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EXPERT OPINION

Dapagliflozin therapy in type-2 diabetes: current knowledge and future perspectives

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Dapagliflozin is a new antidiabetic agent that belongs to the class of sodium glucose transporter 2 (SGLT-2) inhibitors. By decreasing renal glucose absorption, these agents target hyperglycemia independent of insulin secretion or insulin sensitivity. This unique mechanism of action differentiates them from existing antidiabetic agents currently on the market. It has been hypothesized that SGLT-2 inhibitors can be effectively and safely combined with other agents, including insulin, and incretin-based therapies. They can be used either as monotherapy, or in dual- or triple-agent combinations. Dapagliflozin has been shown to be effective and safe in patients with type-2 diabetes, with modest but significant reductions in HbA1c and a number of potentially beneficial and sustained non-glycemic effects, including those on body weight, plasma lipids and systolic blood pressure. In addition, dapagliflozin has been shown to have a generally favorable safety profile and is well tolerated. Ongoing studies may provide definitive answers on the cardiovascular safety and efficacy of SGLT-2 inhibitors in patients with type-2 diabetes.

Keywords: dapagliflozin, glucose, sodium-glucose transporter 2, type-2 diabetes

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1. Introduction

Dapagliflozin is a selective inhibitor of sodium glucose transporter 2 (SGLT-2), which targets hyperglycemia independent of insulin secretion or insulin sensitivity, by decreasing renal glucose reabsorption [1]. Historically, the first agent studied in this class was phlorizin, which enhanced renal glycosuria through inhibition of SGLT-1 (in the small intestine) and SGLT-2 (in the proximal renal tubule) [2]. However, phlorizin was shown to have several limitations, including poor oral bioavailability and severe gastrointestinal side effects. Research efforts were thenceforth focused on the development of selective SGLT-2 inhibitors, such as dapagliflozin.

The first SGLT-2 inhibitor approved for the treatment of patients with type-2 diabetes was canagliflozin, which was launched in the USA in 2013. Thereafter, dapagliflozin and empagliflozin also became available; dapagliflozin has been approved by the European Medicines Agency on 12 November 2012 and by the FDA on 8 January 2014. All three agents are dosed orally and taken once daily [3]. Given the mechanism of action in the kidney, careful monitoring of renal function is required with the use of SGLT-2 inhibitors and lower doses or discontinuation is recommended in patients with moderate renal impairment (e.g., glomerular filtration rate between 45 and 60). Patients with moderate renal dysfunction lay on the inability of the drug to improve glycemic control and not on any risk for deterioration of kidney function [4].

It should be highlighted that SGLT-2 inhibitors have a unique mechanism of action, which differentiates them from any existing antidiabetic agent. Because of this reason, it has been suggested that SGLT-2 inhibitors may be effectively and safely combined with all other existing class of agents, including insulin and

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incretin-based therapies. They can be used either as monotherapy, or in dual or triple combinations. This has opened a fascinating and new era for the treatment of type-2 diabetes.

2. Glycemic and non-glycemic effects

Several data are available on the beneficial effect of dapagliflozin, as monotherapy and in combination, on glycemic control. In a recent meta-analysis of 12 randomized controlled trials [5], it was shown that dapagliflozin improved glycemic control without weight gain when combined with conventional antidiabetic drugs (including metformin, glimepiride, pioglitazone, sitagliptin and insulin), in patients with type-2 diabetes. Another meta-analysis [6] reported that dapagliflozin and incretin-based therapies provided better short-term glycemic control compared with sulfonylurea monotherapy; further, dapagliflozin was the only add-on treatment with a favorable effect on body weight and hypoglycemia in comparison to the other classes of drugs evaluated (including vildagliptin, sitagliptin, linagliptin and exenatide). Similar beneficial effects were found for dapagliflozin when added to metformin [7].

Due to the efficacy and safety of dapagliflozin and SGLT-2 inhibitors in general, these agents are now gaining acceptance as treatment options in therapeutic guidelines for type-2 diabetes. The 2013 American Association of Clinical Endocrinologists algorithm recommended SGLT-2 inhibitors as a treatment option in patients with type-2 diabetes as both monotherapy and in combination therapy; however, there was a warming for using such agents with caution, due to the relative small data available [8]. It is likely that a future update of the joint position statement of the American Diabetes Association and the European Association for the Study of Diabetes will include SGLT-2 inhibitors as a therapeutic alternative.

Dapagliflozin treatment is also notable for a number of beneficial non-glycemic effects [9], including a reduction in body weight and blood pressure, increase in plasma high-density lipoproteins-cholesterol concentrations, and a decrease in serum high-sensitivity C-reactive protein. Canagliflozin has also shown some beneficial effect on plasma triglycerides and low-density lipoproteins-cholesterol levels [10] and further studies may report similar effects with dapagliflozin, but we have to wait for the results. It has to be highlighted that, among these aforementioned parameters, the level of evidence is strongest for body weight reduction, since studies were specifically designed to demonstrate an effect on this variable. Several additional studies investigating the non-glycemic effects of SGLT-2 inhibitors are currently ongoing promising to provide more data in this regard.

3. Expert opinion

Dapagliflozin has a mechanism of action that is independent of insulin; therefore, the risk of hypoglycemia is minimized with the use of this agent or with the use of any SGLT-2 inhibitor in general. Dapagliflozin has not only been shown to be safe and effective in patients with type-2 diabetes, but it also appears to have several important non-glycemic effects, such as those on body weight, plasma lipids and blood pressure (all components of the metabolic syndrome). Thus, it is possible that dapagliflozin may prove to be a useful agent for the prevention and treatment of the metabolic syndrome, a condition that is dramatically increasing worldwide and which represents a major health problem in most western countries. It should be also highlighted that incretin-based therapies also have important non-glycemic effects, including those on inflammatory markers and subclinical atherosclerosis [11-13].

There is currently a debate whether it is necessary to introduce yet another class of drugs for therapy of type-2 diabetes. The basis of this argument is that we already have in the market a number of glucose-lowering agent classes, including insulin, metformin, sulfonylureas, glinides, alpha-glucosidase inhibitors, thiazolidinediones, dipeptidyl peptidase-4 inhibitors and glucagon-like peptide 1 receptor agonists. However, most of these agents have significant side effects and the use of therapies in combination, although beneficial for glucose lowering, further diminishes their tolerability. Therefore, there is a need for newer therapies, and the mechanism of action of SGLT-2 inhibitors is unique, differentiating these agents from any existing antidiabetic treatment.

SGLT-2 inhibitors have been shown to be effective and safe in clinical trials as monotherapy or in combination with other antidiabetic drugs. Yet, a few concerns need to be mentioned. Although SGLT-2 inhibitors are generally well tolerated and very few serious adverse events have been reported, there has been a higher frequency of symptoms suggestive of genital and urinary tract infections with the use of dapagliflozin, canagliflozin or empagliflozin. However, very few patients had to discontinue therapy with all three of these agents, since the majority of these events were mild in severity and responded to standard therapies [14,15]. It has also been suggested to avoid the use of loop diuretics and pioglitazone in patients taking dapagliflozin due to concerns on hypotension and bladder cancer; however, the relationship between SGLT-2 inhibition and cancer formation is still inconclusive and studies with larger sample size, longer exposure duration and different ethnicities are warranted [16].

Another concern is linked to the lack of definitive answers on the cardiovascular safety and efficacy of SGLT-2 inhibitors, including dapagliflozin, in patients with type-2 diabetes. Although these agents have shown beneficial effects on cardiovascular risk factors, such as body weight, plasma lipids and blood pressure, data on cardiovascular outcome is still lacking. However, it should be highlighted that the same situation applies to other antidiabetic agents with novel therapeutic mechanisms, such as the incretin-based therapies. Of interest, Dziuba *et al.* [17], using a mathematical model over a 20-year period, showed that adding dapagliflozin to existing antidiabetic therapies would reduce cardiovascular and

microvascular complications associated with type-2 diabetes, with relative reductions in the incidence of myocardial infarction, stroke and cardiovascular death of 14, 9 and 10%, respectively.

Large cardiovascular outcome trials for all three agents in the SGLT-2 class are currently ongoing. Regarding dapagliflozin, 22,000 patients with type-2 diabetes and a high cardiovascular risk are being studied in The Dapagliflozin Effect on Cardiovascular Events (DECLARE) study, which began recruitment in 2013. The cardiovascular outcomes of studies have evaluated canagliflozin for 2 years are expecting (CANVAS: The Canagliflozin Cardiovascular Assessment Study and EMPA-REG OUTCOME: The Empagliflozin Cardiovascular Outcome Event Trial) given that the recruitment phase was completed in 2012 [18,19]. An additional cardiovascular outcome trial has also started recruitment for ertugliflozin, another SGLT-2 inhibitor.

In summary, dapagliflozin and SGLT-2 inhibitors in general represent a novel and attractive treatment approach for type-2 diabetes. Data available so far are consistent and promising, although some concerns still need to be fully addressed.

Declaration of interest

M Rizzo has given lectures and participated in conferences, advisory boards or trials sponsored by AstraZeneca, Boehringer Ingelheim, Kowa, MSD, Novo Nordisk and Servier. The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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