SGLT2 inhibitors

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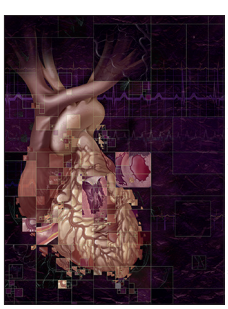
SGLT2 inhibitors: expanding their Empire beyond diabetes

The path from initial discovery to the realisation of SGLT2 inhibitors as a foundational therapy for chronic kidney disease and heart failure, irrespective of diabetes status, has been circuitous and serendipitous. In 1835, French chemists isolated the naturally occurring non-selective SGLT1/2 inhibitor phlorizin from apple tree bark, with subsequent experiments detailing its glycosuric properties.[1] However, it took more than 150 years to clarify the role of SGLTs as key protein regulators of glucose handling in the gut and kidneys and to realise the potential of SGLT2 inhibition as a novel approach to diabetes therapy.[1] Interest in pharmacologically inhibiting SGLT activity increased with the recognition that patients possessing an inherited inactivating mutation of SLGT2 (known as familial renal glycosuria), who have resultant lifelong so-called benign glycosuria, did not have serious adverse clinical consequences. Since phlorizin is non-selective, not well tolerated, and has low oral bioavailability, synthetic SGLT2 inhibitors were developed. Since 2012, four SGLT2 inhibitors have been granted marketing authorisation by the European Medicines Agency and the US Food and Drug Administration for management of hyperglycaemia in type 2 diabetes.

As of 2015, the narrative of SGLT2 inhibitors as cardiorenal drugs accelerated with the unexpected benefits reported in the EMPA-REG OUTCOME trial.[2] In this placebo-controlled cardiovascular outcome trial among 7020 patients with type 2 diabetes and established atherosclerotic vascular disease, empagliflozin significantly reduced major adverse cardiovascular events. Remarkably, benefit was driven by unprecedented reductions in hospital admission for heart failure and cardiovascular mortality, but not by a reduced incidence of myocardial infarction or stroke.[2] Moreover, empagliflozin seemed to slow deterioration in kidney function, and the heart failure benefits persisted in the presence of renal impairment. Cardiovascular outcome trials of three other SGLT2 inhibitors in patients with type 2 diabetes and high cardiovascular risk have since varied in the extent to which they have confirmed the various benefits seen in EMPA-REG OUTCOME.[3] However, the benefits with respect to heart failure and chronic kidney disease have been fairly consistent across all drugs in the class. Since the cardioprotective and renoprotective effects were independent of glucose lowering, a question arose over whether SGLT2 inhibitors might be repurposed for the treatment of chronic kidney disease and heart failure, irrespective of diabetes status. This question has since been answered in the affirmative, with positive results reported from three dedicated outcome trials that enrolled patients with and without type 2 diabetes (receiving excellent background therapy): DAPA-CKD[4] in patients with chronic kidney disease, and DAPA-HF[5] and EMPEROR-Reduced[6] in patients with heart failure and reduced ejection fraction.

Although appreciation of the cardiorenal benefits of SGLT2 inhibitors has matured, there remains considerable debate regarding the potential glucose-independent mechanisms by which these benefits are conferred.[3] Herein, it is relevant to first recognise the close link between heart failure and renal disease (ie, cardiorenal



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axis). As renal disease progresses, fluid volume is retained, which in turn promotes the development and worsening of heart failure. The changes in central venous pressure and arterial blood pressure in heart failure reduce renal perfusion pressures and thereby worsen renal function. This vicious cycle leads to stimulation of proinflammatory cytokines and neurohormonal activation (causing sodium and water reabsorption), which might further worsen cardiac function. Thus, preserving kidney function through both haemodynamic and non-haemodynamic mechanisms,[3] is an important pathway by which SGLT2 inhibitors might protect the heart. However, several other mechanisms have been proposed, including a reduction in blood pressure, a shift towards ketone bodies as a metabolic substrate, increases in haematocrit, decreases in systemic and tissue inflammation and serum uric acid concentrations, attenuation of sympathetic nervous system activity, off-target inhibition of cardiac sodium–hydrogen exchangers, promotion of cardiac reverse remodelling, and reduction of epicardial fat.[3] But perhaps the most prominent proposed mechanisms are the natriuresis and osmotic diuresis and linked differential volume regulation hypotheses, which could account for the rapid onset of heart failure benefits seen in clinical trials. In *The Lancet Diabetes & Endocrinology,* Jesper Jensen and colleagues[7] investigate the volume regulation hypothesis in a prespecified renal substudy of the Empire HF trial.

Dysregulation of sodium and fluid homeostasis is central in in the pathophysiology of heart failure. The resulting congestion (in both vascular compartment [plasma volume] and interstitial space [extracellular volume]) is a main driver of symptoms and hospital admissions, is strongly associated with mortality, and is a major target for heart failure treatment. Managing congestion is usually achieved through use of loop diuretics, which counteract the increased sodium avidity in heart failure, but at the expense of neurohormonal activation (which might blunt effectiveness). SGLT2 inhibitors can, in part, be regarded as diuretic drugs, but are suggested to differ importantly from classic diuretics. SGLT2 inhibitors promote osmotic diuresis, principally due to glycosuria and, to a lesser extent, initial and mild natriuresis, by acting on the proximal tubule. Generally, within the first days of treatment, this activity leads to an increase in urine volume of 0·5–1·0 L/day, and reductions in measured plasma volume in patients with type 2 diabetes with and without heart failure with reduced ejection fraction.[8] Ultimately, this effect might haemodynamically protect against heart failure by improving filling conditions and reducing whole-body sodium content without neurohormonal activation in view of its mode and location of action. In fact, mediation analyses from the EMPA-REG OUTCOME trial suggested that the consistently observed haemoconcentration upon SGLT2 inhibition (presumed secondary to volume contraction) accounted for about 50% of the cardiovascular benefit.[9] However, SGLT2 inhibitors have also been proposed to directly promote erythropoietin production and thereby further increase haematocrit.[3] An interesting theory stems from a mathematical modelling study, in which treatment with dapagliflozin (*vs* bumetanide) was predicted to result in greater fluid clearance from the interstitial fluid space than from the circulation, potentially resulting in congestion relief with minimal impact on arterial filling, neurohormonal activation, and organ perfusion.[10] This differential volume regulation might be due to osmotic diuresis and linked greater electrolyte-free water clearance (at least initially) with SGLT2 inhibitors compared with traditional diuretics.

In the new substudy of the placebo-controlled Empire HF trial,[7] treatment with empagliflozin for 12 weeks robustly reduced the estimated extracellular fluid volume (adjusted mean difference –0·12 L, 95% CI –0·18 to –0·05; p=0·00056) and estimated plasma volume (–7·3, –10·3 to –4·3; p<0·0001) in patients with heart failure and reduced ejection fraction, most of whom did not have diabetes, and who were treated with guideline-directed background heart failure therapy. These findings provide mechanistic support for the benefits of SGLT2 inhibitors in this population with respect to heart failure morbidity and mortality seen in the DAPA-HF[5] and EMPEROR-Reduced[6] trials. Although the enrolled patients without type 2 diabetes in the substudy of Empire HF probably had less osmotic diuresis than would hyperglycaemic patients with type 2 diabetes in other studies, the effect size of empagliflozin in terms of volume contraction was similar to that reported previously in patients with type 2 diabetes and heart failure with reduced ejection fraction, which requires further study.[7] Unfortunately, some methodological issues with the trial design cause uncertainty regarding the absolute magnitude of volume changes, and the hypothesis that

SGLT2 inhibitors reduce interstitial fluid to a larger extent than plasma volume cannot be definitively rejected or confirmed on the basis of the present study.[7] Specifically, caveats in estimation of volume endpoints and absence of data for sodium balance might hamper interpretation. The Strauss formula used to estimate plasma volume in the study involves haematocrit and haemoglobin, and demands the assumption of constant erythrocyte production, which might be violated in view of the potential primary erythropoietic response with the use of SGLT2 inhibitors.

Based on the cardiorenal benefits seen in cardiovascular outcome trials and in chronic kidney disease and heart failure outcome trials, further elucidation of the mechanisms driving the multisystem benefits of SGLT2 inhibitors in patients with and without type 2 diabetes are of increasing relevance. Such studies might not be necessary to drive implementation, but they are useful for advancing knowledge that will allow innovation in future therapies and their combinations, and for improving communication regarding the rationale for use of these drugs with clinicians and patients. There is little time to waste, as SGLT2 inhibitors have been thrust into the top tier of drugs for potentially treating millions of patients with cardiac or renal disease worldwide, with drug labels rapidly expanding indications and international guidelines starting to adopt recommendations for the use of SGLT2 inhibitors beyond patients with diabetes.

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Public health emergency or opportunity to profit? The two faces of the COVID-19 pandemic

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"Never let a good crisis go to waste".[1] The exploitation of disasters by those in powerful positions is not a modern phenomenon. For centuries, multinational corporations have demonstrated a remarkable ability to turn the misfortunes of others into opportunities for lucrative gains. In the 17th century, the English and Dutch East India Companies, among others, were at the forefront of the European colonial expansion, seeking opportunities to exploit cheap labour and natural resources in foreign lands. Later, England's Royal African Company would provide the logistics that made the Atlantic slave trade possible. In the 20th century, World War 1 brought new opportunities. While arms traders were the obvious beneficiaries, tobacco manufacturers were not far behind. When General John J "Black Jack" Pershing, commander of US forces in World War 1, was asked what he needed to win the war, he replied "tobacco, as much as bullets".[2] More recently, the Canadian writer Naomi Klein has coined the term "disaster capitalism", describing how corporations have profited from natural