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COMMENTARY

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Commentary: SGLT inhibitors in type 1 diabetes: Place in therapy and a risk mitigation strategy for preventing diabetic ketoacidosis - the STOP DKA protocol

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Abstract

In the accompanying article, Goldenberg et al. review the promotion of diabetic ketoacidosis by SGLT2 inihibitors. They have carried out a metanalysis showing a 3.5-fold increase in the risk of diabetic ketoacidosis (DKA) in patients with type 1 diabetes under treatment with SGLT2 inhibitors. They make a number of suggestions for attempting to mitigate the risk of DKA in these patients, notably including blood ketone monitoring and the use of supplemental carbohydrates with additional insulin when ketones suggest incipient DKA. Their proposal merits evaluation in a clinical trial involving type 1 diabetes, which should also assess the possible cardiorenal benefits demonstrated with treatment with SGLT2 inhibitors in type 2 diabetes.

KEYWORDS
Dapagliflozin, diabetes complications, empagliflozin, type 1 diabetes, canagliflozin

The past 25 years have brought us a better understanding of the role of the kidney in glucose metabolism. After eating, renal gluconeogenesis increases and accounts for approximately 60% of endogenous glucose release in the postprandial period; however, the primary renal effect on glucose levels is by reabsorption of filtered glucose in the proximal convoluted tubule, mediated by sodium glucose cotransporters (SGLT).[1-3] In the proximal tubule, there are two primary SGLT molecules. In the usual state, SGLT2 accounts for 90% of glucose reabsorption, with SGLT1 being responsible for 10%.[4]

SGLT2 inhibitors were developed to treat diabetes by blocking glucose reabsorption and they have been successful in moderately reducing glucose levels and HbA1c, and in inducing modest weight loss. However, the impact of these agents has gone far beyond glycaemic effects. Concerning type 2 diabetes patients, the three recent trials involving SGLT2 inhibitors (CANVAS, DECLARE-TIMI 58 and EMPA-REG OUTCOME) have demonstrated reduced cardiovascular and overall mortality with administration of these agents. In the EMPA-REG OUTCOME trial, empagliflozin treatment led to a 38% reduction in cardiovascular (CV) mortality and a 32% reduction in overall mortality in patients with established CV risk.[5] In the CANVAS trial, there was a 14% reduction in CV mortality and a 13% reduction in overall mortality.[6] In the DECLARE-TIMI 58 trial, dapagliflozin treatment resulted in a 17% reduction in the composite of CV mortality and hospitalization for congestive heart failure.[7]

In each of these trials and in other large-scale studies focused on renal disease, each of these agents has shown benefit in reduced renal progression and events. In the EMPA-REG OUTCOME, empagliflozin treatment was associated with a statistically significant 39% reduction in relative risk of incident or worsening nephropathy as compared to placebo.[8] In the CREDENCE trial, canagliflozin treatment resulted in a 30% improvement in time to reach a composite of end-stage kidney disease, doubling of serum creatinine and renal or CV mortality.[9] In the DECLARE-TIMI 58 trial, the risk of end-stage renal disease or renal death was lower in the dapagliflozin group than in the placebo group (11 [1%] vs 27 [3%]; HR, 0.41 [95% CI, 0.20–0.82]; $P = 0.012$).[10] As a result of the proven cardiorenal and mortality benefits, SGLT2 inhibitors have moved to the forefront in treatment of type 2 diabetes.

Concerning type 1 diabetes, studies of SGLT inhibitors have been of shorter duration and have focused solely on glucose control. As summarized by Goldenberg et al.,[11] dapagliflozin, empagliflozin and sotagliflozin (a combined SGLT2/SGLT1 inhibitor) added to ongoing

treatment with either insulin pumps or multiple daily injections have all shown glycaemic benefit in type 1 diabetes, with modest reductions in HbA1c (0.3%–0.5%), weight and glucose variability, without increased incidence of hypoglycaemia. These benefits are certainly clinically attractive, given the difficulty of achieving normal glucose levels in insulin-dependent patients. In fact, upon approval of canagliflozin for treatment of type 2 diabetes, this agent was used by clinicians outside the approved indication for patients with type 1 diabetes. Despite improved glucose levels, there was a tendency to promote diabetic ketoacidosis (DKA) in some patients. An initial report of 13 episodes in seven patients with SGLT2 inhibitor-treated type 1 diabetes and two patients with type 2 diabetes surfaced.[12] In all cases, recognition of DKA was delayed by deceptively low plasma glucose values. In several cases, re-challenge with the SGLT2 inhibitor was accompanied by renewed ketosis.

Goldenberg et al.[11] have summarized the evidence from the major Phase 3 trials of the SGLT2 inhibitors dapaglizlozin and empagliflozin, and also sotagliflozin, in type 1 diabetes. They carried out a meta-analysis that revealed a 3.5-fold higher incidence of DKA induced by SGLT2 treatment. The biochemical reason for the onset of DKA is unclear. Speculation has focused on decreased insulin levels related to lower glucose values, increased lipolysisis and utilization of fatty acids, dehydration and hyperglucagonaemia, induced by treatment with an SGLT2 inhibitor. In addition to an increased incidence of DKA, there were clearly more acidosis events in the SGLT2-treated cohorts.

Goldenberg et al.[11] are proposing a protocol for attempting to mitigate the risk of DKA in patients with type 1 diabetes undergoing treatment with SGLT2 inhibitors. It should be emphasized that their protocol has not been subjected to clinical trial. Their proposals include careful selection of patients who would diligently self-monitor, not only glucose levels, but also ketone levels. The use of these agents would be directed by physicians with expertise, not only in managing type 1 diabetes, but also in the use of SGLT2 inhibitors in this patient population. They encourage education of patients as to the signs and symptoms of DKA and the need to recognize possible precipitating factors. They advocate frequent blood ketone self-measurements and recommend active self-adjustment of insulin doses based on glucose and ketone levels, with use of supplemental carbohydrate to combat lipolysis. And they advise increasing fluids to combat hypovolaemia.

The suggestions of Goldenberg et al.[11] are practical and reasonable, but there is no guarantee of a reduction in the incidence of SGLT2 inhibitor-promoted DKA. The Phase 3 trials mentioned had already implemented patient and investigator education and many of the procedures described. Patients were provided with blood ketone meters. It may be that experienced diabetologists can select patients more carefully than clinical trial investigators, but that remains to be seen. Many of the trial participants were insulin pump-treated and, therefore, had already undergone a process of selection for the skills and commitment necessary to manage pumps. As we all know, one of the primary causes of DKA in our insulin pump-treated patients is interruption of the continuous flow of insulin as the result of mechanical problems with infusion sets. When this happens, there is no long-acting repository insulin to counteract a rapid metabolic decompensation. Even our most experienced and knowledgeable insulin pump users have fallen into DKA.

The use of concurrent blood glucose and ketone measurements could provide additional data, but our present experience is not yet adequate to fully understand the best response to the values obtained. When ketone values increase, additional fluid intake is definitely helpful. Increased ingestion of carbohydrates and additional insulin may be beneficial as the authors suggest, but we lack confirmation.

The STOP-DKA protocol deserves validation in a clinical trial. As the authors point out, the SGLT2 inhibitor dosage levels selected for the Phase 3 trials may have been higher than that required for benefit in the type 1 diabetes population. A small trial of empagliflozin at a dose of only 2.5 mg did not show an increased incidence of DKA. It would be reasonable to proceed with redesigned trials that fully incorporate the STOP-DKA recommendations.

However, new trials will not be able to address the issue of pregnancy. The risks of SGLT2 inhibitor therapy in pregnant women is, of course, unknown. Testing of an investigational agent during pregnancy is contrary to standard principles of drug development. Type 1 diabetes is predominately a disease of young people, and 50% of them are women, most of whom have childbearing potential; thus, the possibility of pregnancy is higher than it is with many other contraindicated medications. Realistically, as much as we idealize carefully thought out and implemented child bearing, unplanned pregnancies during treatment with SGLT inhibitors are going to occur. In highly planned pregnancies in diabetes patients, the goal prior to conception is to keep HbA1c as close to normal as possible to prevent excess spontaneous abortions and major congenital malformations.[13,14] Tight glycaemic control during the first trimester and throughout pregnancy is required to avoid maternal, foetal and neonatal complications. The recommendation from Goldenberg et al.[11] to immediately discontinue treatment with SGLT2 inhibitors in the event of conception must be examined, because it eliminates women who are considering conception from treatment with SGLT inhibitors. However, paradoxically, withdrawing treatment from women as they attempt conception could worsen glucose levels at this critical time. Furthermore, pregnancy in itself can lead to DKA when glucose levels are poorly controlled[15] and DKA during pregnancy is life threatening, with a high rate of foetal loss.[16] It is also unknown whether the pregnant state may worsen the tendency of SGLT2 inhibitors to promote DKA.

The benefits and risk of SGLT2 inhibition in type 1 diabetes are the focus of the present controversy. Potential benefits include moderately improved diabetes control, weight loss and decreased glycaemic variability, whereas the promotion of acidosis and DKA is a significant risk. It must be remembered that patients continue to die as a result of DKA. Also on the unfavourable side of the ledger, there is the increased incidence of genital infection with treatment with SGLT2 inhibitors. The European Medicines Agency and the Japanese Ministry of Health, Labour and Welfare approved the use of sotagliflozin and dapagliflozin in type 1 diabetes while the United States Food and Drug Administration (FDA) rejected sotagliflozin and dapligliflozin for treatment of type 1 diabetes. Certainly, the FDA

weighed the risks and benefits in their negative decision concerning these agents. Missing from the debate are the possible additional cardiovascular and renal benefits demonstrated in trials concerning SGLT2 inhibitors in the type 2 diabetes population. Clearly, the cardiorenal advantages go far beyond the glycaemic effects and it remains to be proven that type 1 patients may also benefit from these long-term effects.

The article by Goldenberg et al.[11] should be viewed, not as an endorsement of use of SGLT2 inhibitors in type 1 diabetes, but rather, as an invitation for future studies to determine the overall risks and benefits of this proposed form of treatment.

CONFLICT OF INTEREST

The authors have no conflicts of interest.

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