Sodium-glucose co-transporter 2 inhibitor therapy: mechanisms of action in heart failure

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ABSTRACT
Patients with type 2 diabetes mellitus are at a higher risk of developing heart failure compared with the healthy population. In recent landmark clinical trials, sodium-glucose co-transporter 2 (SGLT2) inhibitor therapies improve blood glucose control and also reduce cardiovascular events and heart failure hospitalisations in patients with type 2 diabetes. Intriguingly, such clinical benefits have also been seen in patients with heart failure in the absence of type 2 diabetes although the underlying mechanisms are not clearly understood. Potential pathways include improved glycaemic control, diuresis, weight reduction and reduction in blood pressure, but none fully explain the observed improvements in clinical outcomes. More recently, novel mechanisms have been proposed to explain these benefits that include improved cardiomyocyte calcium handling, enhanced myocardial energetics, induced autophagy and reduced epicardial fat. We provide an up-to-date review of cardiac-specific SGLT2 inhibitor–mediated mechanisms and highlight studies currently underway investigating some of the proposed mechanisms of action in cardiovascular health and disease.

INTRODUCTION
Heart failure is a global pandemic and the current worldwide prevalence of heart failure is estimated at 64.34 million cases accounting for 9.91 million years lost due to disability.1 The prevalence of heart failure increases with age and is associated with other comorbidities like type 2 diabetes mellitus, hypertension and obesity. People with type 2 diabetes are 2.5 times more likely to develop cardiac failure than people without diabetes.2 Concerns regarding cardiovascular adverse events associated with type 2 diabetes have conventionally focused around atherosclerotic events, but with major improvements in the treatment of myocardial infarction, stroke and limb ischaemia over the past few decades, heart failure is increasingly being recognised as one of its earliest and most serious complications.3

The problems of heart failure associated with diabetes are compounded by the fact that several therapeutic glucose-lowering agents are either ineffective or harmful. Thiazolidinediones, such as pioglitazone, activate peroxisome proliferator-activated receptor gamma (PPAR gamma) to improve insulin sensitivity. However, they also cause increased sodium and fluid retention, thereby leading to a 42% increased risk of incident heart failure.4 In contrast, dipeptidyl peptidase 4 inhibitors appear to have a neutral effect on major adverse cardiovascular events although one agent of this class, saxagliptin, has been associated with a 27% increase in hospitalisation for heart failure and a 22% increase in cardiovascular mortality.5 A meta-analysis of more than 24 000 individuals from four large clinical trials reported that the use of insulin for type 2 diabetes was associated with a 27% increase in all-cause mortality and 23% increase in hospitalisation for heart failure.6 Looking at 100 000 individuals in the ‘real-world’ setting of an administrative database, such treatment was associated with an odds ratio of 2.02 for all-cause mortality and 1.42 for heart failure hospitalisation.7 Therefore, there is an unmet need for safer and more effective glucose-lowering therapies for patients with type 2 diabetes and heart failure.

Sodium-glucose co-transporter 2 inhibitor therapy
Sodium-glucose co-transporter 2 (SGLT2) inhibitors are a new class of glucose-lowering drugs. They work by blocking the low-affinity, high-capacity SGLT2 protein located in the proximal convoluted tubule of the nephron. The SGLT2 protein is responsible for the resorption of approximately 90% of filtered glucose while the remainder is reabsorbed by SGLT1 proteins found on the distal part of the proximal convoluted tubule. SGLT2 inhibition results in glycosuria (and natriuresis as the protein is a co-transporter), thereby lowering plasma glucose concentrations7,8 This mechanism is unique compared with all other glucose-lowering agents as it does not interfere with endogenous insulin or incretin pathways.

In recent cardiovascular outcome trials, SGLT2 inhibitors are associated with 30%–35% lower risk of hospitalisation for heart failure.9–12 Other glucose-lowering agents appear to be more potent than SGLT2 inhibitors, but fail to reduce cardiovascular risk, particularly with regard to heart failure outcomes. Moreover, although the glucose-lowering efficacy of SGLT2-inhibitor therapy declines at lower estimated glomerular filtration rates, its cardiovascular benefits are remarkably preserved, even in patients with renal impairment. This implies differing mechanisms of action in glycaemic control and cardiovascular risk reduction.13 These potential cardioprotective mechanisms remain incompletely understood and we aim to describe some of the key theories (table 1) in this review as this could pave the way for targeting future novel therapies for both heart failure and type 2 diabetes.

SGLT2 inhibitor therapy and cardiovascular outcomes
In response to concerns about the increased cardiovascular risk associated with some treatments for
co-administration of loop diuretic therapies, the contribution of osmotic diuresis towards improved heart failure outcomes remains unclear. Glycosuria in the context of SGLT2-inhibitor therapy administration occurs due to a twofold to threefold increase in the filtered and resorbed glucose in presence of hyperglycaemia. Therefore, glycosuria and osmotic diuresis associated with SGLT2 inhibition are dependent on blood glucose concentrations and hence this does not explain the similar benefits observed in normoglycaemic patients with heart failure in the absence of diabetes mellitus.15 16 Although SGLT2-inhibitor therapy is associated with natriuresis and reduction in plasma volume,9 10 it is unclear if these benefits are sustained as there were no differences seen in serum N-terminal pro B-type natriuretic peptide (NT-pro BNP) concentrations in patients with chronic stable heart failure despite improvements in heart failure status.20 Moreover, there was no change in the diuretic dose among most participants during follow-up in the DAPA-HF trial, and the mean diuretic dose was similar between dapagliflozin and placebo groups.13

Recent studies have highlighted important differences between the diuretic effect of SGLT2 inhibitors and loop diuretic therapies. Using mathematical modelling, a recent study showed that both dapagliflozin and bumetanide were associated with a reduction in sodium and interstitial fluid. However, dapagliflozin had little or no effect on plasma volume whereas bumetanide was associated with reductions in intravascular volume, which can pose challenges in the context of hypoperfusion.21 This predicted selectivity of SGLT2 inhibitors for interstitial fluid is supported by observations from ‘the renal and cardiovascular effects of dapagliflozin and placebo groups.13

The desirable cardiovascular effects seen with SGLT2 inhibitor therapy are multifactorial, but key pathways involved are currently being explored. Some of the conventional theories are discussed in the following section.

Conventional potential mechanisms of benefit with SGLT2 inhibition

The desirable cardiovascular effects seen with SGLT2 inhibitor treatment may be multifactorial, but key pathways involved are currently being explored. Some of the conventional theories are discussed in the following section.

Diuretic and antihypertensive effects

It has been suggested that SGLT2 inhibitors improve cardiovascular outcomes due to their diuretic and antihypertensive effects (figure 1). SGLT2 inhibitors cause osmotic diuresis due to glucosuria and natriuresis, although the degree of diuresis and its composition (ie, the amount of natriuresis compared with aquaresis) remains to be established.19 Indeed, in the context of

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## Table 2: Summary of large clinical trials of the SGLT2-inhibitor class

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<th>Study title</th>
<th>Study type</th>
<th>Number of patients enrolled</th>
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| EMPA-REG OUTCOME⁶⁵ | RCT 1:1:1 | 7028 | 3.1 | Patients with:  
  ► Type 2 diabetes mellitus  
  ► Established CV disease  
  ► Body mass index ≤35 kg/m²  
  ► Glomerular filtration rate (GFR) >30 | ▶ Reduction in CV death, non-fatal myocardial infarction or stroke in empagliflozin group vs placebo (HR 0.86, 95% CI 0.74 to 0.99) | ▶ All-cause mortality lower in empagliflozin vs placebo: p<0.01  
  ▶ HF hospitalisation lower in empagliflozin group vs placebo (HR 0.65, 95% CI 0.50 to 0.85)  
  ▶ HF hospitalisation and CV death (excluding fatal stroke) lower in empagliflozin group vs placebo (HR 0.66, 95% CI 0.55 to 0.79) |
| CANVAS trial⁶⁶ | RCT 1:1:1 | 10142 | 2.4 | Patients with:  
  ► Type 2 diabetes mellitus  
  ► High CV risk | ▶ CV death, non-fatal myocardial infarction or stroke (HR 0.86, 95% CI 0.75 to 0.87) | ▶ Reduction in CV death and HF hospitalisation greater in patients with known heart failure (HR 0.78, 95% CI 0.67 to 0.91) |
| DECLARE-TIMI 58⁶⁷ | RCT | 17160 | 4.2 | Patients with:  
  ► Type 2 diabetes mellitus  
  ► Established CV disease or multiple risk factors | ▶ CV death, non-fatal myocardial infarction or stroke (HR 0.93, 95% CI 0.84 to 1.03) | ▶ Reduction in CV death or HF hospitalisation in dapagliflozin vs placebo (HR 0.83, 95% CI 0.73 to 0.95)  
  ▶ Reduction in HF hospitalisation (HR 0.73, 95% CI 0.61 to 0.88)  
  ▶ Reduction in death due to renal or CV causes (HR 0.53, 95% CI 0.43 to 0.66) |
| VERTIS CV trial⁶⁸ | RCT 1:1:1 | 8246 | 3.5 | Patients with:  
  ► Type 2 diabetes mellitus  
  ► Established CV disease | ▶ CV death, non-fatal MI or stroke (HR 0.97, 95% CI 0.85 to 1.11) | ▶ Lower HF hospitalisation in ertugliflozin group vs placebo (HR 0.70, 95% CI 0.54 to 0.90) |
| DAPA-HF trial⁶⁹ | RCT | 4744 | 1.5 | Patients with:  
  ► Symptomatic heart failure  
  ► Left ventricular ejection fraction (LVEF) ≤40%  
  ► 50% patients with type 2 diabetes | ▶ Reduction in CV death, urgent heart failure visit or HF hospitalisation in dapagliflozin group vs placebo (HR 0.74, 95% CI 0.65 to 0.85) | ▶ Fewer HF symptoms reported on KCCQ in dapagliflozin group vs placebo (HR 1.18, 95% CI 0.65 to 0.83)  
  ▶ Reduction in CV death and HF hospitalisation (HR 0.73, 95% CI 0.65 to 0.85)  
  ▶ Benefits seen in both diabetics and non-diabetics |
| EMPEROR-Reduced trial⁷⁰ | RCT 1:1:1 | 3730 | 1.5 | Patients with:  
  ► Chronic HF, NYHA class II/III/IV  
  ► LVEF ≤40%  
  ► HF hospitalisation within 12 months  
  ► 50% patients with type 2 diabetes | ▶ CV death or heart failure hospitalisation, for empagliflozin vs placebo (HR 0.75, 95% CI 0.65 to 0.86) | ▶ Composite renal outcome (chronic haemodialysis, renal transplantation, profound sustained reduction in eGFR): reduced in empagliflozin group vs placebo (HR 0.50, 95% CI 0.32 to 0.77)  
  ▶ All-cause mortality lower in empagliflozin group vs placebo (HR 0.92, 95% CI 0.77 to 1.10)  
  ▶ Benefits seen in both diabetics and non-diabetics |

CI, Confidence interval; CV, cardiovascular; HF, heart failure; HR, Hazard ratio; KCCQ, Kansas City Cardiomyopathy Questionnaire; MI, myocardial infarction; NYHA, New York Heart Association; RCT, randomised controlled trial.
in the absence of diabetes which would be an argument against weight reduction being the primary mechanism of benefit with SGLT2-inhibitor therapy. Moreover, despite the high prevalence of obesity in heart failure, there is little definitive evidence regarding the impact of weight loss on cardiac function, quality of life and exercise tolerance in patients with heart failure. Therefore, weight loss alone cannot explain SGLT2 inhibition–related benefits in heart failure.

**Increase in haematocrit**
SGLT2-inhibitor therapy is associated with increases in renal erythropoietin production, red blood cell mass and haematocrit. Such changes may contribute to improvements in cardiovascular outcomes although similar increases in haematocrit have been reported with darbepoetin alfa and no mortality benefit was observed in patients with left ventricular systolic dysfunction.

Overall, many of these mechanisms and recognised factors have been associated with reductions in cardiovascular risk (figure 1). However, the modest improvements seen with SGLT2-inhibitor therapy in these domains do not provide a clear explanation for the striking benefits observed in heart failure events in the large clinical trials and key pathways involved still require further investigation.

**Novel potential mechanisms of benefit with SGLT2 inhibition**

**Direct cardiac effects of SGLT2-inhibitor therapy**
Cardiac hypertrophy, fibrosis and inflammation lead to adverse cardiac remodelling in heart failure, and this is a key contributor to its severity. Some pre-clinical and clinical studies have demonstrated a role for SGLT2-inhibitor therapies in reversing adverse cardiac remodelling. Although this effect has been observed in patients with type 2 diabetes and left ventricular hypertrophy, it has not been seen in patients with heart failure. This is intriguing, particularly, since the majority of its cardiovascular benefits have been around heart failure outcomes. This raises the possibility that, in the context of heart failure, SGLT2 inhibition may have novel direct cardioprotective effects, beyond that of ventricular loading and remodelling (figure 2).

**Improved myocardial energetics**
Under physiological conditions, nearly 90% of cardiac energy is derived from mitochondrial oxidative metabolism and fuel is derived from free fatty acids, glucose and to a lesser extent from lactate, ketones and amino acids. In type 2 diabetes or heart failure, there is dysregulated fatty acid oxidation and impaired glucose uptake or oxidation causing myocardial dysfunction. In this setting of restricted fuel selection and low energetic reserve, ketone bodies are a ‘super-fuel’, producing ATP more efficiently than glucose or free fatty acids. SGLT2-inhibitor therapy increases hepatic synthesis and decreases the urinary excretion of ketones producing a mild and persistent state of hyperketonaemia. Under these conditions, beta-hydroxybutyrate (ketone body) is freely taken up by the heart and kidney and oxidised in preference to fatty acids and glucose. In mouse hearts, beta-hydroxybutyrate increases external cardiac work and reduces oxygen consumption, thereby improving cardiac efficiency. It has thus been hypothesised that the cardiovascular benefits of SGLT2-inhibitor therapy may be related to a shift in cardiac metabolism away from fatty acids and glucose oxidation towards more oxygen-efficient ketone bodies, thereby improving cardiac efficiency.

**Improved ionic homeostasis in the myocardium**
Calcium homeostasis in the myocardium is a finely balanced mechanism, essential for efficient excitation–contraction coupling. During systole, calcium is actively transported into the cardiomyocyte via L-type voltage-gated calcium channels where it binds to ryanodine receptors on the sarcoplasmic reticulum resulting in ‘calcium-induced calcium release’. This, in turn, activates calcium-sensitive contractile proteins (troponin C, troponin NC) which leads to myocardial contraction. In the setting of type 2 diabetes and heart failure, there is upregulation...
of both sodium-hydrogen exchanger 1 and SGLT1 resulting in markedly increased intra-cytosolic sodium content.\(^{40,41}\) This promotes calcium influx via the membrane bound sodium–calcium exchanger and calcium efflux from the mitochondria (into the cytosol) via mitochondrial sodium–calcium exchanger transporters. The elevated baseline intracellular calcium content results in reduced calcium transients and smaller sarcoplasmic reticulum calcium stores in diabetic cardiomyocytes, thereby inhibiting contractile function.\(^{42}\)

SGLT2-inhibitor therapy reduces cardiac cytosolic sodium content by inhibiting sodium–hydrogen exchanger 1 and SGLT1 transporters in diabetic rat and mice myocytes, thereby reversing calcium overload.\(^{42,47}\) Intriguingly, this effect on sodium–hydrogen exchanger 1 and SGLT1 is independent of diabetes status.\(^{48}\) These findings suggest that altered myocardial calcium handling is involved in the development of diabetic cardiomyopathy and heart failure, and that SGLT2-inhibitor therapy may improve the electrochemical characteristics in the failing myocardium which may contribute to its cardiovascular benefit.\(^{42}\) An ongoing clinical trial will assess the role of altered calcium handling in diabetic cardiomyopathy and heart failure and determine the effects of SGLT2-inhibitor therapy on cardiac calcium homeostasis (NCT04591639). The study uses a novel imaging approach called manganese-enhanced magnetic resonance imaging (MRI). Manganese acts as a calcium analogue and administration of the manganese-based contrast agent results in a marked shortening of the T1 relaxation times in myocardium with intact calcium handling. The rate of T1 shortening therefore acts as a measure of myocardial calcium handling, and this is the primary endpoint of the study.

**Figure 2** Schematic diagram showing proposed novel mechanisms of action of SGLT2 inhibitors in heart failure. AMPK, adenosine monophosphate-activated protein kinase; HIF, hypoxia-inducible factor; NHE, sodium-hydrogen exchanger; SGLT, sodium-glucose co-transporter; SIRT, sirtuin.

**Autophagy**

Autophagy is the process by which cellular physiological equilibrium is maintained by removal of potentially dangerous constituents and recycling of cellular components as an adaptive response to metabolic stress including hypoxia and starvation.\(^{49}\) Experimental induction of autophagy has favourable effects in heart failure as it leads to efficient disposal of dysfunctional mitochondria, which are a major source of reactive oxygen species, promoting oxidative stress and inflammation.\(^{50}\) The pathways of autophagy induction involve activation of adenosine monophosphate-activated protein kinase (AMPK), sirtuin-1 (SIRT1) and hypoxia-inducible factors (HIF-1alfa and HIF-2alfa).\(^{51}\) It has been proposed that SGLT2 inhibitors may induce autophagy by simulating nutrient depletion by periods of increased catabolism due to constant glucosuria. Indeed, various SGLT2-inhibitor therapies have upregulated the expression of AMPK, SIRT1 and HIF-1 alfa.\(^{52,53}\) These actions might explain the phenomenon of autophagy and associated cardiovascular benefits with SGLT2-inhibitor therapy.\(^{54}\)

**Altered adipokine regulation**

Leptin and adiponectin are cytokines produced exclusively by adipocytes. These ‘adipokines’ are essential in the regulation of food intake and energy homeostasis with leptin being implicated in various obesity-related cardiovascular diseases, whereas adiponectin is considered cardioprotective.\(^{55}\) Epicardial fat deposition due to altered adiponectin and leptin regulation is one of the theories implicated in the development of heart failure.\(^{56}\) Increased serum leptin concentrations are seen in patients with heart failure and they are associated with cardiac remodelling due to cardiac fibrosis and inflammation.\(^{57}\) SGLT2 inhibition reduces serum leptin and increases adiponectin concentrations, potentially offering some cardioprotection.\(^{58}\) However, these effects may well be reflective of changes secondary to the systemic effects of SGLT2-inhibitor therapy including weight loss and lipolysis.

**Future directions**

The exact pathways of cardiovascular benefit with SGLT2-inhibitor therapy are yet to be established and newer mechanisms may emerge over time. It is plausible that SGLT2 inhibition interacts with or mediates other key pathways at a cellular level, facilitating cardiovascular benefits. Thus, establishing the exact mechanism of benefit is key to understanding the benefits of...
SGLT2 inhibition and may also open up new and unexplored pathways which could provide rich avenues of understanding for the pathophysiology and potential future novel treatments of heart failure.

There are several ongoing clinical studies investigating the mechanisms of cardiovascular benefits with SGLT2 inhibition such as the effects on cardiac remodelling (NCT03871621), lipolysis and modification of epicardial fat thickness and properties (NCT04219124, NCT04167761 and NCT02235298), myocardial calcium handling (NCT04591639) and endogenous ketone production (NCT03852901, NCT04219124).

These studies will provide significant insights into the key pathways involved in the cardioprotective effects associated with SGLT2-inhibitor therapy.

CONCLUSIONS
SGLT2-inhibitor therapies are a promising new class of drugs for treating type 2 diabetes and heart failure. The cardioprotective effect of SGLT2 inhibition has been demonstrated in models of diabetic cardiomyopathy, heart failure and ischaemic cardiomyopathy. The mechanism through which SGLT2-inhibitor therapy exerts its benefit in patients with heart failure remains incompletely understood. It is possible that a combination of systemic and direct effects of SGLT2 inhibition on the myocardium ultimately leads to the cardiovascular benefits. However, there is strong pre-clinical evidence to suggest that improved myocardial homeostasis has a role to play with regards to the cardiovascular benefits seen with SGLT2-inhibitor therapy. Studies examining the mechanistic role of SGLT2 inhibitor therapy in cardiovascular health will be instrumental in shaping our understanding of heart failure and diabetic cardiomyopathy and may open avenues for the development of future drug therapies that target these pathways.

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REFERENCES
Review


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