REVIEW

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SGLT2 inhibitors and mechanisms of cardiovascular benefit: a state-of-the-art review

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Abstract

Sodium–glucose cotransporter (SGLT)2 inhibitors have been demonstrated to reduce cardiovascular events, particularly heart failure, in cardiovascular outcome trials. Here, we review the proposed mechanistic underpinnings of this benefit. Specifically, we focus on the role of SGLT2 inhibitors in optimising ventricular loading conditions through their effect on diuresis and natriuresis, in addition to reducing afterload and improving vascular structure and function. Further insights into the role of SGLT2 inhibition in myocardial metabolism and substrate utilisation are outlined. Finally, we discuss two emerging themes: how SGLT2 inhibitors may regulate Na^+/H^+ exchange at the level of the heart and kidney and how they may modulate adipokine production. The mechanistic discussion is placed in the context of completed and ongoing trials of SGLT2 inhibitors in the prevention and treatment of heart failure in individuals with and without diabetes.

Keywords Cardiovascular effects · Heart failure · Mechanisms · Review · SGLT2 inhibitors

Abbreviations

BCAA	Branched-chain amino acid
CANVAS	Canagliflozin Cardiovascular Assessment Study
EMPA-REG OUTCOME	Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients–Removing Excess Glucose
HFpEF	Heart failure with a preserved ejection fraction
HFrEF	Heart failure with a reduced ejection fraction
HHF	Hospitalisation for heart failure
NHE	Na^+/H^+ exchanger
βOHB	β-Hydroxybutyrate
SGLT	Sodium–glucose cotransporter

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SGLT2 inhibitors and cardiovascular protection: setting the stage

Sodium–glucose cotransporter (SGLT)2 inhibitors have demonstrated unprecedented cardiorenal benefits in large-scale clinical trials of people who have type 2 diabetes and either established cardiovascular disease or multiple cardiovascular risk factors [1–3]. In the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients–Removing Excess Glucose (EMPA-REG OUTCOME) study, 7020 individuals with type 2 diabetes who had coronary, peripheral or cerebrovascular disease were randomised to receive the SGLT2 inhibitor empagliflozin or placebo [2]. While the primary three-point major adverse cardiac events outcome (cardiovascular death, non-fatal myocardial infarction and non-fatal stroke) was significantly attenuated by empagliflozin, what was particularly noteworthy were the profound and early effects of empagliflozin on cardiovascular death and hospitalisation for heart failure (HHF), which were reduced by 38% and 35%, respectively

[2–4]. In addition, all-cause mortality was reduced by 32%. Importantly, the reductions in cardiovascular death were not clearly accounted for by the reductions in atherothrombotic outcomes; rates of myocardial infarction and stroke remained unchanged with therapy. The thesis that heart failure was the outcome most sensitive to SGLT2 inhibition was confirmed in the Canagliflozin Cardiovascular Assessment Study (CANVAS) Program wherein 10,142 individuals with type 2 diabetes and either established cardiovascular disease or multiple cardiovascular risk factors received canagliflozin or placebo [1]. Despite broader entry criteria, which resulted in the inclusion of both patients for whom canagliflozin was used for primary and secondary prevention of cardiovascular disease, SGLT2 inhibition produced an almost identical reduction in the rates of HHF (HR 0.67 in the CANVAS Program and HR 0.65 in the EMPA-REG OUTCOME study) [5, 6]. The concept that SGLT2 inhibitors reduced cardiovascular events primarily through prevention of heart failure (vs atherothrombotic events) has gained broad acceptance, but several questions remained unanswered, the most important being: 'how'?

In addition to the interest around mechanistic investigations and analyses [7], the results served as a wake-up call to remind the diabetes community of the burgeoning burden of heart failure in diabetes; this cardiovascular outcome had seemed to have been forgotten [8–10]. Although the atherothrombotic/macrovascular complications of diabetes are well appreciated, these data helped remind clinicians and scientists that HHF is one of the most common and serious complications of diabetes and is, in fact, as common (if not more evident) than rates of ischaemic events in diabetes [11]. To date, much has been written about how diabetes directly (in an atherosclerosis-independent manner) affects the myocardium, although the concept of a distinct diabetic cardiomyopathy predisposing individuals to the development of heart failure remains debated [12, 13]. The concept of primary vs secondary prevention is often used to distinguish atherosclerotic risk (and associated atherosclerosis-reducing therapies, such as statins, antiplatelet agents etc.); however, this approach may not be appropriate for distinguishing risk of heart failure in those with diabetes [14]. Individuals who have longstanding diabetes and healthy coronary arteries do not necessarily have normal ventricular mechanics and, hence, are predisposed to developing heart failure [15]. These individuals appear to be equally responsive to SGLT2 inhibitors for the prevention of heart failure [16–18]. Indeed, this proposition is supported by a subgroup analysis of the CANVAS Program, which demonstrated a similar relative risk reduction for HHF in the so-called

primary and secondary prevention cohorts (HR 0.64 and HR 0.68, respectively) [17].

Another important and unanswered question arising from previous trials relates to whether the observed cardiovascular benefit of SGLT2 inhibitors occurred primarily in individuals with a history of heart failure and whether a specific phenotype (heart failure with a preserved ejection fraction [HFpEF] or heart failure with a reduced ejection fraction [HFrEF]) was more sensitive to the observed benefits. Only a minority of participants enrolled in the EMPA-REG OUTCOME study and CANVAS Program (~10%) had a history of investigator-reported heart failure and, as illustrated in Fig. 1, consistent relative risk reductions were observed in people with and without a history of heart failure [5, 6]. Since echocardiographic or biomarker substudies were not performed to evaluate specific cardiac phenotypes that were most responsive to therapy, this question remains unanswered. However, the absolute risk reduction appeared to be greater in those with a history of heart failure [4, 6], suggesting that SGLT2 inhibition may be valuable in both the prevention and treatment of heart failure. It is entirely plausible that a large proportion of the individuals enrolled in these studies had occult HFpEF or HFrEF, a notion that has been substantiated in a previous study focused on individuals with type 2 diabetes [19].

Mechanisms of cardiovascular protection by SGLT2 inhibitors

Several theories have been put forward to explain the profound salutary effects of SGLT2 inhibitors on cardiovascular (Text box and Fig. 2) and renal outcomes [7, 20].
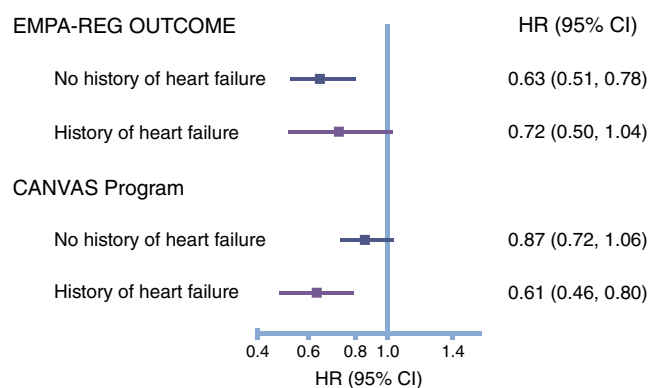

EMPA-REG OUTCOME	HR (95% CI)
No history of heart failure	0.63 (0.51, 0.78)
History of heart failure	0.72 (0.50, 1.04)
CANVAS Program	
No history of heart failure	0.87 (0.72, 1.06)
History of heart failure	0.61 (0.46, 0.80)

HR (95% CI)

Fig. 1 The cardiovascular benefits (relative risk reduction of cardiovascular death and HHF) observed with empagliflozin in the EMPA-REG OUTCOME trial and canagliflozin in the CANVAS Program were apparent in participants with and without a history of heart failure [5, 6]. The forest plot is drawn on a logarithmic ($\log_{10}$) scale. This figure is available as part of a downloadable slideset
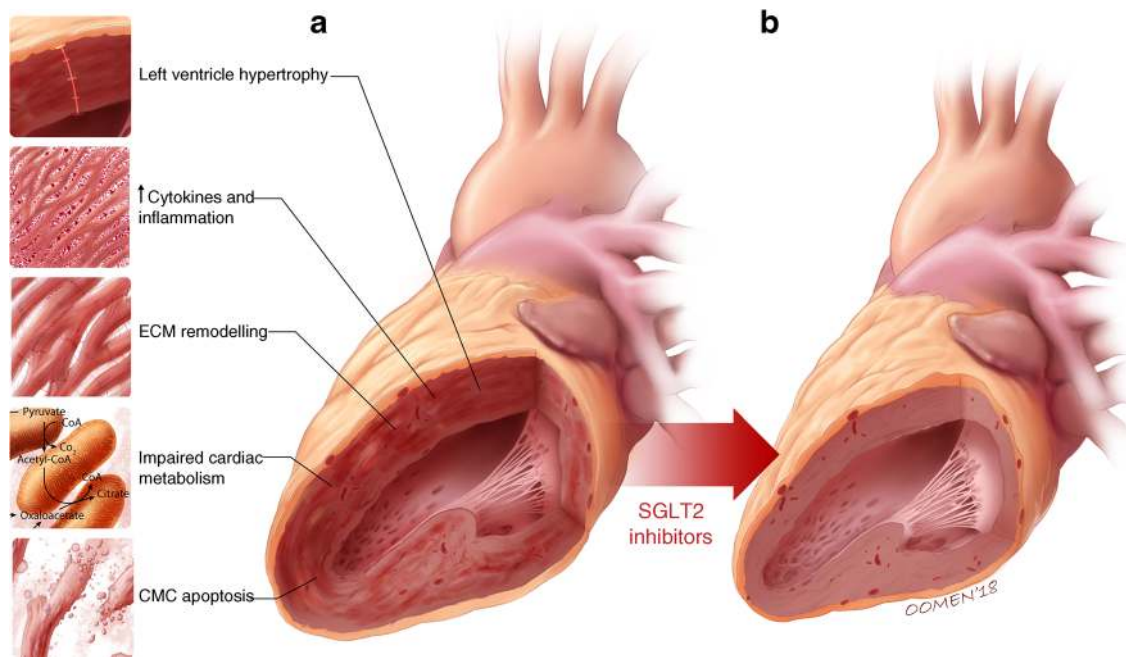
Fig. 2 Diabetes-associated ventricular remodelling (**a**) is characterised by left ventricular hypertrophy, inflammation, increased extracellular matrix (ECM) production, impaired cardiac metabolism and cardiomyocyte (CMC) apoptosis. SGLT2 inhibitors may offer salutary effects on several of the fundamental molecular and cellular pathways involved in the development and natural history of cardiac failure in diabetes (as illustrated by a healthy heart in **b**). © G. Oomen 2018. This figure is available as part of a downloadable slideset

Before delving into these in detail, it is worth noting that these salient effects appear to have little impact on conventional risk factors. First, baseline and time-dependent changes in HbA_{1c}, blood pressure and cholesterol do not seem to determine the overall benefit of SGLT2 inhibitors on cardiovascular outcomes [22]. Second, their benefits on HHF/cardiovascular death have been observed across the spectrum of renal disease, with a similar magnitude of risk reduction being seen in those with eGFRs of 30–60 ml min^{-1} [1.73 m]$^{-2}$, 60–90 ml min^{-1} [1.73 m]$^{-2}$ and >90 ml min^{-1} [1.73 m]$^{-2}$ [23]. Although the glucose-lowering efficacy of SGLT2 inhibitors declines at the lower eGFR range, the cardiovascular benefits are remarkably preserved, suggesting that the mechanism(s) involved in glycaemic control and cardiovascular risk reduction may be dissociated and/or follow a different dose–response curve. Third, it is worth noting that the metabolic fingerprint of these agents appears to be consistent among those with and without diabetes. Studies suggest that SGLT2 inhibition exerts glucosuria and natriuresis, while increasing glucagon and ketones even in individuals who do not have diabetes [24–26]. These data, therefore, argue that the benefits noted may be observed even in those without diabetes, a concept that has been borne out in preclinical experiments [27, 28] and which is being explored in ongoing heart failure treatment studies [29]

with dapagliflozin (ClinicalTrial.gov registration no. NCT03036124) and empagliflozin (ClinicalTrial.gov registration no. NCT03057951 and NCT03057977). In the section below, we highlight some of the key mechanistic themes that have emerged to explain the cardiorenal benefits of SGLT2 inhibitors.

> **Putative mechanisms underlying SGLT2 inhibitor-associated cardiovascular benefits**
>
> 1. Improvement in ventricular loading conditions through a reduction in preload (secondary to natriuresis, osmotic diuresis) and afterload (reduction in blood pressure and improvement in vascular function) [7, 20, 21, 30–38]
>
> 2. Improvement in cardiac metabolism and bioenergetics [39, 40, 44, 45]
>
> 3. Myocardial Na^+/H^+ exchange inhibition [46–48]
>
> 4. Reduction of necrosis and cardiac fibrosis [51, 52, 60]
>
> 5. Alteration in adipokines, cytokine production and epicardial adipose tissue mass [55–57]
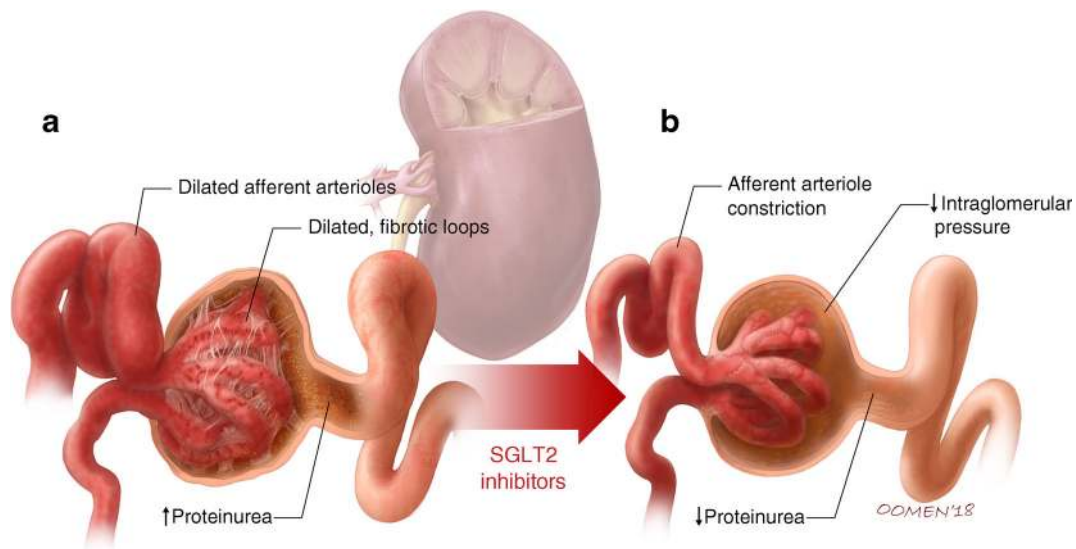
Fig. 3 Diabetes is associated with afferent arteriolar dilatation, which leads to high intraglomerular pressure and hyperfiltration. Ongoing baro-trauma to the glomerulus may lead to proteinuria (**a**). SGLT2 inhibitors, through tubuloglomerular feedback, promote afferent arteriolar vasoconstriction. This in turn serves as a mechanism to reduce intraglomerular hypertension and provide nephroprotection (**b**). © G. Oomen 2018. This figure is available as part of a downloadable slideset

SGLT2 inhibitors improve ventricular loading conditions It has been proposed that one of the main mechanisms by which SGLT2 inhibitors exert their beneficial actions is via improvement of ventricular loading conditions, secondary to a reduction in preload primarily due to the diuretic and natriuretic effects [7, 20]. SGLT2 inhibition in the proximal tubule results in natriuresis and glucosuria, and the ensuing osmotic diuresis may be favourable, particularly in the heart of an individual with diabetes, which functions on a steep Frank–Starling curve. SGLT2 inhibitors are unique among the diuretics available clinically in that they modulate the function of the proximal tubule. The natriuretic response is also a stimulus for tubuloglomerular feedback, which in turn results in afferent arteriolar vasoconstriction with resultant reductions in intraglomerular hypertension (Fig. 3). This process may explain the significant long-term renal preservation noted with SGLT2 inhibitors. Of note, angiotensin converting enzyme inhibitors and angiotensin receptor blockers cause efferent arteriolar vasodilatation and, when used in combination with SGLT2 inhibitors, will likely co-impact on intraglomerular pressure and may account for the initial drop in eGFR observed in patients, which is followed by a plateau over time. Individuals with diabetes are known to have an increase in whole-body sodium content and, in recently completed translational studies in humans, the SGLT2 inhibitor dapagliflozin has been demonstrated to reduce tissue sodium content in people with type 2 diabetes [30]. Mediation analyses from the EMPA-REG OUTCOME trial also point towards volume contraction as being a key determinant of benefit noted within the trial. In fact, approximately 50% of the cardiovascular benefit observed within the trial was ascribed to empagliflozin-induced haemoconcentration [31]. An early haemodynamic benefit would go hand in hand with the observed early separation of the Kaplan–Meier curves noted within the clinical trials when comparing empagliflozin or canagliflozin treatment with placebo. Could diuresis really explain these benefits when other diuretics have not changed prognosis in heart failure? Recent studies point to important differences between SGLT2 inhibitors and classical diuretics. For example, in a comparative study of dapagliflozin and hydrochlorothiazide (a classical diuretic), a reduction in plasma volume and increase in erythrocyte mass was noted with dapagliflozin but not with hydrochlorothiazide over a 12 week period of treatment [32]. In another study comparing dapagliflozin with the loop diuretic bumetanide, though both agents were associated with a reduction in sodium and interstitial fluid, dapagliflozin afforded these effects with little or no change in blood volume whereas bumetanide was associated with greater reductions in intravascular volume [33]. A differential effect in regulating interstitial fluid (vs intravascular volume) may be particularly important in patients with heart failure in whom, in many instances, intravascular contraction is present and often aggravated by diuresis. The ability to selectively reduce interstitial fluid may be a unique feature of SGLT2 inhibitors vs other diuretics (Fig. 4) and this may limit the reflex neurohumoral stimulation that occurs in response to intravascular volume contraction with traditional diuretics.
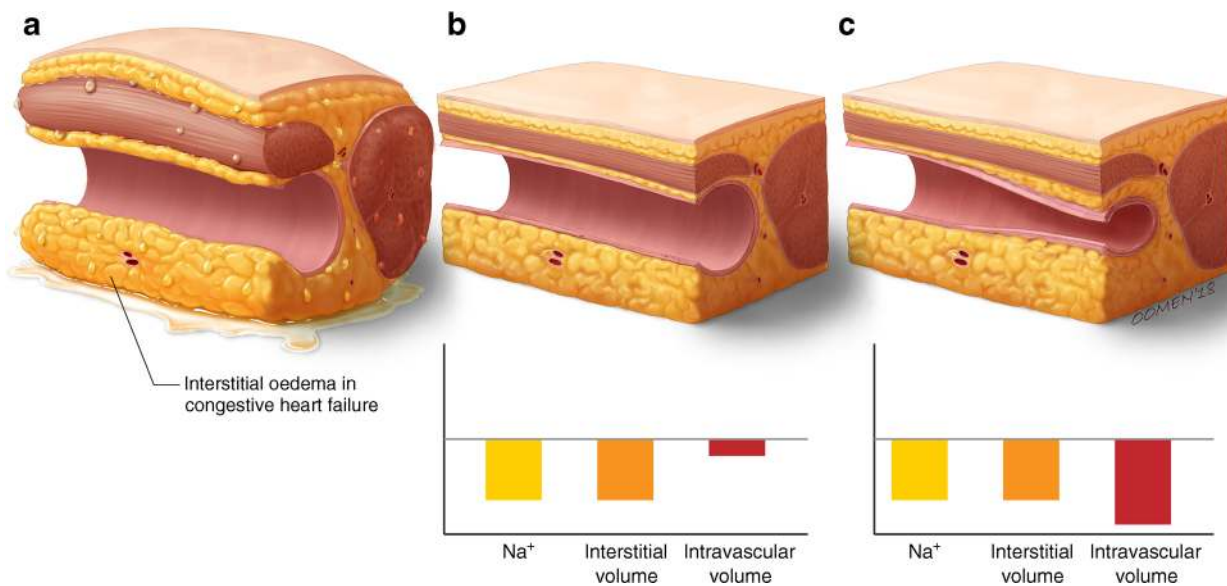
Fig. 4 SGLT2 inhibitors may differentially regulate the interstitial vs intravascular compartment when compared with loop diuretics. In individuals with congestive heart failure, interstitial oedema is evident (**a**). SGLT2 inhibitors may selectively reduce interstitial volume with minimal change in blood volume (**b**) whereas loop diuretics may cause a reduction in both interstitial and intravascular volume (**c**). It has been postulated that this differential volume regulation by SGLT2 inhibitors (interstitial > intravascular) may limit the aberrant reflex neurohumoral stimulation that occurs in the setting of intravascular depletion. © G. Oomen 2018. This figure is available as part of a downloadable slideset

However, this thesis requires further data. Another difference between conventional diuretics and SGLT2 inhibitors relates to their effects on serum uric acid levels. Whereas SGLT2 inhibitors are uricosuric, loop diuretics are associated with an increase in uric acid levels, possibly mediating differences in cardiovascular outcomes [34].

In addition to volume changes, SGLT2 inhibitors may optimise loading conditions through reducing blood pressure and altering vascular function. In a recent study, empagliflozin was shown to reduce central and 24 h systolic and diastolic blood pressure, central pulse pressure and forward wave amplitude in individuals with type 2 diabetes [35]. Other studies have demonstrated that SGLT2 inhibitors improve endothelial function and aortic stiffness indices, and may potentially induce vasodilatation through activation of voltage-gated potassium (Kv) channels and protein kinase G [36–38].

SGLT2 inhibitors improve cardiac metabolism and bioenergetics It has been postulated that SGLT2 inhibitors may improve and/or optimise cardiac energy metabolism and that by improving myocardial energetics and substrate efficiency these agents may improve cardiac efficiency and cardiac output [39, 40]. It is well established that under conditions of diabetes and/or heart failure, the metabolic flexibility of the heart, as it relates to substrate utilisation, is impaired. Accordingly, an over-reliance on NEFAs as a substrate for ATP generation may result in a build-up of free fatty intermediates that may in turn promote lipotoxicity, impair sarcoplasmic reticulum calcium uptake

and promote the development of diastolic dysfunction [41]. SGLT2 inhibitors are known to slightly increase the production of the ketone body β-hydroxybutyrate (βOHB), and it is hypothesised that this may offer an alternative and less expensive myocardial fuel source in those with diabetes [39, 42]. The elevation in ketone levels has been suggested to arise from an effort to raise glucagon levels and possibly through a reduction in ketone body excretion via the kidneys. The underlying concept is that βOHB is a 'superfuel' that is oxidised by the heart in preference to NEFAs and glucose, and that ketones not only improve cardiac function in the failing heart, but also increase mechanical efficiency [43]. This is an interesting postulate but cogent data to support this thesis are scarce. Some support, however, has been provided by preliminary studies carried out in pigs following myocardial infarction, which demonstrate that empagliflozin increases myocardial ketone consumption, and reduces cardiac glucose consumption and lactate production [44]. Others have postulated that SGLT2 inhibitor-induced increases in βOHB levels may inhibit histone deacetylase and prevent prohypertrophic transcription pathways [40]. It is also possible that a decrease in βOHB oxidation results in decreased acetyl-CoA derived from ketone oxidation, thereby increasing the oxidation of glucose-derived pyruvate (i.e. improving myocardial glucose metabolism). A decrease in acetyl-CoA supply may also decrease harmful hyperacetylation of mitochondrial enzymes, thereby improving mitochondrial energy production [40]. Using an elegant untargeted metabolomics strategy, SGLT2 inhibition was suggested to
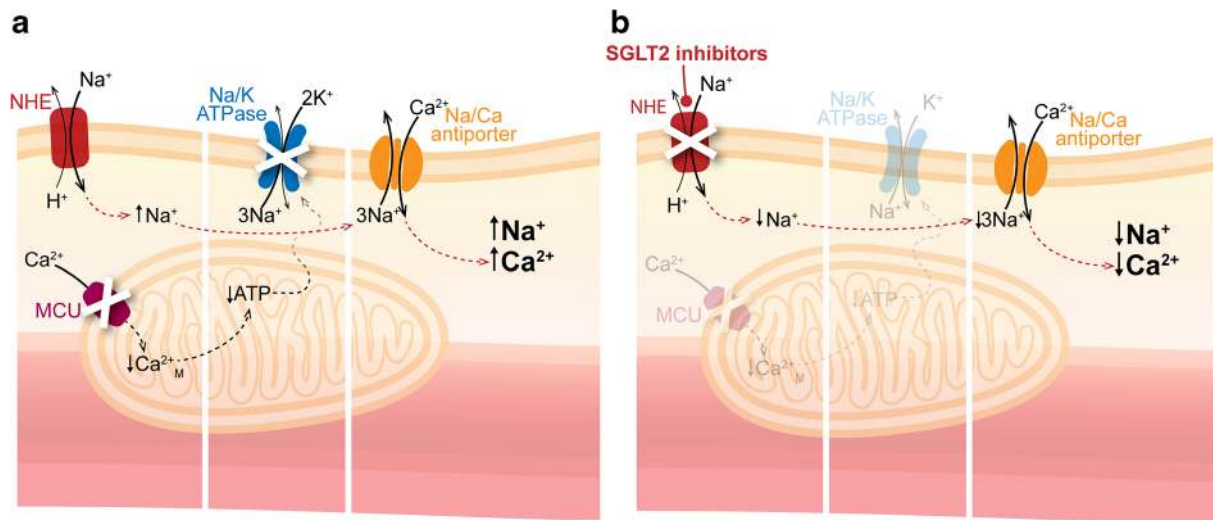
Fig. 5 (**a**) Diabetes-associated heart failure is characterised by an increase in myocardial expression of NHEs. This can lead to elevations in cytoplasmic sodium and calcium levels, which may contribute to the pathology of heart failure. (**b**) Recent data suggest that SGLT2 inhibitors block NHEs, consequently reducing cytoplasmic sodium and calcium, thus offering cardioprotection. Ca^{2+}_M, mitochondrial calcium; MCU, mitochondrial Ca^{2+} uniporter. © G. Oomen 2018. This figure is available as part of a downloadable slideset

promote branched-chain amino acid (BCAA) degradation, thereby providing an alternative fuel source for the failing myocardium. BCAA degradation is known to be impaired in heart failure and may contribute to aberrant myocardial bioenergetics [45]. Although the findings described above are intriguing, it is important to emphasise that we still lack definitive evidence linking myocardial energetics to the beneficial effects of SGLT2 inhibition.

SGLT2 inhibition and direct effects on Na$^+$/H$^+$ exchange in the myocardium An emerging and tantalising hypothesis is that SGLT2 inhibitors may directly inhibit the Na$^+$/H$^+$ exchanger (NHE) 1 isoform in the myocardium [46, 47]. Activation of NHE1 results in increased cytosolic sodium and calcium and has been demonstrated to occur in experimental models of heart failure (Fig. 5). Recently, Baartscheer et al showed that the SGLT2 inhibitor empagliflozin inhibited cardiomyocyte NHE and, through this mechanism, reduced cytoplasmic sodium and calcium levels, while increasing mitochondrial calcium levels [48]. Since SGLT2 receptors are not expressed in the heart, the mechanism by which these effects on cardiomyocyte NHE occur remains elusive. Of note, it has been postulated that SGLT2 inhibitors promote natriuresis by downregulating the activity of NHE3 in the proximal tubule [49]. The expression of NHE3, known to mediate tubular sodium reuptake, is increased in heart failure, and an inhibitory effect on NHE3 may serve as an additional mechanism to restore whole-body sodium homeostasis and reduce cardiac failure. Hence, inhibition of NHE1 and NHE3 may be a common cardio–renal mechanism through which these agents prevent and/or treat heart failure [46].

SGLT2 inhibition and cardiac fibrosis Cardiac fibrosis is widely regarded as a common final pathway through which heart failure develops. This universally involves cardiac structural remodelling due to deposition of extracellular matrix proteins laid down by cardiac fibroblasts, resulting in impeded ventricular compliance and accelerated development of heart failure [50]. Recent experimental data in rat models of post-myocardial infarction demonstrate that dapagliflozin exhibits marked cardiac antifibrotic effects by suppressing collagen synthesis via increasing the activation of M2 macrophages and inhibiting myofibroblast differentiation [51]. Other preliminary studies, using human cardiac fibroblasts, have demonstrated that empagliflozin significantly attenuates TGF-β1-induced fibroblast activation and reduces cell-mediated extracellular matrix remodelling as measured by the collagen fibre alignment index [52]. In the same series of studies, the authors demonstrated that empagliflozin suppressed expression of key pro-fibrotic markers, including type I collagen, α-smooth muscle actin, connective tissue growth factor and matrix metalloproteinase 2. Therefore, an emerging postulate is that SGLT2 inhibition, independent of hyperglycaemia, may have direct and favourable effects on cardiac fibroblast phenotype and function, one of the most important factors of heart failure.

SGLT2 inhibition and adipokines Altered adipokine production and/or action has been proposed as a common mechanism through which cardiovascular disease and insulin resistance develops, particularly in states of obesity [53]. Ectopic fat deposition in the form of perivascular and epicardial fat has been implicated in the genesis of heart failure, in part through altered paracrine regulation of adipokines on the myocardium [54]. It has been suggested that SGLT2 inhibitors may mediate

their benefit, in part, by restoring the balance between pro- and anti-inflammatory adipokines. Recently, SGLT2 inhibitors were postulated to reduce the levels of the adipokine leptin, which may have a pathophysiological role in sodium regulation as well as cardiac inflammation and fibrosis [55]. Indeed, in a 52 week clinical study, canagliflozin reduced serum leptin levels by 25% and increased the levels of the anti-inflammatory adipokine adiponectin by 17%, when compared with the sulfonylurea glimepiride [56]. A marked reduction in the inflammatory cytokine IL-6, but not TNF-α, was also observed in this study. Other studies have demonstrated that dapagliflozin reduces epicardial adipose tissue volume, which has been implicated in the development and natural history of heart failure [57]. The independent changes that SGLT2 inhibitors appear to exert on adipokines need to be interpreted with caution and it is imperative that we work towards distinguishing between the secondary effects that arise from fat mass loss and the direct effects that regulate adipose tissue function. As such, the causal relationship between SGLT2 inhibition and adipose tissue inflammatory cytokines should, for now, be considered hypothesis-generating.

Unanswered mechanistic and translational themes

Despite the growing interest in the cardiovascular and renal protective biology of SGLT2 inhibitors, unanswered questions remain. For example, do SGLT2 inhibitors reverse pathological cardiac remodelling in humans with diabetes? Although preliminary and uncontrolled case series suggest that empagliflozin may be associated with a reduction in left ventricular mass and an improvement in diastolic function (as assessed by echocardiography) [58], persuasive data to support this important question are pending. The ongoing randomised Effects of Empagliflozin on Cardiac Structure in Patients with Type 2

Table 1 Completed and ongoing SGLT2 inhibitor-focused trials

Trial [reference/ClinicalTrial.gov registration no.]	Inclusion criteria	Primary outcomes
Type 2 diabetes + CV disease and/or CV risk factors		
EMPA-REG OUTCOME [2]	Type 2 diabetes and high cardiovascular risk	CV death, non-fatal MI and non-fatal stroke
CANVAS Program [2]	Inadequately controlled type 2 diabetes with a history, or high risk, of CV events	CV death, non-fatal MI and non-fatal stroke Progression of albuminuria
DECLARE-TIMI 58[a] [65]	Type 2 diabetes with a history, or high risk, of CV events	CV death, non-fatal MI and non-fatal stroke CV death or HHF
SCORED[a] [NCT03315143]	Type 2 diabetes, CV risk factors and moderately impaired renal function	CV death, non-fatal MI and non-fatal stroke CV death or HHF
VERTIS CV[a] [NCT01986881]	Type 2 diabetes and established vascular disease	CV death, non-fatal MI and non-fatal stroke
CKD ± type 2 diabetes		
CREDENCE [66]	Type 2 diabetes and moderately impaired renal function	ESRD, doubling of serum creatinine, renal or CV death
Dapa-CKD[a] [NCT03036150]	CKD	≥50% sustained decline in eGFR, ESRD, CV death or renal death
EMPA-Kidney[a] [NCT03594110]	CKD	ESRD, renal death, ≥40% sustained decline in eGFR or CV death
Heart failure ± type 2 diabetes		
Dapa-HF[a] [NCT03036124]	Chronic heart failure, left ventricular ejection fraction ≤0.40% and elevated NT-proBNP	CV death or HHF or an urgent heart failure clinic visit
EMPEROR-Reduced[a] [NCT03057977]	Chronic heart failure, left ventricular ejection fraction ≤0.40% and elevated NT-proBNP	CV death or HHF
EMPEROR-Preserved[a] [NCT03057951]	Chronic HFpEF	CV death or HHF
SOLOIST-WHF[a] [NCT03521934]	Type 2 diabetes and prior heart failure and visit or hospitalisation for worsening heart failure	CV death or HHF

[a] Ongoing trials

CKD, chronic kidney disease; CREDENCE, Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation; CV, cardiovascular; DECLARE-TIMI, Dapagliflozin Effect on CardiovascuLAR Events-Thrombolysis in Myocardial Infarction; eGFR, estimated glomerular filtration rate; EMPEROR-Preserved, EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Preserved Ejection Fraction; EMPEROR-Reduced, EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Reduced Ejection Fraction; ESRD, end-stage renal disease; HHF, hospitalisation due to heart failure; MI, myocardial infarction; NT-proBNP, N-terminal of the prohormone brain natriuretic peptide; SCORED, Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients With Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk; SOLOIST-WHF, Effect of Sotagliflozin on Cardiovascular Events in Patients With Type 2 Diabetes Post Worsening Heart Failure

Diabetes (EMPA-HEART) trial (ClinicalTrial.gov registration no. NCT02998970), evaluating the effects of empagliflozin on left ventricular mass by cardiac magnetic resonance imaging, represents an important step in understanding the effects of SGLT2 inhibitors on ventricular remodelling. Other studies of a similar nature are ongoing with empagliflozin (ClinicalTrial.gov registration no. NCT03198585) and dapagliflozin [59].

There is a paucity of data with respect to the effects of SGLT2 inhibitors on serum and renal biomarkers. Although initial studies have demonstrated that canagliflozin reduces levels of B-type natriuretic peptide and troponin [60], confirmation of this in larger studies with pathway-specific biomarkers (e.g. renin–angiotensin–aldosterone, extracellular matrix markers and proximal tubule injury markers, such as kidney injury molecule-1 [KIM-1]) are needed. In addition, we would encourage further evaluation of uric acid reduction as a biomarker and/or mediator of SGLT2 inhibition, since there is a large body of evidence suggesting that uric acid levels are an important predictor of prognosis in heart failure. It is also important to determine whether the effects of SGLT2 inhibitors are more pronounced in individuals with evidence of structural remodelling (such as left ventricular hypertrophy) or in those with higher levels of natriuretic peptides.

This area of research would also benefit from translational studies evaluating the effects of SGLT2 inhibitors on mechanisms of arrhythmias. Electrophysiological studies evaluating inducible ventricular arrhythmias, atrial tachyarrhythmias and corrected QT intervals would be insightful. Likewise, studies evaluating functional capacity in heart failure are needed; in line with this, two studies investigating empagliflozin in HFpEF and HFrEF, with the 6 min walk test being the primary endpoint, are currently underway (ClinicalTrial.gov registration no. NCT03448406 and NCT03448419).

Physiological studies that evaluate the effects of SGLT2 inhibitors on the sympathetic nervous system and neurohumoral activation are needed. It is also intriguing that, despite volume loss and a decrease in blood pressure, no change in heart rate has been observed with SGLT2 inhibitor therapy and this should be further investigated.

Mechanistic and functional studies that evaluate the effects of SGLT2 inhibitors on peripheral arterial disease and amputation risk are also urgently required. Although an increase in amputation risk was observed exclusively in CANVAS [1, 61, 62], preliminary mechanistic studies in animals subjected to femoral ligation actually demonstrated an improvement in recovery of blood flow in response to canagliflozin [63].

Conclusions

SGLT2 inhibitors have emerged as powerful pharmacological tools in the prevention of heart failure, with the suggestion that, unlike with other glucose-lowering agents [64], this benefit

may be observed across the spectrum of people with type 2 diabetes with and without established cardiovascular disease. The largest outcome study on the effects of SGLT2 inhibitors on cardiovascular disease, the Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events (DECLARE-TIMI 58), which has enrolled about 10,000 participants within a so-called primary prevention cohort, will provide further insights in this regard [65]. A summary of the reported and ongoing SGLT2 inhibitor trials is provided in Table 1. In this review, we have outlined some of the key mechanisms that may explain the notable cardioprotective benefits of SGLT2 inhibitors, including effects on volume and diuresis, myocardial metabolism and the potentially direct myocardial effects, with some preliminary observations suggesting an effect on myocardial metabolism and adipokine kinetics. Whether these agents will emerge as treatment approaches in chronic HFpEF, HFrEF or acute heart failure is an important question; the answer may be provided by trials that are currently underway.

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