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REVIEW

SGLT2 inhibitors: the future for treatment of type 2 diabetes mellitus and other chronic diseases

Christoph Wanner[1] · Nikolaus Marx[2]

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Abstract

Individuals with diabetes mellitus exhibit an increased propensity to develop cardiovascular disorders such as coronary artery disease, stroke and heart failure. Over recent decades, numerous cardiovascular outcome trials in individuals with type 2 diabetes have been published, with data showing a reduction of cardiovascular morbidity and mortality by sodium–glucose cotransporter 2 (SGLT2) inhibitors. These results not only provide novel therapeutic options for this high-risk population but also advance our current understanding of cardiovascular risk reduction in diabetes. The current overview article summarises these aspects and discusses future treatment strategies with SGLT2 inhibitors in diabetic and non-diabetic individuals with chronic kidney disease, liver disease and heart failure.

Keywords Diabetes mellitus · Diabetic kidney disease · Heart failure · Non-alcoholic fatty liver disease · Non-diabetic chronic kidney disease · Review

Abbreviations

DPP-4	Dipeptidyl peptidase-4
EMPA-REG OUTCOME	Empagliflozin, Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients
GLP-1	Glucagon-like peptide-1
GLP-1RA	GLP-1 receptor agonist
LEADER	Liraglutide Effect and Action in Diabetes–Evaluation of Cardiovascular Outcome Results
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
NHE	Na^+/H^+ exchanger
SGLT2	Sodium–glucose cotransporter 2

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✉ Christoph Wanner
wanner_c@ukw.de

[1] Department of Internal Medicine I, Nephrology, University Hospital Würzburg, Oberdürrbacherstr. 6, 97080 Würzburg, Germany

[2] Department of Internal Medicine I, Cardiology, University Hospital Aachen, RWTH Aachen University, Aachen, Germany

Beyond HbA_{1c} targets in type 2 diabetes management

For decades, therapies for individuals with type 2 diabetes mellitus have mainly focused on the reduction of blood glucose levels to within the normal range on the assumption that an intensive glucose-lowering strategy will lead to beneficial micro- and macrovascular effects. This approach has been challenged by large short- and mid-term cardiovascular outcome trials, such as Action to Control Cardiovascular Risk in Diabetes (ACCORD) [1], Action in Diabetes and Vascular Disease (ADVANCE) [2] and Veterans Affairs Diabetes Trial (VADT) [3], which failed to show a significant reduction in macrovascular events in individuals with long-duration type 2 diabetes. Moreover, analyses from these studies suggested that certain therapeutic strategies may even be harmful to individuals with type 2 diabetes and may be responsible for clinically meaningful adverse events, such as hypoglycaemia and weight gain. Still, appropriate glucose control is mandatory for reducing microvascular events such as retinopathy, nephropathy and neuropathy. This has led to the recommendation that HbA_{1c} target values should be individualised based

on age, duration of diabetes and presence of cardiovascular or comorbid disease (European Society of Cardiology [ESC]/EASD Guidelines 2013) [4]; in addition, patients taking certain drugs known to cause, hypoglycaemia and weight gain should be monitored so that hypoglycaemia and weight gain are avoided. A recent exploratory analysis from the Empagliflozin, Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) suggested that changes in HbA_{1c} had only a modest mediatory effect on the HR for cardiovascular death when evaluating empagliflozin vs placebo; thus, effects were largely not due to glucose lowering [5].

Individualised drug therapy for cardiovascular risk reduction

Many cardiovascular outcome trials have examined the effect of novel glucose-lowering drugs on cardiovascular safety. These trials began after 2008, when the regulatory landscape changed, meaning that dedicated cardiovascular outcome trials were required for novel glucose-lowering drugs to attain or maintain regulatory approval. These cardiovascular outcome trials tested dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) analogues and sodium–glucose cotransporter 2 (SGLT2) inhibitors vs placebo in individuals with type 2 diabetes and were designed as non-inferiority examinations to prove the cardiovascular safety of a specific drug rather than to assess improvement over the standard glucose-lowering strategy. Therefore, glycaemic equipoise was supposed to be achieved between groups to ensure that potential cardiovascular effects were attributed only to the glucose-lowering drug tested. Many of these trials confirmed cardiovascular safety: Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR) [6], Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) [7] and Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) [8] for DPP4-inhibitors and Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) [9] and Exenatide Study of Cardiovascular Event Lowering (EXSCEL) [10] for GLP-1 receptor analogues (GLP-1RAs).

Two recent clinical trials with SGLT2 inhibitors, EMPA-REG OUTCOME [11] and Canagliflozin Cardiovascular Assessment Study (CANVAS) Program [12], reported a significant reduction in the incidence of cardiovascular events with empagliflozin and canagliflozin, respectively. Most likely, this benefit was achieved through a reduction in heart-failure-related events involving mechanisms that include haemodynamic, metabolic and other effects. In addition, recent mediation analyses of EMPA-REG OUTCOME suggested that changes in markers of plasma volume were the most important mediators of the reduction in risk of cardiovascular death with empagliflozin vs placebo [5]. Studies with other SGLT2 inhibitors, such as ertugliflozin and dapagliflozin, or combined SGLT1/2 inhibitors, such as sotagliflozin, are ongoing. Moreover, clinical trials with the GLP-1 analogues liraglutide (Liraglutide Effect and Action in Diabetes–Evaluation of Cardiovascular Outcome Results [LEADER]) and semaglutide (Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes [SUSTAIN6]) also showed a significant reduction in cardiovascular events [13, 14]. These results suggested that certain glucose-lowering drugs reduce cardiovascular events in high-risk individuals with type 2 diabetes, most likely in a manner independent of their glucose-lowering properties. The discovery of these glucose-independent benefits also changed the focus of type 2 diabetes therapy. This paradigm shift raises new questions for the future of treatments for diabetes mellitus:

1. Do these glucose-lowering drugs reduce cardiovascular events in all individuals with type 2 diabetes or do certain subgroups with various comorbidities benefit more than others?
2. How can we stratify individuals that may benefit from a certain therapeutic approach?

Subgroup analyses from large cardiovascular outcome trials such as LEADER [13] suggested that the cardiovascular benefit in treated participants was mainly achieved in those with cardiovascular disease; a similar effect was not seen in those with only risk factors. Similarly, in the CANVAS Program [12], death from cardiovascular causes was non-significantly reduced (HR 0.87; 95% CI 0.72, 1.06) with canagliflozin treatment in individuals with vs without prevalent cardiovascular disease. With respect to their glucose-lowering property, all of these drugs are effective in improving glycaemic control.

The subgroup analyses mentioned above may give a first hint towards individualised therapy; ideal stratification should be based on multiple factors rather than single variables since a variety of factors will most likely be responsible for the variability in treatment responses. Data from the upcoming Dapagliflozin Effect on Cardiovascular Events (DECLARE-TIMI 58) trial [15], which enrolled a large proportion of participants without prevalent cardiovascular disease, will provide additional information regarding the extent to which SGLT2 inhibitors reduce cardiovascular events in this group of individuals with type 2 diabetes. Thus, future strategies should be individualised by taking comorbidities and other factors into account. This requires a very thorough phenotyping of individuals with diabetes mellitus to identify the heterogeneous responses to treatments and will enable subsequent segregation of patient populations accordingly. To achieve truly individualised patient care, better decision tools

based on thorough phenotyping are needed to ensure each patient receives appropriate therapy.

Use in other chronic diseases irrespective of the presence of diabetes

SGLT2 inhibition results in the excretion of about 80 g of glucose per day in individuals with normal kidney function. This process has multiple consequences that may be helpful in the development of treatments for heart failure and kidney disease progression and may also provide the basis for treatments for fatty liver disease (Fig. 1).

Heart failure One of the underestimated comorbidities in individuals with diabetes mellitus is heart failure. Epidemiological and clinical data from recent years have led to the recognition that, in addition to myocardial infarction and other atherosclerosis-related cardiovascular events, heart failure is a major contributor to cardiovascular morbidity and mortality in individuals with type 2 diabetes (reviewed in [16, 17]). Various treatment options over the last three decades have led to a reduction in macrovascular events such as myocardial infarction and stroke [18] but similar reductions have not been achieved for the morbidity and mortality of heart failure or for cardiovascular death [19]. This is particularly true for individuals who have heart failure with preserved ejection fraction, a highly prevalent comorbidity in diabetes mellitus. Given that heart failure is associated with a worse prognosis in individuals with diabetes mellitus, it is of utmost importance to ensure that glucose-lowering drugs do not have an effect on heart failure decompensation. Ideally, they should have beneficial effects on heart-failure-associated endpoints, as seen with empagliflozin in EMPA-REG OUTCOME and canagliflozin in the CANVAS Program [20, 21]. However, the underlying molecular mechanisms explaining the benefit of SGLT2 inhibitor treatment in heart failure are poorly understood. Haemodynamic effects, changes in cardiac substrate utilisation (the ketone body superfuel hypothesis) and mitochondrial function and alterations in the kidney–heart interaction are only a few of the currently discussed potential mechanisms (reviewed in [22]). SGLT2 inhibitors may block the actions of the Na^+/H^+ exchanger (NHE) 1, which links the pathophysiology and treatment of diabetes mellitus with that of heart failure [23, 24], in addition to blocking NHE3 in the kidney thereby reducing intraglomerular pressure [24]. Recently, Hallow et al hypothesised that osmotic diuresis induced by SGLT2 inhibition may result in greater electrolyte-free water clearance and, ultimately, greater fluid clearance from the interstitial fluid space than from the circulation, potentially resulting in congestion relief with minimal impact on blood volume, arterial filling and organ perfusion [21].

SGLT2 inhibition may reduce intracellular sodium load and restore mitochondrial function and redox state in the failing heart

Heart failure is a major contributor to cardiovascular morbidity and mortality in type 2 diabetes.

Several glucose-lowering drugs are associated with reduced risk of macrovascular events (e.g. myocardial infarction and stroke) but few reduce risk of heart failure or cardiovascular death.

The SGLT2 inhibitors empagliflozin and canagliflozin have beneficial effects on heart-failure-associated endpoints, as seen in the EMPA-REG OUTCOME study and CANVAS Program, respectively.

The molecular mechanisms underlying the benefits of SGLT2 inhibitors in heart failure are poorly understood, but may include:

1. Haemodynamic effects
2. Changes in cardiac substrate utilisation (ketone body superfuel hypothesis) and mitochondrial function
3. Alterations in the kidney–heart interaction
4. Inhibition of NHE1 in the heart
5. Increased osmotic diuresis, resulting in greater fluid clearance from the interstitial fluid space (not the circulation), potentially resulting in congestion relief

It is possible that the beneficial effects of SGLT2 inhibition on heart failure may be extended to non-diabetic individuals with heart failure, a concept that is currently being tested (e.g. in the EMPEROR-Reduced/Preserved and Dapa-HF clinical trials).

Overall, SGLT2 inhibition is an intriguing prospect for reducing morbidity and mortality in heart failure and this approach may even be extended to non-diabetic individuals with heart failure, a concept that is currently being tested in various clinical outcome trials (EMPEROR-Reduced/-Preserved [ClinicalTrials.gov registration no. NCT03057977/NCT03057951] and Dapa-HF [NCT03036124]).

Diabetic and non-diabetic chronic kidney disease The SGLT2 inhibitors were originally developed to treat hyperglycaemia in people with diabetes mellitus. Large placebo-controlled trials have shown that they also reduce the risk of cardiovascular and renal disease progression in people with diabetes and prior cardiovascular disease [11, 12, 25], even in the presence of chronic kidney disease [26, 27]. The mechanism by which SGLT2 inhibition improves cardiovascular and renal outcomes

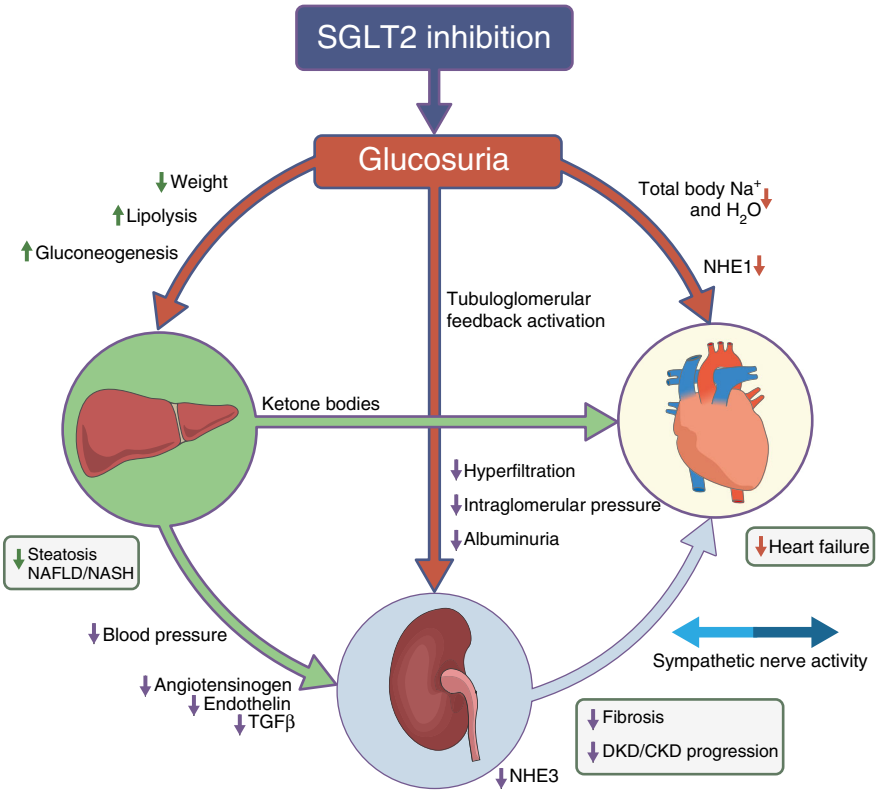

Fig. 1 Consequences of inhibition of SGLT2 on glucose, salt and water excretion, as well as its potential metabolic impact on kidney, liver and heart function. Continuous loss of energy through glucosuria (weight loss, lipolysis in adipose tissue), the many changes in cellular function through natriuresis, and osmotic diuresis-induced intercellular free water clearance have a powerful impact on cardiovascular outcomes. A reduction in visceral fat and an improvement in blood glucose may also reduce the risk of NAFLD/NASH. SGLT2 may be functionally linked to NHE3, such that SGLT2 inhibition may also inhibit NHE3 in the proximal tubule, with implications for effects on natriuresis, GFR and blood pressure. A similar effect may be initiated through NHE1 inhibition, with a reduction in intracellular sodium load and restoration of mitochondrial function in the heart. Sympathetic nerve activity, as measured by heart rate or microneurography in studies of SGLT2 inhibition in patients with type 2 diabetes, has been shown to remain unchanged. CKD, chronic kidney disease; NHE1, sarcolemmal Na^+/H^+ exchanger isoform 1, NHE3; tubular Na^+/H^+ exchanger isoform 3; DKD, diabetic kidney disease. This figure is available as a downloadable slide

is unclear but improved blood pressure, reduced total body sodium and water, improved glucose control and weight loss are all associated with improved outcomes in individuals with type 2 diabetes [27]. The lowering of intraglomerular pressure may also play an important role, as evidence suggests that SGLT2 inhibitors may exert a protective effect on the kidney by activating renal tubuloglomerular feedback through increased delivery of sodium to the macula densa, restoring adenosine production. The increase in sodium delivered to the macula densa leads to adenosine-mediated vasoconstriction in the afferent renal arterioles which, in turn, results in a lowering of intraglomerular pressure, suppression of hyperfiltration and a reduction in albuminuria [28, 29]. This mechanism is complementary to the inhibition of the renin–angiotensin system.

Intraglomerular hypertension and consequent hyperfiltration have long been considered key steps in the pathogenesis of chronic kidney disease progression. The accompanying barotrauma is of particular relevance to people with diabetes mellitus and/or obesity, who commonly have a supraphysiological GFR and consequently develop albuminuria early in the disease [30]. Hyperfiltration is driven in part by neurohormonal stimuli, which cause either a net reduction in afferent glomerular arteriolar resistance or a net increase in efferent arteriolar resistance [30]. The Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) study (ClinicalTrials.gov registration no. NCT02065791) with canagliflozin will be the first to report kidney outcomes as a primary endpoint in diabetic kidney disease. Glomerular hyperfiltration is not unique to diabetes mellitus and has been recognised in people with impaired glucose tolerance and hypertension [31] and who are obese [32]. Moreover, in those with reduced nephron mass (including many people with reduced kidney function), the remaining nephrons undergo structural hypertrophy and increase the single nephron glomerular filtration [30]. This is a potential common pathway for progression for many forms of chronic kidney disease. Two large clinical trials with kidney-specific endpoints in the primary composite endpoint have been initiated (Dapa-CKD [ClinicalTrials.gov registration no. NCT03036150] and EMPA-Kidney) to evaluate the effect of dapagliflozin or empagliflozin on renal outcomes and cardiovascular mortality, irrespective of the presence or absence of type 2 diabetes.

Non-alcoholic fatty liver disease Non-alcoholic fatty liver disease (NAFLD) is the most prevalent liver disease worldwide and there is no approved pharmacotherapy. NAFLD is a spectrum of disorders characterised by excessive fat accumulation in the liver (steatosis). The term non-alcoholic steatohepatitis (NASH) defines a subgroup of NAFLD wherein steatosis coexists with hepatocyte injury and inflammation (steatohepatitis), with or without fibrosis. Since the presence of NAFLD is associated with a worse prognosis, as well as the occurrence of cardiovascular events [33], future therapeutic strategies should encompass the modulation of NAFLD. In addition, type 2 diabetes is strongly associated with liver-related mortality due to NAFLD/NASH. Experimental and early clinical data suggest that GLP-1RAs and SGLT2 inhibitors modulate NAFLD and NASH [34, 35]. Semaglutide, a novel GLP-1RA is currently in a phase 2 randomised placebo-controlled trial investigating the efficacy and safety of three different doses delivered subcutaneously once daily vs placebo in 372 participants with NASH (ClinicalTrials.gov registration no. NCT02970942). Several pilot studies with SGLT2 inhibitors reported significant reduction in alanine aminotransferase levels, body weight and the fatty liver index in individuals with NAFLD [36–39]. In addition, many pilot studies, mainly conducted in Japan, have investigated the effect of empagliflozin on hepatocellular lipid content, liver energy metabolism and body composition and this is now being investigated in a randomised controlled trial in newly diagnosed type 2 diabetes patients (ClinicalTrials.gov registration no. NCT02637973). Targeting hepatic fat accumulation and preventing steatosis are the main focuses of treatment strategies for ameliorating NAFLD/NASH development. Clinical data in individuals with type 2 diabetes and NASH suggest that SGLT2 inhibition is linked to an improvement in body composition: a reduction in visceral fat occurs together with improved liver tests, decreased insulin concentrations and decreased blood glucose [35].

Summary

SGLT2 inhibitors were initially developed to treat individuals with type 2 diabetes mellitus and have recently emerged as potential therapeutic options in other diseases. This class of drugs is currently under investigation in diabetic and non-diabetic patients with heart failure, chronic kidney disease and NAFLD. When choosing a drug therapy for cardiovascular disease and metabolic disorders, the phenotype of the individual as well as the heterogeneous response to treatments should be considered in order to achieve appropriate and truly individualised patient care.

Duality of interest CW has been a speaker for Boehringer Ingelheim, FMC, Sanofi-Genzyme, Lilly and MSD, has received research grants from Sanofi-Genzyme and Actelion and has served on advisory boards for AbbVie, Akibia, Amgen, Bayer, Boehringer Ingelheim, Chiesi, Daiichi-Sankyo, Sanofi-Genzyme, GSK, Protalix and Vifor-FMC. NM has been a speaker for Amgen, Bayer, Boehringer Ingelheim, Sanofi-Aventis, MSD, BMS, AstraZeneca, Lilly and NovoNordisk, has received a research grant from Boehringer Ingelheim and has served on advisory boards for Amgen, Bayer, Boehringer Ingelheim, Sanofi-Aventis, MSD, BMS, AstraZeneca and NovoNordisk. NM declines all personal compensation from pharma or device companies

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