Published in final edited form as:

Diab Vasc Dis Res. 2015 March ; 12(2): 74–77. doi:10.1177/1479164114563303.

Sodium-glucose co-transporter inhibition in the treatment of diabetes: Sweetening the pot

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Introduction

Many innovative and clinically relevant advances have taken place in the realm of pharmacotherapy for type 2 diabetes mellitus (T2DM) since the introduction of sulfonylureas in the 1950s. The surge of new medications approved for clinical use for T2DM accelerated in the mid-1990s, with the introduction of metformin, alpha-glucosidase inhibitors, the meglitinides and the thiazolidinediones (TZDs). Incretin mimetics, in the form of glucagon-like peptide-1 (GLP-1) receptor agonists, were first brought to market in 2005, and the first of the dipeptidyl peptidase-4 inhibitors was approved in 2006. Amylin, colesevelam and bromocriptine were also approved by the US Food and Drug Administration (FDA) for the treatment of T2DM in the 2000s. The rapid proliferation of diabetes drug development over these past 20 years was largely driven by an increase in the global incidence and prevalence of T2DM, effectively doubling during this time period, and to address limitations of existing therapies.^{1,2} Moreover, it has become clear that patients with T2DM commonly fail to achieve glycaemic goals on monotherapy, thereby necessitating additional medications with differing and often complementary mechanisms of action.^{3,4} Despite such rapid progress in drug development, the management of hyperglycaemia in the setting of T2DM remains a challenge due to the progressive nature of the disease, physiological alterations in beta-cell survival and function, ongoing uncertainty with regard to efficacy of available and emerging T2DM medications for micro- and macro-vascular disease complications and adverse effects of available therapies such as hypoglycaemia with insulin and sulfonylureas, heart failure with the TZDs and weight gain with all three classes.

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Declaration of conflicting interests: Drs Alvarez and Neeland report no conflicts of interest relevant to this article. Dr McGuire discloses honoraria for trial leadership and consultation from GlaxoSmithKline, Takeda, Novo Nordisk, Orexigen, Cubist, Janssen, Eli Lilly, Bristol Myers Squibb, Astra Zeneca, Boehringer Ingelheim, Merck, Regeneron, Lexicon, Eisai.

A novel class of glucose-lowering medications, the sodium-glucose co-transporter 2 (SGLT2) inhibitors, was introduced for clinical use in Europe in 2012, and in the United States in 2013.^{5,6} These drugs target transporter proteins in the kidneys to affect glucose lowering. The kidneys influence glucose homeostasis through several mechanisms, including gluconeogenesis, glucose utilization and glucose reabsorption.⁷ The transport of glucose from the filtered urine into renal tubular epithelial cells is facilitated by a family of adenosine triphosphate (ATP)-dependent proteins (SGLT) involved in the transport of glucose against a concentration gradient with simultaneous transport of sodium down a concentration gradient.⁸ By inhibiting SGLT, the renal tubular threshold for glucose reabsorption is lowered and glucosuria occurs at lower levels of circulating glucose. SGLT2 inhibition lowers blood glucose through an insulin-independent mechanism, thereby addressing many of the limitations of existing therapies, and also exhibits important non-glycaemic effects, such as altering body composition and lowering blood pressure.

Although this new class of medications was introduced only in the past few years for clinical use, the basis of this clinical development and targeted mechanism of action has a history almost two centuries old. Phlorizin, a naturally occurring compound discovered in apple trees, was first isolated by French chemists in 1835 and is widely considered to be the prototypical SGLT inhibitor.⁹ It was first studied for use as an antipyretic in patients with infectious diseases, particularly malaria.⁹ While studying phlorizin as an antipyretic, it was observed to induce glucosuria. In the 1950s, studies shifted from assessing phlorizin as an antipyretic to evaluating it as a glucose-lowering medication.⁹ However, the development of phlorizin as a glucose-lowering medication was halted due to severe diarrhoea and dehydration attributed to effects of an active metabolite's inhibition of SGLT1 in the gastrointestinal (GI) tract, low oral bioavailability with wide variation in systemic exposure and low affinity for the SGLT2 isoform.⁹ Several compounds in the early stages of development contemporary with phlorizin more specifically targeting SGLT2 inhibition but without the drawbacks of phlorizin failed due to enzymatic inactivation resulting in short half-lives in vivo.^{10–12}

These initial failures, although disappointing, did not deter companies from continuing to probe SGLT inhibition as a therapeutic target. This class of drugs and its mechanism of action remained attractive due to the glucose-lowering effects independent of insulin, the low risk for hypoglycaemia and the ability to cause weight loss on that basis, and improve insulin sensitivity.¹³ Dapagliflozin, canagliflozin and empagliflozin are the three medications in the SGLT2 inhibitor class that have been approved for clinical use in the United States and Europe, with several others in advanced global development (ertugliflozin, remogliflozin, sotagliflozin – a dual SGLT1 and SGLT2 antagonist) or regional development/approval for clinical use (e.g. ipragliflozin, luseogliflozin, tofogliflozin).¹⁴ Each of these is structurally similar to phlorizin, but they are more potent inhibitors of SGLT2, have longer half-lives and have better oral bioavailability.

In the present issue of the *Diabetes & Vascular Disease Research*, we invited some of the most established authorities in the field to provide history, insight and commentary regarding the rapidly evolving therapeutic concept of targeting the SGLT system for the treatment of diabetes. In these three review articles, content is focused on (1) the basic

physiology and distribution of the SGLT transporters (SGLT 1-predominantly GI; SGLT2-renal), their role in diabetes and the basis for targeting the SGLT transporters for glucose-lowering therapy in both type 2 and type 1 diabetes; (2) the potential for cardiovascular risk modulation for SGLT2 inhibitors; and (3) an introduction to a dual SGLT1/2 inhibitor, sotagliflozin.

Gallo et al. provide a comprehensive review of glucose handling by the kidney in people with and without diabetes, with extensive description and characterization of the SGLT transporters. The authors discuss both SGLT2 and SGLT1 as potential therapeutic targets, and the molecular rationale underpinning the inhibition of these transporters as treatment in T2DM. They also comment on the mechanistic and physiologic changes that occur beyond SGLT2 inhibition on the kidney.

Inzucchi et al. discuss the intersection between cardiovascular disease (CVD) and diabetes, and potential pathways by which SGLT2 inhibitors may modulate CVD risk. The authors describe both the glycaemic and non-glycaemic effects of SGLT2 inhibitors. Specifically, with regard to non-glycaemic effects, the authors comment on the influence of SGLT2 inhibition on blood pressure, arterial stiffness, weight and visceral adiposity, oxidative stress, serum uric acid, sympathetic activity and cholesterol metabolism. Robust clinical data are currently available describing the effects of SGLT2 inhibitors on intermediate markers, such as HbA1c. While reducing HbA1c reduces micro-vascular risk,¹⁵ it has not been proven to be useful as a marker for reducing CVD in large clinical trials.^{16–18} Thus, in 2008, the US FDA and the EU European Medicines Agency released guidance to the pharmaceutical industry to conduct prospective, blinded CVD safety studies for a minimum of 2 years prior to a drug's approval for use.^{19,20} This guidance was released in response to the association of specific medications and medication classes with elevated CVD risk.^{21–26} While there may be beneficial off-target effects of SGLT2 inhibitors on intermediate markers of CVD risk and disease, their effect on CVD clinical outcomes are yet to be demonstrated. Therefore, Inzucchi et al. discuss the design and objectives of the ongoing, large international randomized clinical outcomes trials of SGLT2 inhibitors seeking to assess the CVD safety and efficacy of these medications. The first reporting of results from these trials is anticipated in the first quarter of 2015, with completion of the EMPA-REG OUTCOME™ trial of empagliflozin.

Sotagliflozin, a novel dual inhibitor of SGLT1/2, is introduced in a review by Lapuerta et al. SGLT2 inhibitors were developed with the purpose of creating compounds with higher affinity for the SGLT2 transporter compared with the SGLT1 transporter. This experience is based on the backdrop of knowledge that functional mutations in the SGLT1 gene cause glucose-galactose malabsorption producing severe and often life-threatening diarrhoea.^{27,28} Lapuerta et al. present data suggesting that SGLT1 inhibition concomitantly with SGLT2 inhibition may be efficacious for patients with diabetes, with potential efficacy for both type 2 and type 1 diabetes. The authors postulate that compounds with the proper ratio of dual SGLT1/2 inhibition, such as sotagliflozin, produce greater HbA1c reductions than SGLT2 inhibition alone, and with less potent SGLT1 inhibition may do so without prohibitive GI adverse effects. Similar off-target effects of sotagliflozin to SGLT2 inhibitors were demonstrated with the addition of postprandial glucose reduction and GLP-1 elevation.

Limited studies are available to fully assess the safety of sotagliflozin, and research is ongoing.

The efficacy of medications for any condition must be assessed in context with safety considerations. SGLT2 and dual SGLT1/2 inhibitors have adverse effects that may influence their potential use in patients with diabetes. Increased risk for genitourinary tract infection, most frequently genital yeast infection, is the most common adverse effect reported in clinical studies.^{29,30} These infections are much more common in women than in men, and more common in uncircumcised versus circumcised men. Reductions in glomerular filtration rate have been reported, although it is theorized that this reduction is a consequence of reduced hyperfiltration and less likely nephrotoxicity.³¹ SGLT2 inhibitors have been shown to modestly increase low-density lipoprotein cholesterol (LDL-C) concentrations, although it is unclear how this finding may affect CVD outcomes.^{30,32}

In summary, T2DM is on the rise and the armamentarium to treat hyperglycaemia in these patients is increasing in parallel. SGLT2 and dual SGLT1/2 inhibitors present an option for patients who have a novel mechanism of action that is insulin independent. This class of drugs has myriad favourable cardiometabolic effects; however, it will remain unclear whether these medications will ameliorate CVD risk until prospective cardiovascular outcome trials are complete. As with all medications, clinicians need to balance the benefits with the risks and individualize therapy taking into account the patient perspective. We look forward to discovering more about the role of SGLT inhibition for the treatment of cardiovascular and metabolic diseases in the near future.

Acknowledgments

Funding: This work was supported (C.A.A.) by the National Institutes of Health (K08DK101602).

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