Diabetologia (2018) 61:2075–2078
https://doi.org/10.1007/s00125-018-4673-4

EDITORIAL

The bark giving diabetes therapy some bite: the SGLT inhibitors

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Published online: 22 August 2018

Abbreviations

CVD	Cardiovascular disease
DKA	Diabetic ketoacidosis
EMPA-REG OUTCOME	Empagliflozin, Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients
NAFLD	Non-alcoholic fatty liver disease
SGLT	Sodium–glucose cotransporter

Following on from the success of last year's special edition of *Diabetologia*, celebrating 60 years' clinical use of metformin, for this year's special edition we have chosen to focus on the newest class of glucose-lowering agents, the sodium–glucose cotransporter (SGLT) inhibitors. The 2015 update to the 2012 joint position statement from the EASD and the ADA suggested that metformin was in general the optimal first-line glucose-lowering agent, and, based on their beneficial effects on glucose, weight and blood pressure, placed the SGLT inhibitors as second- or third-line agents, together with all the other classes [1]. The statement pointed out that data on microvascular and macrovascular outcomes were lacking for almost all agents. Since then, new evidence has accumulated, particularly for the SGLT2 inhibitors, which has delighted us and challenged us to rethink our approach to glucose lowering in type 2 diabetes.

In a previous editorial, I suggested that an ideal glucose-lowering agent would 'address the underlying pathophysiology of type 2 diabetes and have added value in terms of reducing non-glycaemic risk factors for, and the incidence of, micro- and macrovascular complications of diabetes' [2]. In 2015, to commemorate 50 years of *Diabetologia*, several authors gave personal views on how glucose-lowering agents would develop over the next 50 years. Kahn and Buse endorsed the demands of regulators for cardiovascular outcome trials and highlighted forthcoming trial results, including those using the SGLT2 inhibitors [3]. In addition, Ahrén suggested the need for glucose-lowering agents with physiological targets other than beta cells and insulin resistant tissues, with few side effects [4]. At that time, short-term studies had already confirmed that SGLT2 inhibitors were effective glucose-lowering agents that also reduced weight and blood pressure. Estimates suggested that the reductions in HbA_{1c} and blood pressure were, to a large extent, independent of weight loss [5]. Thus, the beneficial reductions in weight, HbA_{1c} and blood pressure with the SGLT2 inhibitor empagliflozin compared with placebo in the Empagliflozin, Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) study were not surprising [6]. However, few people anticipated the cardiovascular endpoint results. For the first time, a randomised controlled trial of a glucose-lowering agent had demonstrated significant cardiovascular benefit in individuals with type 2 diabetes and pre-existing cardiovascular disease (CVD). Broadly similar results using another agent from the same drug class, canagliflozin [7], and from a non-randomised, 'real world' registry study [8] have suggested that these cardiovascular benefits are a class effect. In addition, these and other trials have demonstrated consistent reductions in albuminuria and possible slowing of decline in renal function [6, 7, 9, 10]. The wealth of knowledge with regard to the benefits (and risks) of SGLT inhibitor use continues to build. Hence, to bring us all up to date, this year we devote our special issue to this important group of drugs.

It was in the 1930s that several critical pieces of information came together to lay the foundations that eventually led to the development of SGLT inhibitors. First, Himsworth demonstrated a parallel relationship between blood and urine glucose concentrations [11]: below a certain blood glucose concentration, glucose filtered by the glomerulus was reabsorbed by the renal tubule and no glucose appeared in the urine; however, as blood glucose rose above this level, glucose appeared in the urine and increased with blood glucose concentration. Second, in a literature review, Hjarne

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described 19 individuals in several generations of one Swedish family who appeared to have inherited renal glucosuria, a rare, apparently benign, condition in which individuals have persistent glucosuria despite normal blood glucose concentrations [12]. Third, Poulsson built on the earlier work of von Mering and Minkowski to demonstrate, in dogs, that phlorizin, derived from apple tree bark, induced glucosuria by blocking tubular reabsorption of glucose [13–15]. Thus, the stage was set: glucose was reabsorbed by the renal tubule, reabsorption was dependent on an 'inherited' factor and could be inhibited.

We begin our special issue by tracing the development of the SGLT inhibitor class from these early roots. In their review, Rieg and Vallon provide an overview of the development of both SGLT1 and SGLT2 inhibitors, and dual inhibitors [16]. They give details on how phlorizin, which competitively inhibits SGLT1 and SGLT2, provided insights into potential SGLT inhibitor efficacy, but also how its intestinal side effects and short half-life hampered its use as a therapeutic agent. Genetic mutations in SGLT1 and SGLT2 in humans and genetically modified mouse models have helped to establish the respective roles of these transporters and have indicated that their inhibition could potentially represent a safe treatment for diabetes. Moreover, the authors explain how mathematical modelling predicted some of the mechanisms underlying the benefits and adverse effects of SGLT inhibitors. The authors also discuss the expanding list of SGLT inhibitors in development or on the market and present general considerations for drug discovery in the field of metabolism.

SGLT inhibitors lower the glucose burden, in part, by increasing excretion of the glucose filtered by the kidneys into the urine. To help us better understand this mechanism of action, Wright and colleagues describe the physiology of renal glucose handling in their review [17]. These authors shed light on how SGLT1, SGLT2 and GLUT2 were discovered to be the key players in renal glucose transport. Specifically, they illustrate how SGLT1 and SGLT2 facilitate glucose transport across epithelial cells in the proximal tubule, leading to glucose accumulation within the epithelium. This generates a glucose concentration gradient between the cell and plasma that, in turn, drives net passive exit of glucose towards the plasma via GLUT2. The bulk of glucose reabsorption is enabled by SGLT2 in the early proximal tubule, with SGLT1 'mopping up' the remaining glucose in the late proximal tubule. As explained by the authors, the functional properties and location of SGLT1 and SGLT2 are critical factors, not only in glucose homeostasis, but also in the efficacy of SGLT inhibitors. They provide evidence to illustrate how inhibition of either SGLT2 or SGLT1 promotes glucose excretion in the urine, but to different extents. Based on the assumption that SGLT2 is responsible for the bulk of glucose reabsorption, SGLT2 inhibitors have been developed for the treatment of diabetes. However, Wright and colleagues suggest that, while monotherapy with SGLT2 inhibitors does lower blood glucose levels, the huge reserve capacity of SGLT1 in the late proximal tubule might support the combined use of both SGLT1 and SGLT2 inhibitors for modulating renal glucose excretion.

Much of the interest in the SGLT2 inhibitors has centred on their pleiotropic effects (reviewed in [18]). In this edition of *Diabetologia*, Thomas and Cherney discuss the effects of SGLT2 inhibitors not only on glucose metabolism, but also on adiposity, renal function and blood pressure in type 2 diabetes [19]. They explain how SGLT2 inhibitor-induced glucosuria triggers several compensatory pathways, including a shift in substrate metabolism in the body: SGLT2 inhibitor therapy increases lipolysis, NEFA uptake and ketone generation, and utilisation of both these substrates. Furthermore, SGLT2 inhibitors may reduce inflammation within fat and augment fat browning. By promoting glucosuria, these drugs also achieve negative energy balance and weight loss. With regard to renal function, Thomas and Cherney describe how SGLT2 inhibitors have beneficial effects on GFR and albuminuria and protect against renal/tubular injury. In the kidney, SGLT2 inhibition promotes natriuresis, which activates tubuloglomerular feedback, thus reducing the transcapillary pressure gradient, GFR, albeit acutely, and albuminuria. Following the initial, immediate fall, the GFR stabilises, so that over the longer term GFR falls less than with placebo treatment. The natriuretic effects are also associated with reduced plasma volume, decreasing blood pressure and, potentially, improving vascular outcomes. Finally, SGLT2 inhibition can suppress tubular injury pathways, and reduce circulating and tissue levels of inflammatory and oxidative stress molecules.

In terms of pleiotropic effects, the most striking results so far come from SGLT2 inhibitor studies investigating the cardiovascular effects of these drugs. In a review published shortly after the results of the EMPA-REG OUTCOME trial were released, Sattar et al described the 14% reduction in the primary composite endpoint of myocardial infarction, stroke or CVD death as 'welcome but modest', but the 30–40% reductions in hospitalisation for heart failure, and cardiovascular and all-cause deaths, as 'highly impressive and unexpected' [20]. As part of this special series, Verma and McMurray outline the proposed mechanisms underpinning this unprecedented benefit, observed in people with type 2 diabetes with established CVD or multiple cardiovascular risk factors [21]. Specifically, they describe the ability of SGLT2 inhibitors to improve ventricular loading conditions by reducing preload, mainly via their diuretic and natriuretic effects, and/or by reducing blood pressure and altering vascular function. These inhibitors are also proposed to optimise cardiac energy metabolism by increasing production of the ketone body β-hydroxybutyrate, a 'superfuel' that is preferred by the heart, resulting in improved cardiac efficiency and cardiac output. SGLT2 inhibitors may also inhibit Na^+/H^+ exchange in the

myocardium [22–24] and prevent cardiac fibrosis, potentially contributing to their cardiovascular benefits. Reduced atherosclerotic plaque size, with less inflammatory marker infiltration into plaque, has also been reported [25]. Finally, Verma and McMurray discuss the impact of SGLT2 inhibition on adipokine production and/or action [21]. Despite the wealth of knowledge in this area, there are still many unanswered questions and the authors outline ongoing trials which should provide further answers.

Despite their glucose-lowering ability, glucose-independent effects and potential cardioprotective outcomes, the place of SGLT2 inhibitors in the management of type 2 diabetes is still hotly debated. To explain why, Lupsa and Inzucchi review the benefits and adverse effects of SGLT2 inhibitors approved for use in the USA and Europe, namely, canagliflozin, dapagliflozin, empagliflozin and ertugliflozin [26]. In addition to their blood glucose-lowering effects, these SGLT2 inhibitors induce some weight loss, lower blood pressure and have a low risk of hypoglycaemia. On the basis of these benefits and their ability to improve cardiovascular outcomes in high-risk individuals and possibly slow the progression of diabetic kidney disease, the authors propose that SGLT2 inhibitors should be considered reasonable second-line treatment options for individuals at risk of cardiovascular events or those with underlying nephropathy, if good glycaemic control has not been achieved with metformin monotherapy. Adverse effects associated with this class include urinary frequency and dehydration. Other potential side effects include genitourinary tract infections and euglycaemic diabetic ketoacidosis (DKA), while canagliflozin has been linked to lower-extremity amputations and bone fractures. The authors advise that individuals at risk of these complications should be monitored closely and treatment should be reconsidered or discontinued if they occur.

Describing the efficacy of SGLT inhibitors in type 1 diabetes, McCrimmon and Henry discuss the results of two recent 24 week Phase III randomised controlled clinical trials, inTandem3 and DEPICT-1, which studied sotagliflozin (a dual SGLT1/2 inhibitor) and dapagliflozin (an SGLT2 inhibitor), respectively [27]. Addition of an SGLT inhibitor resulted in a mean reduction in HbA_{1c} of 5–6 mmol/mol (0.4–0.5%), accompanied by weight loss (3–4 kg) and reductions in total daily insulin dose (10–15%). Hypoglycaemia rates were not increased, but the risk of DKA was significantly increased. The authors conclude that, although these early results are promising, longer-term clinical trials (≥52 weeks) as well as observational cohort studies are needed to define clearly the cohort of people with type 1 diabetes who will benefit most from adjunctive therapy with SGLT inhibitors. In addition, these studies will provide further data on safety and persistence of benefit. The authors emphasise that if SGLT inhibitors are to be used in routine care, specific patient and healthcare professional educational packages will be needed to ensure patient safety and to minimise risk.

To discuss SGLT2 inhibitors in the context of the future of diabetes therapy, Wanner and Marx reflect on the initial treatment target: to reduce blood glucose levels to within the normal range [28]. We know that a single therapeutic strategy does not work for all patients and, although glucose control is mandatory for reducing microvascular events in individuals with diabetes, it is now recommended that HbA_{1c} target values are individualised based on patient age, diabetes duration and presence of CVD or comorbidities. Cardiovascular outcome trials have confirmed cardiovascular safety (i.e. absence of harm) of most classes of glucose-lowering agents. However, upon discovering that SGLT2 inhibitors improve cardiovascular outcomes, the focus of type 2 diabetes therapy has shifted from glucose-lowering alone, to CVD risk reduction. Wanner and Marx go on to discuss the effects of SGLT2 inhibitors on other chronic diseases, in individuals with and without diabetes, including heart failure, kidney disease and non-alcoholic fatty liver disease (NAFLD) and outline the future treatment strategies for these diseases with SGLT2 inhibitors.

The development of the SGLT inhibitors marked the beginning of an incredibly exciting period for diabetes research and clinical care. In summary, in this special issue, we trace the development of the SGLT inhibitor class, critically examine the evidence of benefits, explore mechanisms of action, summarise their currently recommended use in diabetes and speculate how they may be used in the future, in individuals with and without diabetes. We are also reminded about the importance of heart failure as a major cause of morbidity and mortality in type 2 diabetes. However, we do not yet fully understand where SGLT2 inhibitors fit into the glucose-lowering armamentarium and many questions remain unanswered. Are they the 'best' drugs for everyone with type 2 diabetes or only those with CVD? Is it possible to identify those who will do well on the drugs and those who will not [29]? Can we predict those who are at risk of DKA? Current data suggest that there is no specific high-risk clinical phenotype, with individuals who develop DKA having a wide range of age, body weight and duration of SGLT2 inhibitor prescription [30]. Do the reductions in albuminuria and stabilisation of GFR translate in the longer term to reductions in renal failure? Can equivalent reductions in heart failure be achieved by intensified multifactorial intervention without SGLT2 inhibition, as described recently in the Steno-2 study [31]? Are SGLT2 inhibitors safe in the long term? At least in the short term, there does not appear to be an increase in risk of cancer [32], but there is a small but significant increase in serum magnesium [33]. Will they be used routinely in people without diabetes to manage weight [34], or treat renal disease, heart failure and NAFLD? A recent study demonstrated significant reductions in multiple hepatocyte injury markers with dapagliflozin alone, and a reduction in liver fat content when dapagliflozin was given with *n*-3 carboxylic acids [35]. Ongoing studies will answer these and many more questions over the next few years.

We are delighted that so many leading experts have contributed to this special edition on SGLT inhibitors. We hope you enjoy reading their contributions.

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