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SGLT2-inhibitors: Should they be considered anti-remodeling drugs?

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Heart failure (HF) is a complex syndrome characterized by multiple aetiologies and a progressive clinical course with a strong impact in terms of morbidity, mortality and public health costs [1].

According to the neurohormonal hypothesis, HF with reduced ejection fraction (HFrEF) is considered a neurohormonal disease and HF patients benefit from the use of medications that interfere with and modulate the negative effects of neurohormonal systems (i.e. permanent renin–angiotensin–aldosterone system activation) [2]. The foundation of HF treatment includes the combination of well-known neurohormonal antagonists such as angiotensin receptor neprilysin inhibitors, beta-blockers, and mineralocorticoid receptor antagonists [2]. However, recently, Sodium-Glucose Cotransporter-2 Inhibitors (SGLT2-i) have emerged as a new additional cornerstone of HF treatment – they are now regarded as one of the four keystone drugs to be introduced as first line therapy in HFrEF (class I recommended drug)(2). Moreover, SGLT2-i have been shown to decrease combined endpoints of cardiovascular mortality and worsening HF regardless of ejection fraction (EF) [3], and also to prevent the onset of HF in patients who are at high cardiovascular risk [4].

The pathophysiologic mechanisms that may explain the benefit in clinical outcomes of the SGLT2-i in patients with HF are still incompletely understood. Therefore, it is of great interest to analyze the biological changes, which may occur in patients taking SGLT2-i because this may be helpful to elucidate how SGLT2-i may lead to improved cardiovascular outcomes. In this context, the meta-analysis published in the European Journal of Internal Medicine by Fan et al. [5] is timely and relevant because it evaluates the potential structural and functional impact of SGLT2-i in human heart giving possible translational understandings of the biologic consequences caused by SGLT2-i.

The authors included a total of 15 randomized controlled trials with a total of 1343 patients. SGLT2-i administration was associated with lower heart rate, lower left atrium volume index (LAVi), E/e', left ventricular mass index (LVMI), left ventricular end-systolic volume

(LVESV), and higher left ventricular ejection fraction (LVEF). These effects on cardiac dimensions and function were mainly significant with the use of empagliflozin, in patients with HF and in patients with HFrEF. Indeed in subanalysis improvement in LVEF was present in patients with HFrEF but not in patients with HF and preserved EF (HFpEF).

These findings should be interpreted within the context of some limitations, which include the presence of study heterogeneity among some statistically significant outcomes which may also derive from the inclusion of studies with small sample sizes and with variable follow up duration (ranging from 1.5 to 12 months). The absolute changes in the functional parameters could be considered modest, however, the meta-analysis included only randomized trial with mainly double-blind design, which may guarantee good quality of data. Importantly, these findings suggest that SGLT2-i may have an early influence on cardiac remodeling, which may help to explain one of the potential mechanisms related to the therapeutic advantages seen in patients with diabetes and or with HF. Indeed, cardiac remodeling plays a crucial role in determining patient morbidity and long-term outcomes. Successful therapy-induced reverse remodeling has largely been understood as responsible for the significant improvement in the prognosis of HF and it is currently acknowledged as a key prognostic tool and a measure of therapy efficacy. However important questions remain open: which are the potential direct and indirect mechanisms to explain the effects of SGLT2-i on myocardial remodeling? Moreover the fact that the presence in the human heart of SGLT2 receptors is uncertain and therefore SGLT2-i could not bind to cardiac tissue, make their capacity to exert a cardiac remodeling effect even more fascinating.

Reduction in preload, principally as a result of the drug's natriuretic and diuretic actions, could be hypothesized as one mechanism by which an SGLT2-i agent may reduce filling pressure and influence chambers volumes, especially in patients with elevated filling pressure and volumes at baseline. However, interestingly, despite the fact that SGLT2-i administration was associated with a reduction in chambers size, no

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overall association between SGLT2-i therapy and NT-proBNP levels was observed. Indeed, the effect of SGLT2-i on urinary sodium excretion and volume depletion appears to be modest at best [6], and the idea that a long-lasting diuretic impact would explain the advantages of SGLT2-i is not convincing to explain mortality benefits. However the diuretic effect may also be responsible for the antihypertensive effect of SGLT2-i, which may translates in LVMI reduction [7]. Moreover a diuresis-mediated haemoconcentration and SGLT2-i-associated increase in erythropoietin production SGLT2-i [8] may improve myocardial function by directly enhancing myocardial and systemic tissue oxygen delivery. Indeed a fascinating hypothesis it is a SGLT2-i mediated increase in cardiac bioenergetic state through a switch in myocardial “fuel” metabolism with a subsequent improvement in cardiac function and mechanical efficiency [9]. Urinary glucose excretion produced by SGLT2-i may mimic also a fasting state like response; this induces a low-grade ketonemia that favours the preferential myocardial utilization of ketone bodies over glucose (through beta-hydroxybutyrate metabolism) allowing greater ATP production with lower O₂ consumption. Moreover, the activation of nutrient deprivation signaling has the concomitant benefits of promoting autophagy and mitochondrial health, reducing the production of reactive oxygen species, and suppressing inflammation and fibrosis [10,11]. The enhancement of SIR-T1/AMPK (sirtuin-1/ Adenosine Monophosphate-activated protein kinase) and attenuation of Akt/mTOR (protein kinase B / Mammalian target of rapamycin) signaling which seems characteristic of SGLT2-i drugs, has been noted also with conventional neurohormonal antagonists suggesting that SGLT2-i may act also as a neurohormonal antagonists in chronic HF [12].

As discussed, it is plausible that SGLT2-i intervene with several mechanisms intersecting hemodynamic, metabolic, and neurohumoral pathways that go beyond the glucose-lowering effect, and recent data on the effects of empagliflozin and SGLT2-i on cardiac remodeling have been recently reported [7,13,14]. At the same time, together with some possible new and unconventional pathways, some “simple” established effects of SGLT2-I as modest weight loss and blood pressure reduction, diuretic and reno-protective effects may be specifically advantageous in patients with obesity, those with hypertension and patients with HF and renal disease.

In the era of the so called “precision medicine”, it is intriguing to have a such good treatment for HF patients but still be unable to determine with certainty the main pathophysiological mechanisms of their benefit. While the absence of a clear mechanism should not deter the prescription of SGLT2-i in HF patients given the demonstrated statistically significant reduction in hard endpoints, our effort to understand the pathophysiological disease process in our specific patient should remain a crucial moment in HF patient management, even in the era of positive mega trials. Indeed, aetiological characterization of structural and functional cardiac dysfunction remains of fundamental importance because also the removal of a triggering cardiac insult (uncontrolled hypertension, presence of ischemia, valvular heart disease, tachycardia-induced cardiomyopathy, toxin-induced cardiomyopathy, cardiac amyloids etc. as examples) may significantly contribute to reversal remodeling. This methodological approach should be coupled with the introduction of optimal medical therapy and in this perspective SGLT2-i seem a promising class of drug that could be added in the armamentarium of anti-remodeling drugs.

Further efforts should be directed to identify also asymptomatic patients, but with cardiac structural or functional abnormalities, which may represent subclinical LV systolic dysfunction, and expose the patients at high risk of HF. In these patients, often undetected and untreated, potential chronic deleterious pathomechanisms should be early blocked with stringent “preventive” strategies and with early initiation of appropriate pharmacological therapy in order to promote regression or prevent further cardiac remodeling. However, because some therapies may be less effective in lower-risk populations [15], further dedicated studies are needed to confirm the anti-remodeling effect of

SGLT2-i in different settings, and also to elucidate what are, most likely, the distinct beneficial mechanisms of action in various subset of patients where clinical benefits have been seen, especially in patients with HFpEF. Furthermore, cardiac reverse remodeling might be considered as a predictor of long-term treatment benefits on outcomes. In the meantime, SGLT2-i should be introduced early in the natural history of HF or in those at higher risk of developing HF considering the broad benefits showed by SGLT2-i in terms of clinical outcomes.

Declaration of Competing Interest

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