome of cardiovascular death or heart failure hospitalization achieved with the association of sacubitril/valsartan and dapagliflozin[21] and sacubitril/ valsartan and empagliflozn,[22] in addition to what was achieved by sacubitril/valsartan administration alone compared with valsartan treatment.[26] In the post hoc analysis performed on the data from the study with empagliflozin, no interaction was detected between the angiotensin receptor inhibitor neprilysin (ARNI) and SGLT2i.[25]

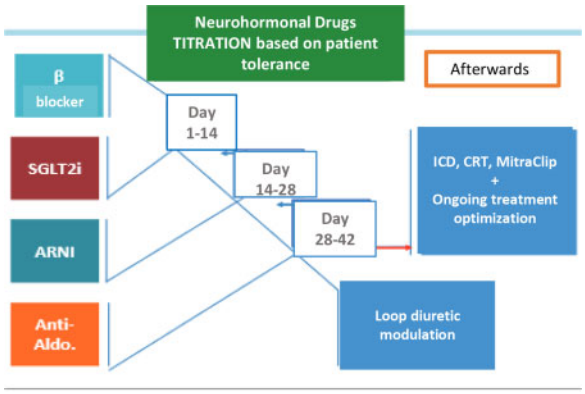

Figure 5 Care strategy for the treatment of reduced ejection fraction heart failure. The figure schematizes the order of adoption of each of the four classes of molecules that have been shown to significantly reduce adverse outcomes in reduced ejection fraction heart failure. Priority adoption of beta-blocker and sodium-glucose co-transporter type 2 (SGLT2i) therapy is justified for the beta-blocker by its greater efficacy in reducing overall mortality[30] and for SGLT2i by its efficacy on mortality and hospitalization outcomes for heart failure in the absence of confounding undesirable effects, particularly with regard to blood pressure and heart rate. The remaining therapy should be introduced on the basis of tolerance of the pharmacological effects induced by the angiotensin receptor inhibitor and neprilysin (ARNI) and the anti-aldosterone on blood pressure and renal function and in the absence of the need to increase therapy with loop diuretic, whose administration should be modulated to obtain the minimum effective dose. The time windows of 2 weeks are, therefore, to be considered arbitrary and susceptible to change based on prevailing clinical considerations that may recommend its reduction or require its extension.

from the introduction of therapy which justifies the timeliness of their introduction in the clinical management of the patient.[30] Furthermore, the same data indicate that the broadest benefit on expected outcomes can be achieved with the immediate adoption of all classes of drugs effective in the treatment of HFrEF. Unfortunately, this strategy is generally not feasible. Rather, the adoption of criteria is required to limit the undesirable effects that can be produced by these drugs, such as arterial hypotension, electrolyte imbalance, worsening of renal function, and much more.

Data from the literature concordantly indicate that in patients with HFrEF, the greatest impact on survival was achieved by beta-blockers. These drugs reduced the relative risk of overall mortality by 35%.[31] It is, therefore, logical to introduce beta-blockers as the first therapy, knowing full well that the efficacy of the drug depends on the administration of the maximum dose recommended in the guidelines or maximum tolerated by the patient. This requires the adoption of an intervention strategy adaptable to the needs that arise case by case since only careful management of titration allows to overcome possible side effects. For this reason, the concomitant association of the beta-blocker with an SGLT2i, a class of molecules that has little effect on blood pressure and limited undesirable effects, appears appropriate and consistent with the reduction in cardiovascular mortality demonstrated in the study with empagliflozin[22] (*Figure 5*). The beta-blocker up-titration phase can generally last from 1 to 2 weeks. In this time frame ARNI up-titration can be associated only if arterial pressure remains stably above 100 mm Hg, without the need to increase diuretic therapy. It has to be highlighted ARNI is a potent lowering pressure agent that could generate symptomatic hypotension, limiting its efficacy that is dose-related.[32] If the hypotensive effect of ARNI is not tolerable, its introduction should follow the pressure stabilization obtained with beta-blocker therapy and the modulation of diuretic therapy. Subsequently, based on data on renal function and plasma electrolyte stability, it would be appropriate to introduce anti-aldosterone therapy (*Figure 5*). The decision to place ARNI administration ahead of anti-aldosterone is consistent with evidence that ARNI lowered cardiovascular mortality, whereas anti-aldosterone eplerenone reduced the combined outcome for heart failure hospitalization and cardiovascular death in patients with heart failure and mild symptoms treated with beta-blockers (*Figure 5*).[33,34]

In the indicated course of care, the dose of loop diuretic, if any, will require adjustments consistent with the pharmacological effects induced by the different drugs that in addition to the hypotensive action associate the effect on natriuresis, hyperkalaemia, azotaemia, etc. due to the association of SGLT2i, ARNI, and aldosterone. This is to allow the introduction of life-saving neurohormonal therapies, using the minimum effective dose of a loop diuretic. The cardiologist must be aware that the ascertained lower tolerance of 'life-saving' drugs indicates a less favourable prognosis and, for this reason, the appropriate introduction of the various drugs is destined to change the future of patients.

Conclusions

Published data indicate that SGLT2i are drugs of great relevance for cardiovascular prevention and treatment. The safety profile documented by these molecules and the extension of their benefits starting from diabetics with primary risk to those with secondary risk as well as to diabetics and non-diabetics with chronic renal insufficiency and/or HFrEF, has led to a rapid spread in the cardiology field due to their timely association with other active drugs to which they add the benefit.

According to the analysis of the data from studies conducted with SGLT2i, the ANMCO Scientific Society declares its position on the use of this class of drugs by issuing the following recommendations:

(1) Canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin are indicated for the prevention of hospitalizations due to heart failure in T2D patients.
(2) Canagliflozin and dapagliflozin are recommended for the prevention of hospitalizations for heart failure in T2D patients with severe chronic kidney disease. Dapagliflozin has shown equal safety and efficacy even in non-diabetic patients with severe chronic renal insufficiency.
(3) Dapagliflozin and empagliflozin are both indicated for the treatment of diabetic and non-diabetic patients with HFrEF. The indication concerns the reduction of the combined risk of heart failure and cardiovascular death. Empagliflozin is effective and safe even in patients with eGFR $\geq$20 mL/min/1.73 m^2 reducing adverse renal events along with the combined primary outcome.
(4) Dapagliflozin and empagliflozin, in association with ARNI, have been shown to amplify the effectiveness of the therapy in reducing the primary combined outcome of cardiovascular death or hospitalization for heart failure. This association, however, will require reconsidering the significance of natriuretic peptides in the course of HFrEF treatment.

In conclusion, SGLT2i are the fourth class of drugs that has produced robust evidence in improving the prevention and treatment of HFrEF. The efficacy and safety data confirmed in all studies recommend the prescription of these drugs in diabetic and non-diabetic patients with HFrEF, in diabetic patients with cardiovascular disease, and non-diabetics with chronic renal failure to prevent heart failure. The action of these molecules takes place in a clinical context of undisputed competence in cardiology as well as in diabetology and nephrology. The immediate association with the beta-blocker renders the prescription of SGLT2i as an elective therapy for patients with HFrEF. This orientation would allow to reduce the entry times of the other drugs indicated by the guidelines and to reach the maximum benefit of the treatment in the shortest time. All this would have a highly positive impact on the outcomes of patients whose prognosis is known to be unfavourable. In diabetics treated with insulin, the cardiologist's prescription of SGLT2i must take into account the opinion of the diabetologist to limit the risk of hypoglycaemia and possible ketoacidosis.

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