



eDiabetes Review VOLUME 2, ISSUE 10

RISKS AND BENEFITS OF SGLT-2 INHIBITOR AGENTS



In this Issue...

SGLT-2 inhibitors are a newer class of oral antidiabetes medications that may provide important benefits to many patients. In this issue, Dr. Anne Peters, director of the USC Clinical Diabetes Program at the Keck School of Medicine of the University of Southern California, reviews recent publications describing the clinical benefits and risks of these agents in improving diabetes management.

LEARNING OBJECTIVES

After participating in this activity, the participant will demonstrate the ability to:

- Describe the glucose, weight, and blood pressure lowering effects of SGLT-2 inhibitors and their persistence over time.
- Discuss the cardiovascular benefits reported with the use of SGLT-2 inhibitors.
- Summarize the risks of SGLT-2 inhibitors, including diabetic ketoacidosis and bone fractures.

The Johns Hopkins University School of Medicine takes responsibility for the content, quality, and scientific integrity of this CME activity.

GUEST AUTHOR OF THE MONTH

Commentary:



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Guest Faculty Disclosure

Anne Peters, MD has indicated that she has been on the advisory board or consulted for Abbott Diabetes Care, Becton Dickinson, Bigfoot Biomedical, Bidel, Boehringer Ingelheim, CVS/Caremark, Eli Lilly and Company, Bristol-Myers Squibb/AstraZeneca, Intarcia, Merck, Janssen, Lexicon, Novo Nordisk, OptumRx, and Thernalin. She has received research grant funding from Janssen and Medtronic Foundation, and editorial fees from Medscape.

Program Information

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Length of Activity

- 1.0 hour Physicians
- 1.0 contact hour Nurses

Launch Date

May 26, 2016

Expiration Date

May 25, 2018

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Unlabeled/Unapproved Uses

Anne Peters, MD has indicated that there will be references to the unlabeled or unapproved uses of SGLT-2 inhibitor agents for managing type 1 diabetes.

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COMMENTARY

SGLT-2 inhibitors are a newer class of oral antidiabetes medications. As with all treatments, our knowledge of risks and benefits grows over time. The Nauck et al extension study illustrates the well-known effects and side effects of these agents. First, they are essentially a "diuretic" for glucose — the mechanism of action causes glycosuria by inhibiting SGLT-2 in the kidney, leading to renal glucose wasting. This effect lowers blood glucose levels modestly, along with providing reductions in weight and systolic blood pressure. The effect differs from that seen with sulfonylureas, which initially improve blood sugar levels to a greater degree but whose effect wanes over time. Additionally, use of sulfonylurea agents showed a nearly 10-fold increase in the risk for hypoglycemia, which can be a serious side effect. With dapagliflozin, the weight and blood pressure effects of SGLT-2 inhibitors seemed to persist over 104 weeks in the patients who continued in the trial.

As has been seen in all trials with SGLT-2 inhibitors, there was an increase in genital mycotic infections, particularly in females and uncircumcised males. Although these occur more often early in treatment with these agents, they can occur at any time. It is important to prepare patients for this risk, with instructions for special attention to hygiene (in uncircumcised males, in particular). Additionally, suggesting use of over-the-counter antifungal preparations and/or treating with fluconazole early can help to resolve this side effect. Rates of UTIs were increased with dapagliflozin, although not of more serious

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genitourinary (GU) infections. Interestingly, the FDA recently issued a warning of reports of pyelonephritis and urosepsis in people treated with SGLT-2 inhibitors.¹ Thus, it is important to advise patients to report any signs or symptoms of UTI to ensure early treatment. In addition, because patients will likely note an increase in urination when they start on SGLT-2 inhibitor therapy, they should be counseled about the differences between urinating a bit more frequently than usual because of the diuretic effect of the drug and the much more frequent and often painful urination seen with a UTI.

In contrast to the annoyance of genital mycotic infections and usually benign UTIs, the EMPA-REG trial (Zinman et al) showed that empagliflozin reduced the risk of cardiovascular death, congestive heart failure requiring hospitalization, and overall mortality. These benefits were seen within just weeks of starting the empagliflozin, indicating a volume-related/hemodynamic effect of these agents. The exact mechanism(s) for these benefits is under investigation. Repeating these findings with other SGLT-2 inhibitors will reveal whether this is a class effect, but the data from the empagliflozin trial are compelling in demonstrating cardiovascular benefit with this agent and differentiates it from all of the other antidiabetic agents, none of which has shown actual cardiovascular benefit. In the EMPA-REG trial, as in the other studies with SGLT-2 inhibitors, the A1c reduction was approximately 0.5% compared to placebo, with a sustained reduction in SBP, as well as weight loss. The A1c reduction is not likely to be the sole cause of the improved CVD outcomes, nor are the changes in weight and blood pressure alone responsible. The current research appears to indicate that both these effects, combined with thus far unelucidated additional benefits SGLT-2 inhibitors provide (which may include improvement in or preservation of renal function), may be responsible for the EMPA-REG trial's remarkable findings.

In addition to benefiting individuals with type 2 diabetes, the insulin-independent effect of SGLT-2 inhibitors suggests they could be beneficial in those with type 1 diabetes as well. The phase II study performed by Henry et al assessing the benefits of canagliflozin in individuals with type 1 diabetes showed promise in A1c reduction with some weight loss and no increase in hypoglycemia, at least with the 100 mg dose. In my experience in using SGLT-2 inhibitors off-label in people with type 1 diabetes, a reduction in glycemic variability is seen, which many patients find helpful. However, the Henry trial showed that the maximal dose of canagliflozin was too high: 300 mg daily had a higher risk for diabetic ketoacidosis (DKA) and severe hypoglycemia than did the 100 mg dose. Therefore, submaximal doses of SGLT-2 inhibitors should be studied for use in type 1 diabetes and their use in type 1 diabetes limited to research trials or centers familiar with their off-label use.

Two additional concerns are DKA in people with type 2 diabetes and an increased risk for fracture, so far noted primarily in the canagliflozin trials. The label has a warning for an increased risk for DKA in people with type 1 and type 2 diabetes for all SGLT-2 inhibitors, as well as a warning for an increased risk of fracture for those on canagliflozin. In our case series (Peters et al) we described the phenomenon of euglycemic DKA (although hyperglycemic DKA occurs as well). Our concern with euglycemic DKA is that it is being missed as a clinical diagnosis, and therefore patients are not being appropriately treated. Finally, the fracture risk was primarily of the extremities and occurred in the older population with more comorbidities and a higher rate of falls in the CANVAS cardiovascular outcomes trial (Watts et al), although there may also be a direct effect on bone mineral density that is possibly related to weight loss and other factors (Bilezikian).

In summary, the SGLT-2 inhibitors are an intriguing new class of medication for treating type 2 diabetes. They appear to provide both glycemic and macrovascular benefits, although the latter has been proved only with empagliflozin to date. Clinicians considering prescribing these agents should be familiar with the prescribing guidelines (see eGFR cutpoints in the label and consider DKA if a patient presents with an anion gap metabolic acidosis) and the expected benefits and side effects. Further, they should warn patients to expect increased urination and to be aware of risk of mycotic genital infection and UTI, as well as the potential risk for fractures. Those safety considerations aside, however, clinicians should be enthusiastic about the glycemic, weight, blood pressure, and potential CVD benefits these agents can provide.

Reference

1. FDA Drug Safety Communication: FDA revises labels of SGLT2 inhibitors for diabetes to include warnings about too much acid in the blood and serious urinary tract infections. [Link available at: http://www.fda.gov/Drugs/DrugSafety/ucm475463.htm](http://www.fda.gov/Drugs/DrugSafety/ucm475463.htm)

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DURABILITY OF SGLT-2 INHIBITOR EFFECTS

Nauck MA, Del Prato S, Duran-Garcia S, et al. Durability of glycaemic efficacy over 2 years with dapagliflozin versus glipizide as add-on therapies in patients whose type 2 diabetes mellitus is inadequately controlled with metformin. *Diabetes Obes Metab.* 16:1111-1120, 2014.



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This study was a 52 week, double-blind, active-controlled RCT comparing the addition of dapagliflozin (n = 406) vs glipizide (n = 408) in patients with type 2 diabetes who were not at target on metformin therapy, with an extension period up to 104 weeks. Approximately half of the patients who completed the 52 week trial continued in the extension phase. The glycemic results showed noninferiority in HbA1c reduction (mean = 0.52%) between the two groups, with the glipizide-treated patients exhibiting a much more rapid fall in A1c initially that by 52 weeks had increased to meet the dapagliflozin treated group. From weeks 52 to 104, A1c increased in both groups, with a greater increase in the sulfonylurea agent-treated group, resulting in a dapagliflozin vs glipizide difference of - 0.18% (P = .0211).

There were significant differences in weight. Those in the dapagliflozin treated group lost weight and maintained their weight loss over the trial (- 3.4 kg at 52 weeks and - 3.7 kg at 104 weeks), whereas the glipizide-treated group gained weight (+ 1.6 kg at 52 weeks; + 1.4 kg at 104 weeks). Systolic blood pressure was reduced in the dapagliflozin treated group at 52 weeks as well (- 3.8 mmHg vs + 0.9 mmHg with glipizide), and a reduction remained throughout the 104 weeks of the study (- 2.7 mmHg vs + 1.2 mmHg with glipizide).

For side effects, 4.2% of subjects reported at least one hypoglycemic event with dapagliflozin, compared to 45.8% with glipizide. Overall, there were 26 hypoglycemic events with dapagliflozin and 843 with glipizide. Rates of genital infections were higher in the dapagliflozin-treated subjects: 14.8% compared to 2.9% in the glipizide-treated group, more common in women. UTI's were also increased: 13.5% in the dapagliflozin- treated group and 9.1% in the glipizide-treated group. Three patients in the glipizide- treated group developed pyelonephritis, but none did in the dapagliflozin-treated group. No deaths were reported in the dapagliflozin-treated group, whereas four deaths occurred in the glipizide-treated group.

Although this was a long term extension study with a high dropout rate, it shows the differences and similarities between sulfonylurea agent therapy and dapagliflozin when added to metformin in individuals with type 2 diabetes. Patients on sulfonylureas had a more rapid fall in blood glucose levels but then had a gradual increase over this study. Blood sugar levels fell more gradually with dapagliflozin but were lower over time. Dapagliflozin reduced weight and systolic blood pressure levels and was associated far fewer episodes of hypoglycemia. It did cause the expected increase in genital infections, particularly in females, and a smaller increase in UTIs (but not in serious genitourinary tract infections). Overall, the A1c reduction was modest with both agents (~ 0.5%), but the impact appeared more durable with dapagliflozin.

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CARDIOVASCULAR BENEFITS FOUND WITH EMPAGLIFLOZIN

Zinman B, Wanner C, Lachin J, et al; EMPA-REG OUTCOME Investigators. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *NEJM*. 373;22:2117- 2128, 2015.



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Zinman et al present the results from the cardiovascular outcomes trial involving the SGLT-2 inhibitor empagliflozin. In that trial, 7,020 individuals from sites in 42 countries around the world were included, with 2345 randomized to empagliflozin 10 mg, 2342 to empagliflozin 25 mg, and 2333 to placebo. All these patients had preexisting cardiovascular disease, over half had had diabetes for over ten years, and approximately half were taking insulin at the start of the trial. Seventy-five percent were male. Other than adding empagliflozin or placebo, patients were treated following usual care standards. As a whole, these patients were well risk-modified, with an average LDL cholesterol of ~ 85 mg/dl and blood pressure of ~ 135/77 mmHg; and patient baseline characteristics were well balanced between the empagliflozin and placebo groups. Most were on a statin, plus an ACE-I or ARB, and aspirin. The primary outcome was a composite of death from cardiovascular causes, nonfatal myocardial infarction (excluding silent MI), or nonfatal stroke.

Ninety-seven percent of patients completed the study, which was concluded when 691 primary outcome events had occurred. The median duration of treatment was 2.7 years, with a median duration of observation was 3.1 years. The primary outcome occurred in 10.5% of the empagliflozin-treated group and 12.1% of the placebo-treated group (hazard ratio 0.86, 95.02% confidence interval, 0.74 to 0.99, $P < .001$ for noninferiority and $P = .04$ for superiority). Doses of 10 mg or 25 mg of empagliflozin behaved similarly. There was a 38% relative risk reduction in death from cardiovascular causes, a 32% reduction in overall death, and a 35% relative risk reduction in hospitalization for congestive heart failure. There was a slight but nonsignificant increase in the risk of stroke, but these events tended to occur in the month after the empagliflozin was stopped while still on treatment.

The A1c fell from ~ 8.0% to ~ 7.5% and rose over the duration of the treatment. At week 206 the adjusted mean A1c was 7.81% in the pooled empagliflozin groups and 8.16% in the placebo group. Systolic blood pressure and also fell with empagliflozin. There was an increase in mycotic genital infections but no increase in diabetic ketoacidosis (DKA) or bone fracture.

This is the first CVOT to show a significant benefit on cardiovascular outcomes in high-risk individuals with type 2 diabetes. These are similar to benefits seen with commonly used CVD-modifying drugs such as statins and ACE-inhibitors. The impact of empagliflozin was nearly immediate, with benefit starting within a few weeks and increasing over time.

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SGLT-2 INHIBITORS: SAFETY AND EFFICACY IN TYPE 1 DIABETES

Henry RR, Thakkar P, Tong C, Polidori D, Alba M. Efficacy and Safety of Canagliflozin, a Sodium-Glucose Cotransporter 2 Inhibitor, as Add-on to Insulin in Patients with Type 1 Diabetes. *Diabetes Care*. 2015;38:2258-2265.



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This article reports on the outcomes of a phase 2 double blind, parallel-group, multicenter trial performed to assess the benefit of adding canagliflozin to the insulin regimen of individuals with type 1 diabetes. Because the mechanism of action of SGLT-2 inhibitors is insulin-independent, these agents have the potential to improve glycemia in people with

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type 1 diabetes and type 2 diabetes. In this 18 week trial, 351 patients were randomized— one-third treated with placebo, one-third with canagliflozin 100 mg daily, and one-third with canagliflozin 300 mg daily. Doses of basal insulin were downtitrated by ~ 10%-20% at the investigator's discretion when the study drug was started.

The primary endpoint was a composite of the proportion of patients with both an A1c reduction of > 0.4% and no increase in body weight. This endpoint was reached in the canagliflozin 100 mg group in 36.9% of patients, in the 300 mg group in 41.4%, and in the placebo group in 14.5% (P < .001). There was a 3.1% decrease in body weight with the 100 mg dose of canagliflozin and a 5.1% fall with the 300 mg dose, compared to a 0.3% increase in the placebo treatment group.

Side effects included a dose-dependent increase in the risk for diabetic ketoacidosis (DKA) and ketosis-related side effects. The rates for ketosis-related side effects (canagliflozin 100 mg, 300 mg, placebo) were 5.1%, 9.4%, and 0%, respectively; for specific DKA, the rates were 4.3%, 6.0%, and 0%, respectively. Rates of severe hypoglycemia were 1.7% in the placebo group, 2.6% in the canagliflozin 100 mg group, and 6.8% in the canagliflozin 300 mg group. As in other reports, DKA episodes were triggered by an additional event, such as infection or pump failure. However, rates of DKA or ketosis-related events were zero in the placebo treated group, who had similar coexisting mild adverse events and did not develop DKA.

This RCT showed the benefits of SGLT-2 inhibitor use in type 1 diabetes, with reduction in blood sugar levels, glucose variability, and hypoglycemia (on the 100 mg dose). However, it showed that the 300 mg dose increased the risk for ketosis-related events to a level that would be worrisome in clinical practice and suggests that lower doses should be studied in individuals with type 1 diabetes.

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SGLT-2 INHIBITORS AND INCREASED RISK FOR DKA

Peters AL, Buschur EO, Buse JB, Cohan P, Diner JC, Hirsch IB. Euglycemic Diabetic Ketoacidosis: a Potential Complication of Treatment with Sodium-Glucose Cotransporter 2 Inhibition. *Diabetes Care*. 2015 Sep;38(9): 1687-93.



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This article is a case series of 13 episodes of euglycemic diabetic ketoacidosis (DKA) that occurred in nine patients taking an SGLT-2 inhibitor. Seven of the patients had type 1 diabetes and two had type 2 diabetes. These patients were from around the country, with varying weights, ages, and durations of diabetes. In three of the patients, DKA recurred after restarting on an SGLT-2 inhibitor. In nearly all of the cases, a precipitant such as infection, surgery, insulin dose reduction, or infusion set occlusion precipitated the DKA. All individuals recovered with treatment of their DKA with IV insulin, fluids, and glucose. However, in many cases the DKA was missed, either because the presenting blood glucose level was not elevated or because the patient had type 2 diabetes.

This report represents the largest published series of DKA occurrence in association with SGLT-2 inhibitors. Since this publication, the FDA has added a warning to the label of all SGLT-2 inhibitors, alerting providers to this risk in patients with both type 1 and type 2 diabetes. DKA can be either hyperglycemic or euglycemic, but it is the euglycemic cases that may be missed.

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INCREASED RISK OF EXTREMITY FRACTURE SEEN WITH CANAGLIFLOZIN

Watts NB, Bilezikain JP, Usiskin K, et al. Effects of Canagliflozin on Fracture Risk in Patients with Type 2 Diabetes Mellitus. J Clin End Metab. 2015 Nov 18 (epub)



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Bilezikian JP, Watts NB, Usiskin K, et al. Evaluation of bone mineral density and bone biomarkers in patients with type 2 diabetes treated with canagliflozin. J Clin Endocrinol Metab. 2015 Nov 18:jc20151860.



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The study by Watts et al is a meta-analysis from nine randomized phase III studies with canagliflozin involving 10,194 individuals (one of these studies was the cardiovascular outcomes trial known as CANVAS, which has not yet reported its final results). The primary outcome was incidence of adjudicated fracture adverse events (AEs), fall-related AEs, and volume depletion-related AEs.

The incidence of fracture with canagliflozin was similar between the canagliflozin- treated and noncanagliflozin-treated groups (1.7% vs 1.5% respectively) in the pooled trial data (not including CANVAS). In CANVAS there was a significant increase in fractures of the upper and lower limbs (4.0% vs 2.6%, canagliflozin vs placebo). When all 10 studies were analyzed, there was a higher incidence of fractures with canagliflozin compared to noncanagliflozin-treated patients (2.7% vs 1.9%). In the CANVAS treated group there was also an increased incidence of reported falls, which may have been related to volume depletion-related AEs.

Patient treated in CANVAS were on average older than those in the other trials, and many either had a history of CVD and/or were at high risk for CVD. These patients also had lower baseline eGFR and higher rates of baseline diuretic use.

The Bilezikian article discusses the results of a 26 week, double-blind, placebo-controlled study with a 78 week extension phase. It was designed to assess differences in bone mineral density (BMD) as well as changes in markers of bone turnover. In that trial, 716 individuals with inadequately controlled type 2 diabetes were enrolled. One of two doses of canagliflozin (100 mg or 300 mg) or placebo was added to the current regimen.

Bone mineral density was decreased by 0.9% (100 mg canagliflozin) or 1.2% (300 mg) at the hip (total hip BMD) but not at other sites. Canagliflozin was also associated with an increase in beta-CTX that was correlated with a reduction in body weight and an increase in osteocalcin. Canagliflozin has been found to be associated with an increased risk for fracture of the extremities, particularly in older individuals at high risk for CVD (as seen in the CANVAS study). These fractures could be related to an increased risk of falls related to volume changes when canagliflozin is started. However, this increased risk of fracture appears to be multifactorial, with a significant reduction in total hip BMD seen on DEXA scanning, along with increases in bone formation and resorption markers. Thus, this risk needs to be addressed in patients started on canagliflozin, and other agents may be preferable in individuals suffering from significant osteoporosis.

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KEY TAKEAWAYS

- SGLT-2 inhibitors have been shown to reduce glucose, blood pressure, and weight.
- Empagliflozin (specifically) has been shown to reduce the risk for CVD mortality by 38% in individuals with type 2 diabetes and preexisting CVD.
- SGLT-2 inhibitors can cause euglycemic (and hyperglycemic) DKA in people with both type 1 and type 2 diabetes.
- Canagliflozin has been associated with an increased risk of hip fractures, primarily in one trial of older people, and in mechanistic trials the drug has been shown to reduce bone density.

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