The 2021 guidelines of the European Society of Cardiology on the diagnosis and therapy of heart failure (HF) introduced relevant changes in the pharmacological treatment of chronic HF. Among these, certainly the most significant was the introduction in the therapeutic flow-chart (with the highest recommendation level) of the sodium glucose co-transporter 2 (SGLT2) inhibitors. In fact, SGLT2 inhibitors are responsible for major paradigm shifts in the care of patients with or at high risk for HF, progression of chronic kidney disease, or both. SGLT2 inhibition demonstrated to improve cardiovascular outcomes in patients with HF over a wide range of ejection fractions, regardless of diabetic status, and have a strong nephroprotective effect. There are several important interactions between heart disease and kidneys disease. Indeed, acute or chronic dysfunction of the heart or kidneys can induce acute or chronic dysfunction in the other organ. The term ‘cardiorenal syndrome’ has been applied to these interactions. Since kidneys dysfunction in the setting of HF has a strong prognostic relevance, drugs that can slow down the decline of renal function are of utmost importance. Here, we discuss about the beneficial effects of SGLT2 inhibitors on the kidneys function in patients with HF and how these effects can improve both renal and cardiovascular outcomes.

Until the mid-1980s, heart failure (HF) was considered just a haemodynamic disorder due to reduced myocardial systolic function and correlated changes in the preload and afterload. In that period, cardiologists had only digitalis and diuretics in their therapeutic armamentarium, meanwhile betablockers and renin-angiotensin-aldosterone system (RAAS) inhibitors were regarded with scepticism.

The comprehension of the pivotal role of neuro-hormonal activation in HF pathophysiology completely revolutionized the treatment of HF, starting a new era. The neuro-hormonal system then became the main therapeutic target and angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARBs), mineralocorticoid receptor antagonists (MRAs), and betablockers were increasingly used in the treatment of HF patients. Several clinical trials demonstrated that neuro-hormonal blockade reduces symptoms of HF, reverses cardiac remodelling, and improves survival, becoming for these reasons the mainstay of the modern pharmacological approach to HF treatment. In spite of these progresses, HF remains a complex syndrome burdened by an unacceptable morbidity and mortality.

The euphoria unleashed by this ‘Copernican revolution’ in medical therapy gradually faded out over the years, replaced by the awareness that neuro-hormonal blockade was the larger and conclusive step of the fight to HF. No relevant progress or novelty were seen in HF medical treatment for almost 20 years, meanwhile other areas, such as cardiac electrophysiology and invasive cardiology, considerably innovated their techniques and technologies.
Moreover, previous observations showed that sacubitril/valsartan was superior to enalapril (relative reduction in the composite of cardiovascular death and HF hospitalization of 20%) in patients with HF due to reduced ejection fraction (HFrEF) were an injection of new enthusiasm in the HF community. It was necessary to wait 5 years more because a new class of antidiabetic drugs, the sodium glucose co-transporter 2 (SGLT2) inhibitors (also called gliflozins), demonstrated their ability to significantly reduce cardiovascular mortality and HF hospitalizations in patients with HFrEF, irrespective of diabetic status. These outstanding results were translated into the 2021 European guidelines on HF treatment introducing both sacubitril/valsartan and SGLT2 inhibitors in the therapeutic flow-chart of HFrEF as first-line drugs with the highest recommendation level.

While mechanisms of action of sacubitril/valsartan have been extensively described, it is still matter of debate how SGLT2 inhibitors impact in such effective way outcomes in HFrEF patient. Beyond the several neurohormonal, remodelling, diuretic, and metabolic mechanisms proposed (Figure 1), both experimental and clinical studies demonstrated a strong nephroprotective action of SGLT2 inhibitors, even higher than that demonstrated by ACEi or ARBs, considered the most effective drugs of the modern era for preserving kidney function in HF patient. Moreover, previous observations showed a large potential eligibility to these drugs, possibly anticipating their wide use in clinical practice.

Kidneys disease is one of the most common comorbidities in HF and is a powerful predictor of morbidity and mortality. There are several important interactions between heart disease and kidneys disease. The interaction is bidirectional, as acute or chronic dysfunction of the heart or kidneys can induce acute or chronic dysfunction in the other organ. The term ‘cardiorenal syndrome’ (CRS) has been applied to these interactions. CRS is further grouped into five subtypes based on disease acuity and sequential organ involvement. The most relevant to our discussion is the CRS type 2—i.e. chronic cardiac dysfunction that results in a sustained reduction in renal function—since the majority of studies on SGLT2i investigated chronic HF patients. The pathophysiology of this condition is complex and involves both haemodynamic (i.e. prerenal hypoperfusion, increased venous pressure) and non-haemodynamic pathways (i.e. persistent sympathetic nervous system and RAAS activation, chronic inflammation, imbalance in the proportion of reactive oxygen species/nitric oxide production).

Preserving renal function in HF patients is a key target of medical therapy and has been demonstrated to significantly improve outcomes in this cohort. In this setting, should be noted that clinical trials on gliflozins showed outstanding results on renal outcomes, basically making

**SGLT2-INHIBITORS: FAVORABLE EFFECTS**

**Cardiac effects**
- Reduction of myocardial hypertrophy and fibrosis
- Reverse cardiac remodeling
- Improved energy efficiency of myocardiocytes
- Reduction of oxidative stress
- Inhibition of the Na+/H+ exchanger
- Epicardial fat reduction

**Vascular and hemodynamic effects**
- Reduction of blood pressure
- Reduction of arterial stiffness
- Improvement of endothelial function
- Reduction of interstitial volume
- Reduction of pre and afterload
- Increased hematocrit
- Reduction of the activity of the sympathetic nervous system

**Metabolic effects**
- Weight loss
- Reduction of body and visceral adipose tissue
- Increased insulin sensitivity
- Increased muscle uptake of fatty acids
- Reduction of uricaemia
- Reduction of hepatic steatosis

*Figure 1* Non-renal mechanisms of action of gliflozins.
SGLT2 inhibitors the most promising drug for improving cardio-renal interactions. 10

The nephron has the ability to preserve its function, even in the presence of significant changes in blood pressure and/or volume, keeping the glomerular flow, and therefore the filtration rate, fairly constant. This homeostatic autoregulation is possible mainly due to the ‘tubuloglomerular feedback’, an adaptive mechanism intrinsic to the kidney that links the rate of glomerular filtration to the concentration of salt in the tubule fluid at the macula densa. Indeed, increased distal tubular sodium concentration causes the macula densa cells to swell, thus providing the signalling for constriction of the nearby afferent arteriole (through the activation of RAAS) and consequent decrease of glomerular filtration rate (GFR) of the same nephron. This forms a negative feedback loop in which the increased distal tubular load of sodium is decreased by reducing the GFR and subsequently allowing more time for sodium reabsorption because flow is slower. 15 In HF, the reduction of renal perfusion, secondary to low cardiac output, decreases the tubular load of sodium in the filtrate, activating the described negative feedback. This ends up in the vasodilatation of the afferent arteriole with a consequent rise in intra-glomerular pressure, increase of glomerular filtration, microalbuminuria (as a marker of the increased glomerular pressure), and finally the injury of the glomerulus. Indeed, the constant increase of intra-glomerular pressure that try to preserve the filtration rate, finally breaks the thin mesangial structure of the glomerular capillaries, ending up in tubuloglomerular fibrosis and end-stage renal failure. Gliiflozins contrast this counter regulatory mechanism blocking the SGLT2 and consequentially reducing the tubular reabsorption of glucose and sodium. The consequence is a large deliver of sodium to macula densa, which induce the vasoconstriction of the afferent arteriole of the glomerulus, therefore reducing its flow. The effect on macula densa also involves RAAS modulation, ending up in a progressive vasodilatation of the efferent arteriole. The result is a drop in intra-glomerular pressure, with a consequent protective effect on glomerular endothelium against podocyte injuries. 16

The reason why these antidiabetic drugs are so effective in HF could be also accounted by some similarities in the pathophysiology of kidneys in diabetes and HF. Indeed, in diabetics, there is a high level of glucose in the tubular lumen, freely filtered from the blood, that up-regulate the function of both the SGLT1 and SGLT2, therefore increasing the reabsorption of both glucose and sodium (since SGLT work as cotransporters). The increase in sodium reabsorption reduces its tubular concentration, that is sensed by macula densa as a signal of reduced perfusion. The consequence is the activation of RAAS, the vasodilatation of the afferent arteriole and the rise in intra-glomerular pressure, similar to what occurs in HF. 17

Another relevant renal effect of SGLT2 is the increased systemic availability of oxygen. It is well known that in the kidneys there are two types of SGLT: SGLT2 in the first part of the proximal tubule (S1 segment), reabsorbing up to 80% of the filtered glucose, and SGLT1 in the distal part of the proximal tubule (S2-S3 segments), responsible for the reabsorption of 10-15% of the filtered glucose. In patients with diabetes, the proximal tubules are overtaxed by excessive glucose reabsorption and the increased oxygen requirement causes tubulointerstitial hypoxia. Consequently, erythropoietin production is impaired because ‘neural crest-derived’ fibroblasts surrounding the damaged renal tubules undergo transformation into dysfunctional fibroblasts. SGLT2 inhibitors reduce the workload of the proximal tubules and improve tubulointerstitial hypoxia, allowing fibroblasts to resume normal erythropoietin production. The hypoxic microenvironment around the proximal tubules also increases afferent sensory nerve activity and provokes systemic sympathetic hyperactivity. Suppression of sympathetic hyperactivity by correcting renal abnormalities could be an important additional mechanism underlying the cardiovascular mortality benefit of gliiflozins. 18 The resulting elevation of haematocrit allows for larger systemic oxygen availability and participates to the improvement of functional capacity, quality of life and symptoms.

In conclusion, SGLT2 inhibitors are effective substances for the treatment of HFrEF and chronic renal disease, with impressive benefits on cardiorenal protection when these diseases coexist. In fact, gliiflozins may counteract the development of the cardiorenal syndrome through the restoration of tubuloglomerular feedback and the correction of well-established pathophysiological mechanisms such as tubular hypoxia and sympathetic overdrive.

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