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REVIEW

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SGLT-2-Inhibitors in Heart Failure

Stefano Pandolfi and Giuseppe Cocco*

Cardiology office, Switzerland

Abstract

Heart failure is a frequent and highly debilitating pathology. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, β-blockers, mineralocorticoid receptor antagonists, and valsartan/sacubitril have been shown to reduce mortality in chronic heart failure with reduced ejection fraction. Recently, glifozines (SGLT-2 inhibitors) have become another effective therapeutic option for heart failure with reduced ejection fraction, in patients with and without diabetes mellitus. The review presents the effects of SGLT-2 inhibitors on the cardiovascular system and heart failure.

Keywords: *SGLT-2 inhibitors, Glifozines, Heart failure, Diabetes mellitus*

Introduction

Heart failure is a frequent disease with increasing prevalence, primarily due to an aging population. Indeed, 20% of people shall develop Chronic Heart Failure (CHF) during their lifetime and CHF is the predominant cause of hospitalization in individuals aged over 65 years [1-3]. For clinical purposes, considering the left ventricular Ejection Fraction (EF), CHF is classified as a) with reduced EF (HFrEF), i.e. EF < 40 %; b) with midrange EF, i.e. EF 40 to 49 %, and c) with preserved EF, i.e. EF >50% [4].

In patients with HFrEF Angiotensin-Converting Enzyme Inhibitors (ACEI), Angiotensin Receptor blockers (ARB), β-blockers, mineralocorticoid receptor antagonists, and valsartan/sacubitril (VALS/SCA) reduce mortality [4]. Nonetheless patients with CHF continue to have a poor prognosis, partially because many do not receive the effective doses of drugs [5].

Interplay between diabetes mellitus and CHF

Type 2 Diabetes Mellitus (T2DM) induces CHF by eliciting metabolic and inflammatory changes [6], consequently causing micro- and macrovascular complications through increased myocardial mass and diastolic stiffness, and promotion of endothelial dysfunction [7,8]. Compared to patients without CHF, those with CHF have a 4-fold prevalence of T2DM [9]. Also, compared with patients with T2DM, those without T2DM show a 2.5-fold increased risk for CHF. Indeed, in hospitalized patients with CHF the prevalence of T2DM is up to 40% higher [9,10] and in patients aged more than 65 years the coexistence of T2DM and CHF increases the mortality risk up to 10-fold [9,10].

Glifozines in the therapy of CHF

Drug repurposing refers to switching the therapeutic indication of a drug. Known examples of drug repurposing are: a) aspirin (switched from antipyretic therapy to an antiplatelet agent), b) hydroxychloroquine switched from malaria therapy to treat rheumatic diseases), and c) methotrexate (switched from cytostatic therapy to treat autoimmunity pathologies). Glifozines, i.e. sodium-glucose-2 transporters (SGLT-2) inhibitors, were introduced for the therapy of T2DM [11,12]. At present, 4 SGLT-2 inhibitors are marketed: canagliflozin, dapaglifozin, empaglifozin and ertuglifozin. Clinical studies have proven that these drugs exert beneficial effects in HFrEF and, with drug repurposing, SGLT-2 inhibitors have now a recognized role in cardiology [4,5,12,13].

Energetic needs of the heart

Under normal conditions the heart derives 70% of its energetic needs from Free Fatty Acids (FFA) and 30% from glucose [14]. FFA are overabundant in the presence of diabetes mellitus and CHF [15]. In the presence of hyperglycemia, the heart can reduce the oxidation of FFA, but overabundant FFA uncouple and impair the mitochondrial ATP production [16], thus reducing the heart's efficiency for satisfying its energetic needs [14-17]. As a consequence, perivascular and cellular fibrosis develop and reduce the myocardial elasticity and relaxation [15,18]. Furthermore, both T2DM and CHF increase the oxidative stress and enhance the Na+-glucose cotransport, therefore augmenting the myocardial Na+ concentration [19].

Effects of SGLT-2 inhibitors on the cardiovascular system

The SGLT-2 cotransporter is located in the proximal renal tubule and reabsorbs 90% of the filtrated glucose [5,12,13]. Independently from insulin, SGLT-2 inhibitors reduce the reabsorption of glucose and therefore, the body's amount of glucose thus decreasing the body's weight [20] and shifting the fuel energetics through the metabolism of ketones: for the heart the oxidation of ketones is more efficient that the oxidation of FFA and is advantageous for its energetic demands; furthermore, the reduced oxidation of FFA counteracts the oxidative stress [21].

SGLT-2 inhibitors exert a diuretic effect by inducing glycosuria and natriuria [5,11-13].

SGLT-2 inhibitors also exert hemodynamic effects by interacting with the renin-angiotensin-aldosterone system and increasing levels of circulating glucagon [5,11,12]. Indeed, several trials with dapaglifozin [22-26], and the EMPA-REG study with empagliflozin [21] have shown that these glifozines reduce the blood pressure values by 4%.

Furthermore, by a feed-back effect, the increased Na+ concentration in the macula dens constricts the vasa afferents, thus reducing the hydrostatic pressure of the glomeruli, opposing the glomerular hyperfiltration and reducing the albuminuria [5,9]. Because of these effects SGLT-2 inhibitors, as ACEI, ARB and VALS/SAC protect the renal function.

Furthermore, SGLT-2 inhibitors increase cardiac output, heart rate, O2 consumption, coronary blood flow. improve cardiac filling (by reduced preload and afterload), improve systolic and diastolic function, reduction in left ventricular mass, inhibition of cardiac fibrosis, improved myocardial autophagy, improve endothelial function, increase circulating proangiogenic progenitor cells and erythropoietin [5,11,13,16,21].

The cardiovascular effects of SGLT-2 inhibition are summarized in Table 1.

1.	Osmotic diuresis (by glycosuria and natriuresis).
2.	Improved myocardial energetics (by improved myocardial substrate metabolism).
3.	Reduction in myocardial Ca^{2+}/calmodulin-dependent protein kinase II activity and inhibition of myocardial Na^{+}/H^{+} exchange.
4.	Increased cardiac output, heart rate, O_2 consumption, coronary blood flow (by increased levels of circulating glucagon).
5.	Improved cardiac filling (by reduced preload and afterload).
6.	Improved systolic and diastolic function, reduction in left ventricular mass, inhibition of cardiac fibrosis, improved myocardial autophagy.
7.	Improved endothelial function.
8.	Increased circulating proangiogenic progenitor cells
9.	Increased erythropoietin

Table 1. Effects of SGLT-2 inhibition on cardiovascular system.

Effects of SGLT-2 inhibitors on the cardiovascular system

The CANVAS trial [27,28] studied the effects of the SGLT2-inhibitor canagliflozin in patients with T2DM with established atherosclerotic disease or at high risk for cardiovascular events and has proven that the drug exerts significant beneficial effects.

The DECLARE-TIMI 58 trial [22-26] studied the effects of the SGLT-2 inhibitor dapaglifozin on CHF in patients with T2DM with either multiple cardiovascular risk factors (59.4%) or established atherosclerotic disease (40.6%). The trial proved that dapaglifozin reduces significantly CHF or cardiovascular death and lowers the rate of CHF; the benefit was consistent in patients with and without recognized atherosclerotic disease and also without a previous history of CHF. Recent sub-analyses of the DECLARE-TIMI 58 trial [24,25] have shown that dapaglifozin reduced CHF both in patients with and without a previous myocardial infarction, and in patients with and without peripheral artery disease. Also, it has been proven that, in patients with HFrEF, dapaglifozin improves outcome irrespective of NT-proBNP concentration [26].

The EMPRISE study [29] and the EMPA-REG OUTCOME [29-33] studied the effects of the SGLT-2 inhibitor empagliflozin in patients with T2DM and established atherosclerotic disease. Empagliflozin significantly reduced CHF. The cardiovascular benefits were consistent when adjusted for baseline glycated hemoglobin levels, and were independent of glucose levels and renal function [32,33].

A recent meta-analysis [34] showed that SGLT-2 inhibitors as a class reduce the risk of CHF by 31%; this risk reduction (ca. 30% reduction in all groups) was consistent in patients with and without recognized atherosclerotic disease and in patients with and without a history of CHF. Lastly, the OPTIMIZE-HF trial [9], the REACH registry [10], and the ongoing EMPRISE trial [29] have also confirmed the positive effects of SGLT-2 inhibitors on CHF prevention in patients with T2DM irrespective of the atherosclerotic disease status. Of note, the effect of SGLT-2 inhibitors in reducing CHF is rapid and manifests before significant metabolic effects are detectable. This indicates that the benefits of SGLT-2 inhibitors are mainly related to hemodynamic and metabolic effects and not directly related to the effects on glycemia [10].

Safety of SGLT-2 inhibitors

The current evidence in patients with T2DM suggests that SGLT-2 inhibitors are generally well tolerated [5,11]. However, genital infections are a common side effect of SGLT-2 inhibitors, which typically manifests early during treatment exposure [11,31-33]. Infection can be prevented if appropriate hygiene measures are taken, and that, should infection occur, it can be effectively managed [35,36].

Diabetic ketoacidosis can occur in diabetic patients treated with SGLT-2 inhibitors, although cases are very rare and mainly associated with the use of insulin [5,11,31-33]. Current guidelines suggest that, should symptoms of diabetic ketoacidosis arise in patients receiving SGLT-2 inhibitors, treatment should be discontinued immediately [36-38].

In the CANVAS trial [27-28] the overall incidence of lower limb amputations was low, but compared to placebo, the frequency of these events was significantly greater in patients treated with canagliflozin. Accordingly, caution is needed when prescribing SGLT-2 inhibitors in patients at high risk of amputation [38]. Of note, neither the studies EMPA-REG OUTCOME with canagliflozin [21] nor the DECLARE-TIMI 58 trial with dapaglifozin [23-26] showed an increase in the incidence of amputations. Furthermore, a meta-analysis [21,22] of the results from the CANVAS [23,24], EMPA-REG OUTCOME [21] and DECLARE-TIMI 58 [21,22] trials showed significant heterogeneity among the three trials with respect to amputations, suggesting that an increased risk of these events was evident only in the CANVAS trial (with canagliflozin).

Data are also inconsistent with regard to risk of bone fractures during SGLT-2 inhibitor treatment. Although in the CANVAS trial [23,24] the incidence of fractures was significantly greater with canagliflozin versus placebo this finding was not mirrored in the EMPA-REG OUTCOME trial [21], the DECLARE-TIMI 58 trial [21,22], and the CANVAS-R trial [28], or in registry data [38].

Conclusion

CHF is a highly debilitating pathology affecting millions of individuals and his prevalence is going to increase due to aging population. ACEI, ARB, β-blockers, mineralocorticoid receptor antagonists and VALS/SAC have been shown to reduce mortality in patients with HFrEF, unfortunately not in those with preserved EF. SGLT-2 inhibitors have emerged as another therapeutic option in the treatment of HFrEF, both with and without T2DM. Ongoing trials are assessing several aspects of SGLT-2 inhibitors in the treatment of different subtypes of CHF and may help to provide the answer the unknown questions..

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Correspondence: G. Cocco, M.D, EFESC, Cardiology Office, Marktgasse 10A, CH-4310 Rheinfelden, Switzerland, Tel: 0041 831 45 55, Fax: 0041 833 97 56

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