A Review of the Efficacy and Safety of Sodium–Glucose Cotransporter 2 Inhibitors: A Focus on Diabetic Ketoacidosis

Ashley M. Zurek,[1] Raghunandan Yendapally,[2] and Elizabeth M. Urteaga[2]

Diabetes is a complex, chronic medical condition affecting 29.1 million people in the United States (9.3% of the population) and is projected to affect one in three Americans by 2050 if the current trend continues (1). Diabetes management can be challenging, often requiring multiple therapeutic agents as the disease progresses. Current guidelines recommend metformin as first-line pharmacological therapy for the treatment of type 2 diabetes. Multiple second-line options are available for patients whose A1C goal is not achieved with monotherapy, and selection should be based on patient- and drug-specific factors. Sodium–glucose cotransporter 2 (SGLT2) inhibitors, the newest U.S. Food and Drug Administration (FDA)–approved oral antidiabetic agents, are among these options for patients with type 2 diabetes. Canagliflozin, dapagliflozin, and empagliflozin are the currently available SGLT2 inhibitors in the United States (2,3).

Mechanism of Action

Sodium–glucose cotransporter 1 (SGLT1) is predominantly located in the small intestine, but is also expressed in the kidneys, trachea, heart, and colon (4,5). In the kidneys, SGLT1 is primarily located in the S3 segment of the proximal convoluted tubule (PCT) (4). SGLT2 is expressed in the kidneys and primarily located in the S1 and S2 segments of the PCT (4,5). In normoglycemic adults, about 180 g of glucose (Figure 1) is filtered per day in the glomerulus, and most is reabsorbed (4,6). In people with diabetes, reabsorption of glucose is increased compared to people without diabetes (7,8). SGLT1 and SGLT2 are located in the apical membrane and facilitate the transport of glucose with sodium from the renal tubular lumen into the cells (Figure 2) (4).

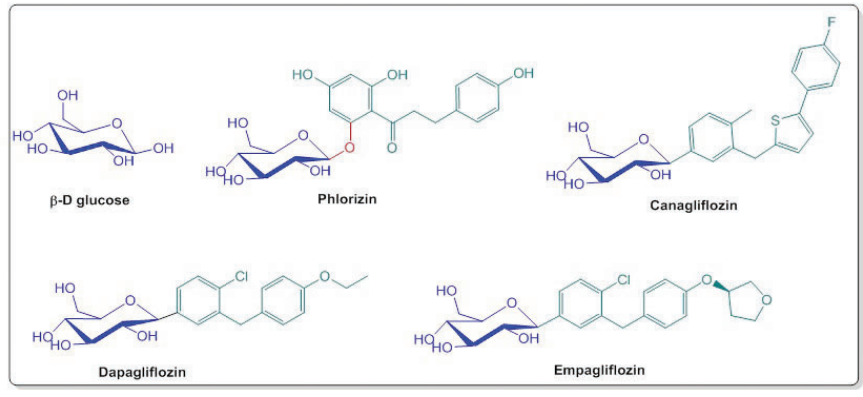

FIGURE 1. Structures of glucose, phlorizin, canagliflozin, dapagliflozin, and empagliflozin.

[1]San Antonio Military Medical Center, Fort Sam Houston, TX

[2]Feik School of Pharmacy, University of the Incarnate Word, San Antonio, TX

Corresponding author: Ashley M. Zurek, ashley.m.zurek.civ@mail.mil

https://doi.org/10.2337/ds16-0030

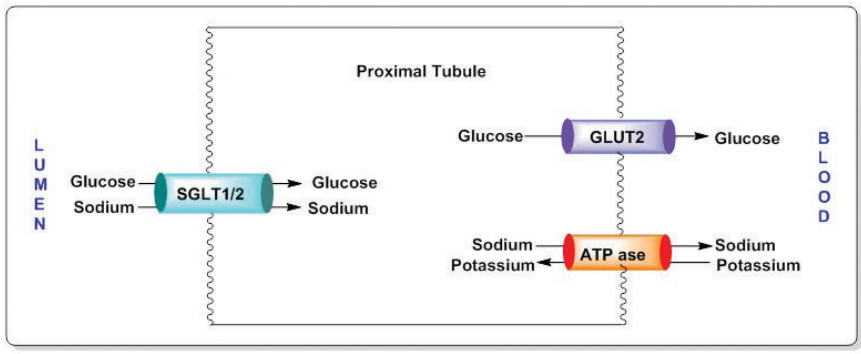

FIGURE 2. Cotransport of glucose and sodium by SGLT1 and SGLT2 in the PCT.

Phlorizin (Figure 1), an *O*-glucose derivative/*O*-glycoside, was discovered in 1835 from apple tree bark (9,10). Phlorizin is a dual SGLT inhibitor, inhibiting both SGLT1 and SGLT2 (10). Canagliflozin, dapagliflozin, and empagliflozin are *C*-glucose derivatives and selectively inhibit SGLT2 (11). SGLT2 inhibitors are structurally similar to glucose, as shown in Figure 1, and thereby competitively inhibit glucose, leading to increased levels of glucose in the urine (5,6). Clinically available SGLT2 inhibitors block ~30–50% of filtered glucose (6).

Efficacy

The efficacy of SGLT2 inhibitors as monotherapy, dual and triple oral therapy, and in combination with insulin has been established in randomized, controlled trials. A1C reduction associated with SGLT2 inhibitors ranges from 0.5–1% and varies based on dose, severity of diabetes, and other patient-specific factors (12–15).

Because of the insulin-independent mechanism of action of SGLT2 inhibitors, they may be used at all stages of type 2 diabetes, including more severe stages, in which endogenous insulin secretion has declined significantly. This mechanism explains why the risk of hypoglycemia is rare, although it may still occur when an SGLT2 inhibitor is used in combination with an insulin secretagogue or exogenous insulin (16). SGLT2 inhibitors are also associated with a consistent reduction of systolic and diastolic blood pressure by 2–4 and 1–2 mmHg, respectively, as a result of their osmotic diuretic effect (12,17). Weight loss of ~2 kg has been observed with SGLT2 inhibitors as a result of their glucosuric effect, and even greater weight reductions have been observed in patients with a higher baseline BMI (14,18).

As with many other antidiabetic agents, data on microvascular outcomes with SGLT2 inhibitors are lacking. However, macrovascular and mortality outcomes with empagliflozin are now available, and cardiovascular and mortality trials of canagliflozin and dapagliflozin are underway. EMPA-REG OUTCOME, a 3-year trial in patients with type 2 diabetes and high cardiovascular risk, found that empagliflozin significantly decreased the primary composite outcome with a number needed to treat of 63, driven by a reduction in cardiovascular death (19). Neither myocardial infarction, stroke, nor hospitalization for unstable angina was reduced compared to placebo. Hospitalization for heart failure was 2.7% with empagliflozin compared to 4.1% with placebo ($P = 0.002$) (19). Although the precise explanation for empagliflozin's beneficial clinical outcomes is unknown, it is likely multifactorial. Potential reasons include the agent's effects on arterial stiffness, cardiac function, and cardiorenal function (19,20). Empagliflozin's ability to reduce albuminuria, uric acid, body weight, visceral adipose tissue, and blood pressure may provide additional mechanisms (19,21,22). CANVAS is an ongoing randomized, double-blind, placebo-controlled trial studying the effect of canagliflozin on cardiovascular outcomes and death in patients with uncontrolled type 2 diabetes and a history of cardiovascular events (23). DECLARE-TIMI 58 is an ongoing randomized, double-blind, placebo-controlled trial investigating the effect of dapagliflozin on cardiovascular death, myocardial infarction, and stroke in patients ≥40 years of age with type 2 diabetes (24). These trials will provide more insight regarding the cardiovascular effects of SGLT2 inhibitors.

Safety

SGLT2 inhibitors are generally well tolerated, but some disadvantages are associated with this therapy. An increase in urogenital infections has been observed because of their effect on increased urinary glucose. A pooled analysis of clinical trials found 11 and 4% increased risks of genital mycotic infection in women and men, respectively, compared to placebo. Events were generally mild to moderate in severity and responded to standard therapy (25). The FDA has since issued a warning regarding the risk of urinary tract infections leading to urosepsis and pyelonephritis with SGLT2 inhibitors (26). Health care providers should ask whether patients have a history of urogenital infections before initiating SGLT2 inhibitor therapy.

SGLT2 inhibitors are also associated with a small, reversible decrease in estimated glomerular filtration rate (eGFR), thereby decreasing the magnitude of their effect on glucose excretion and thus their efficacy as renal function declines (21,22,27). Hence, canagliflozin, dapagliflozin, and empagliflozin have variable dosing adjustments and restrictions based on eGFR. The FDA strengthened a warning on the labels of canagliflozin and dapagliflozin in June 2016 after receiving 101 case reports of acute kidney injury and recommends considering predisposing factors

before initiating these therapies (28). However, this warning does not apply to empagliflozin, which recently was reported in a subanalysis of EMPA-REG OUTCOME to be associated with a slower progression of kidney disease compared to placebo in patients with mild renal dysfunction (29). It is unknown whether this is a class effect. The concept of renal protection relates to SGLT2 inhibitors' ability to decrease uric acid levels, tubular glucose toxicity, and diabetes-induced hyperfiltration (30). The CREDENCE trial, now underway, will shed light on whether canagliflozin has beneficial renal effects in patients with type 2 diabetes and stage 2 or 3 chronic kidney disease (31).

Because of SGLT2 inhibitors' effects on blood pressure, their use may lead to postural hypotension and dizziness, particularly in elderly patients, those taking loop diuretics, or those with tenuous intravascular volume. Therefore, caution and dose adjustments may be warranted in such patients (32,33). Pooled trial data from long-term canagliflozin therapy showed an increase in bone fracture rates, leading the FDA to issue a new warning in September 2015 for decreased bone mineral density and to strengthen its warning about increased bone fracture risk (34). SGLT2 inhibitors increase serum phosphate levels, likely via tubular reabsorption, thereby increasing both parathyroid hormone (PTH) and fibroblast growth factor (FGF) 23. PTH and FGF 23 promote phosphaturia and have opposite effects on vitamin D metabolism, although evidence has shown that SGLT2 inhibitors decrease mean 1,25 dihydroxyvitamin D levels (35). Neither dapagliflozin nor empagliflozin carry bone fracture risk warnings (36,37).

There have also been concerns of bladder and breast cancer with dapagliflozin because it was associated with a nonsignificant increase in phase 2 and 3 trials. However, this may be attributable to detection bias (38–40). Molecular and animal evidence does not suggest a positive link between SGLT2 inhibitor exposure and cancer risk (41). Minimal increases in LDL cholesterol also have been noted with SGLT2 inhibitors, potentially resulting from metabolic changes such as increased lipoprotein lipase activity, but the exact mechanism is unknown (22,42).

FDA Warning for Ketoacidosis

Diabetic ketoacidosis (DKA) is a potentially life-threatening complication in people with diabetes, predominantly those with type 1 diabetes. DKA typically is defined as the triad of hyperglycemia (blood glucose >250 mg/dL), anion gap metabolic acidosis, and the presence of urine or plasma ketones (43). Euglycemic DKA (euDKA) is rare and defined as DKA with a blood glucose level ≤250 mg/dL. It may be precipitated by incomplete DKA treatment or reduced insulin dose, food restriction, alcohol consumption, or inhibition of gluconeogenesis (44). Metabolic changes during pregnancy may also predispose patients to euDKA (45).

After reviewing FDA Adverse Event Reporting System database entries since the approval of canagliflozin in March 2013, the FDA issued a warning in May 2015 about the risk of DKA associated with SGLT2 inhibitors. The report found 73 cases of DKA in patients with type 1 diabetes or type 2 diabetes treated with SGLT2 inhibitors, specifically 44 cases in type 2 diabetes, 16 in type 1 diabetes, 13 unspecified, and 1 in a patient with latent autoimmune diabetes in adults (LADA) (26). Canagliflozin, dapagliflozin, and empagliflozin were associated with 21, 4, and 4 DKA cases, respectively (26). Concomitant dehydration, infection, and changes in insulin dose were reported in 73% of the cases. Management took place in emergency departments or inpatient settings in all of the cases, and the FDA identified possible risk factors, including infection, low-carbohydrate diet or reduced caloric intake, alcohol use, and reduced dose or discontinuation of insulin or oral insulin secretagogue therapy (26). The FDA has added this warning to the labels of all SGLT2 inhibitors, and post-marketing pharmacovigilance studies are ongoing.

Possible Mechanisms of DKA

Although the exact mechanism is not fully understood, the following proposed mechanisms may explain how SGLT2 inhibitors cause euDKA (46):

1. Reduced insulin levels and enhanced glucagon secretion. SGLT2 inhibitors act by blocking the reabsorption of filtered glucose in the PCT, leading to an increased excretion of glucose in the urine and decreased levels of glucose in the blood (47,48). The lower blood glucose levels result in the reduced secretion of insulin from the pancreatic β-cells. This enhances the secretion of glucagon from the pancreatic α-cells, which is referred to as an indirect effect of SGLT2 inhibitors on glucagon (49,50). Additionally, in vitro human and in vivo mice studies show that dapagliflozin directly acts on the pancreatic α-cells and triggers the secretion of glucagon, providing evidence that SGLT2 inhibitors are indeed α-cell secretagogues (51). Eventually, reduced insulin and increased glucagon levels will initiate lipolysis in adipose tissues and β-oxidation of fatty acids, leading to the formation of ketone bodies in the liver and potentially causing euDKA (47,49). Patients with reduced insulin levels, whether from a reduction in insulin dose or an insulin deficiency, may be at increased risk.
2. Reduced renal clearance of ketone bodies. SGLT2 inhibitors also may contribute to decreased excretion of ketone bodies synthesized in the body because phlorizin decreases the renal clearance of ketone bodies (46).

TABLE 1. Case Reports of DKA in Patients With Type 2 Diabetes Receiving SGLT2 Inhibitor Therapy

Case Report	Patient Age (Years), Sex	SGLT2 Inhibitor (Days of Therapy Before Event)	Changes in Other Antidiabetic Agent(s) (Days Before Event)	Other Factors	Event
Venkatesh et al. (52)	63, male	Empagliflozin (not provided)	None	Elective surgery	euDKA
Storgaard et al. (53)	44, male	Dapagliflozin (5)	Discontinued insulin glargine (196)	None	DKA
Hayami et al. (54)	32, female	Ipragliflozin (13)	Discontinued glimepiride, metformin, and linagliptin (13)	Low-carbohydrate diet	euDKA
Roach and Skierczynski (55)	64, female	Empagliflozin (5)	Discontinued NPH and regular insulin (21)	One alcoholic drink	euDKA
Peters et al. (56)	58, male	Canagliflozin (not provided)	None	Elective surgery	euDKA
Peters et al. (56)	64, female	Canagliflozin (>180)	Discontinued insulin detemir (not provided)	Elective surgery	euDKA

DKA and SGLT2 Inhibitors: Literature Review

DKA in People With Type 2 Diabetes

In people with type 2 diabetes, no clear signal to suggest DKA was noted in large clinical development programs for any of the three marketed SGLT2 inhibitors. Several case reports are now noted in the literature (Table 1) (52–56). As evidenced by case reports, sudden withdrawal of insulin therapy or secretagogues during the initiation of SGLT2 inhibitors may increase the risk of DKA. Additionally, patients following a low-carbohydrate diet may be at risk, and ensuring appropriate hydration is essential because dehydration may lead to acceleration of ketogenesis (54). Two cases of euDKA developed in the postoperative period, and further research will be needed to provide recommendations for SGLT2 inhibitor therapy in the pre- and postoperative periods (56).

Further information is available from trial data. Erondu et al. (57) reviewed DKA events in the canagliflozin type 2 diabetes clinical program. Twelve of the 17,596 patients developed DKA or related events while receiving canagliflozin. However, half of the 12 patients were reported to have type 1 diabetes or LADA. The EMPA-REG OUTCOME study conducted for 3 years with 7,020 patients found no difference in the rate of DKA with empagliflozin compared to placebo (19). Based on >18,000 patients with type 2 diabetes in randomized, controlled study programs, the frequency of DKA in those exposed to dapagliflozin is <0.1% (44).

DKA in People With Type 1 Diabetes

Although SGLT2 inhibitors are not FDA-approved for use in people with type 1 diabetes, they have been used off label in practice. An 18-week phase 2 study of 351 patients with type 1 diabetes assessed the efficacy and safety of canagliflozin as add-on treatment to insulin (58). Twelve patients in the canagliflozin group developed DKA that required hospitalization. No patients in the placebo group experienced a ketone-related adverse effect. Five of the 12 patients had a blood glucose level <250 mg/dL at the time of hospitalization (58). Additional cases of canagliflozin-associated euDKA in type 1 diabetes have been reported in the literature (56). Precipitating factors such as illness, change in diet, increased activity, and reduction or omission of insulin led to the DKA episodes (56,58).

Conclusion

SGLT2 inhibitors are a second-line or later therapy option for the management of type 2 diabetes. However, a recent FDA warning regarding SGLT2-associated DKA has raised concerns. The proposed mechanism relates to SGLT2 inhibitors' indirect effects on reducing endogenous insulin levels and enhancing glucagon secretion, while also reducing renal ketone clearance. Although case reports have demonstrated an increased risk of DKA in both type 1 and type 2 diabetes, larger randomized, controlled trials are expected to provide greater understanding. Patients should be educated about the risks of DKA. Interruption of SGLT2 inhibitor treatment may be warranted during periods of prolonged fasting due to illness or surgery, low-carbohydrate diet, dehydration, stress, or changes in insulin or insulin secretagogue medications.

Duality of Interest

No potential conflicts of interest relevant to this article were reported.

References

1. Centers for Disease Control and Prevention. Diabetes 2014 report card [Internet]. Available from http://www.cdc.gov/diabetes/pdfs/library/diabetesreportcard2014.pdf. Accessed 20 January 2016

2. American Diabetes Association. Sec. 7. Approaches to glycemic treatment. In *Standards of Medical Care in Diabetes—2016*. Diabetes Care 2016;39(Suppl. 1):S52–S59

3. Garber AJ, Abrahamson MJ, Barzilay JI, et al. Consensus statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm—2016: executive summary. Endocr Pract 2016;22:84–113

4. Wright, EM, Loo DD, Hirayama BA. Biology of human sodium glucose transporters. Physiol Rev 2011;91:733–794

5. Mudaliar S, Polidori D, Zambrowicz B, Henry RR. Sodium–glucose cotransporter inhibitors: effects on renal and intestinal glucose transport: from bench to bedside. Diabetes Care 2015;38:2344–2353

6. Liu JJ, Lee T, DeFronzo RA. Why Do SGLT2 inhibitors inhibit only 30–50% of renal glucose reabsorption in humans? Diabetes 2012;61:2199–2204

7. Mogensen CE. Maximum tubular reabsorption capacity for glucose and renal hemodynamcis during rapid hypertonic glucose infusion in normal and diabetic subjects. Scand J Clin Lab Invest 1971;28:101–109

8. Gerich JE. Role of the kidney in normal glucose homeostasis and in the hyperglycaemia of diabetes mellitus: therapeutic implications. Diabet Med 2010;27:136–142

9. Petersen C. Analysis of phloridzin. Ann Acad Sci Francaise 1835;15:178 [in French]

10. Ehrenkranz JR, Lewis NG, Kahn CR, Roth J. Phlorizin: a review. Diabetes Metab Res Rev 2005;21:31–38

11. Nauck MA. Update on developments with SGLT2 inhibitors in the management of type 2 diabetes. Drug Des Devel Ther 2014;8:1335–1380

12. Vasilakou D, Karagiannis T, Athanasiadou E, et al. Sodium-glucose cotransporter 2 inhibitors for type 2 diabetes: a systematic review and meta-analysis. Ann Intern Med 2013;159:262–274

13. Zhang M, Zhang L, Wu B, Song H, An Z, Li S. Dapagliflozin treatment for type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials. Diabetes Metab Res Rev 2014;30:204–221

14. Yang XP, Lai D, Zhong XY, Shen HP, Huang YL. Efficacy and safety of canagliflozin in subjects with type 2 diabetes: systematic review and meta-analysis. Eur J Clin Pharmacol 2014;70:1149–1158

15. Liakos A, Karagiannis T, Athanasiadou E, et al. Efficacy and safety of empagliflozin for type 2 diabetes: a systematic review and meta-analysis. Diabetes Obes Metab 2014;16:984–993

16. Rosenstock J, Jelaska A, Frappin G, et al. Improved glucose control with weight loss, lower insulin doses, and no increased hypoglycemia with empagliflozin added to titrated multiple daily injections of insulin in obese inadequately controlled type 2 diabetes. Diabetes Care 2014;37:1815–1823

17. Baker WL, Smyth LR, Riche DM, Bourret EM, Chamberlin KW, White WB. Effects of sodium-glucose co-transporter 2 inhibitors on blood pressure: a systematic review and meta-analysis. J Am Soc Hypertens 2014;8:262–275.e9

18. Bolinder J, Ljunggren O, Kullberg J, et al. Effects of dapagliflozin on body weight, total fat mass, and regional adipose tissue distribution in patients with type 2 diabetes mellitus with inadequate glycemic control on metformin. J Clin Endocrinol Metab 2012;97:1020–1031

19. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117–2128

20. Cherney DZ, Perkins BA, Soleymanlou N, et al. The effect of empagliflozin on arterial stiffness and heart rate variability in subjects with uncomplicated type 1 diabetes mellitus. Cardiovasc Diabetol 2014;13:28

21. Barnett AH, Mithal A, Manassie J, et al. Efficacy and safety of empagliflozin added to existing antidiabetes treatment in patients with type 2 diabetes and chronic kidney disease: a randomized, double-blind, placebo-controlled trial. Lancet Diabetes Endocrinol 2014;2:369–384

22. Cefalu WT, Leiter LA, Yoon KH, et al. Efficacy and safety of canagliflozin versus glimepiride in patients with type 2 diabetes inadequately controlled with metformin (CANTATA-SU): 52 week results from a randomized, double-blind, placebo-controlled phase 3 non-inferiority trial. Lancet 2013;382:941–950

23. Neal B, Perkovic V, de Zeeuw D, et al. Rationale, design, and baseline characteristics of the Canagliflozin Cardiovascular Assessment Study (CANVAS): a randomized placebo-controlled trial. Am Heart J 2013;166:217–223.e11

24. ClinicalTrials.gov. Multicenter trial to evaluate the effect of dapagliflozin on the incidence of cardiovascular events (DECLARE-TIMI 58) [Internet]. Available from https://clinicaltrials.gov/ct2/show/NCT01730534?term=declare+timi&rank=1. Accessed 12 January 2016

25. Nyirjesy P, Sobel JD, Fung A, et al. Genital mycotic infections with canagliflozin, a sodium glucose co-transporter 2 inhibitor, in patients with type 2 diabetes mellitus: a pooled analysis of clinical studies. Curr Med Res Opin 2014;30:1109–1119

26. U.S. Food and Drug Administration. 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 [Internet]. Available from http://www.fda.gov/Drugs/DrugSafety/ucm475463. Accessed 12 January 2016

27. Jabbour SA, Hardy E, Sugg J, et al. Dapagliflozin is effective as add-on therapy to sitagliptin with or without metformin: a 24-week, multicenter, randomized, double-blind, placebo-controlled study. Diabetes Care 2014;37:740–750

28. U.S. Food and Drug Administration. Canagliflozin (Invokana, Invokamet) and dapagliflozin (Farxiga, Xigduo XR): drug safety communication: strengthened kidney warnings [Internet]. Available from http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm506554.htm?source=govdelivery&utm_medium=email&utm_source=govdelivery. Accessed 16 June 2016

29. Wanner C, Inzucchi SE, Lachin JM, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. N Engl J Med 2016;375:323–334

30. Gilbert RE. Sodium-glucose linked transporter-2 inhibitors: potential for renoprotection beyond blood glucose lowering? Kidney Int 2014;86:693–700

31. ClinicalTrials.gov. Evaluation of the effects of canagliflozin on renal and cardiovascular outcomes in participants with diabetic nephropathy (CREDENCE) [Internet]. Available from https://clinicaltrials.gov/ct2/show/NCT02065791. Accessed 20 January 2016

32. Mikhail N. Safety of canagliflozin in patients with type 2 diabetes. Curr Drug Saf 2014;9:127–132

33. Sinclair A, Bode B, Harris S, et al. Efficacy and safety of canagliflozin compared with placebo in older patients with type 2 diabetes mellitus: a pooled analysis of clinical studies. BMC Endocr Disord 2014;14:37

34. U.S. Food and Drug Administration. Invokana and Invokamet (canagliflozin): drug safety communication: new information on bone fracture risk and decreased bone mineral density [Internet]. Available from http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm461876.htm. Accessed 2 February 2016

35. Taylor SI, Blau JE, Rother KI. SGLT2-inhibitors trigger downstream mechanisms that may exert adverse effects upon bone. Lancet Diabetes Endocrinol 2015;3:8–10

36. Ljunggren O, Bolinder J, Johansson L, et al. Dapagliflozin has no effect on markers of bone formation and resorption or bone mineral density in patients with inadequately controlled type 2 diabetes mellitus on metformin. Diabetes Obes Metab 2012;14:990–999

37. Wanner C, Toto RD, Gerich J, et al. No increase in bone fractures with empagliflozin in a pooled analysis of more than 11,000 patients with type 2

diabetes (Abstract). J Am Soc Nephrol 2013;24(Suppl.):ATH-PO452

38. Ptaszynska A, Johnsson KM, Parikh SJ, de Bruin TW, Apanovitch AM, List JF. Safety profile of dapagliflozin for type 2 diabetes: pooled analysis of clinical studies for overall safety and rare events. Drug Saf 2014;37:815–829

39. U.S. Food and Drug Administration. FDA briefing document: dapagliflozin tablets, 5 and 10 mg [Internet]. Available from http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/ucm262994.pdf. Accessed 8 March 2016

40. Lin HW, Tseng CH. A review on the relationship between SGLT2 inhibitors and cancer. Int J Endocrinol 2014;2014:719578

41. Reilly TP, Graziano MJ, Janovitz EB, et al. Carcinogenicity risk assessment supports the chronic safety of dapagliflozin, an inhibitor of sodium-glucose co-transporter 2, in the treatment of type 2 diabetes mellitus. Diabetes Ther 2014;5:73–96

42. Ptaszynska A, Hardy E, Johnsson E, Parikh S, List J. Effects of dapagliflozin on cardiovascular risk factors. Postgrad Med 2013;125:181–189

43. Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN. Hyperglycemic crises in adult patients with diabetes. Diabetes Care 2009;32:1335–1343

44. Rosenstock R, Ferrannini E. Euglycemic diabetic ketoacidosis: a predictable, detectable, and preventable safety concern with SGLT2 inhibitors. Diabetes Care 2015;38:1638–1642

45. Modi A, Agrawal A, Morgan F. Euglycemic diabetic ketoacidosis. Curr Diabetes Rev 2016. Epub ahead of print (DOI: 10.2174/1573399812666160421121307)

46. Taylor SI, Blau JE, Rother KI. SGLT2 inhibitors may predispose to ketoacidosis. J Clin Endocrinol Metab 2015;100:2849–2852

47. Ogawa W, Sakaguchi K. Euglycemic diabetic ketoacidosis induced by SGLT2 inhibitors: possible mechanism and contributing factors. J Diabetes Investig 2015;7:135–138

48. Ferrannini E, Muscelli E, Frascerra S, et al. Metabolic response to sodium-glucose cotransporter 2 inhibition in type 2 diabetic patients. J Clin Invest 2014;124:499–508

49. Singh AK. Sodium-glucose co-transporter-2 inhibitors and euglycemic ketoacidosis: wisdom of hindsight. Indian J Endocrinol Metab 2015;19:722–730

50. Merovci A, Solis-Herrera C, Daniele G, et al. Dapagliflozin improves muscle insulin sensitivity but enhances endogenous glucose production. J Clin Invest 2014;124:509–514

51. Bonner C, Kerr-Conte J, Gmyr V, et al. Inhibition of the glucose transporter SGLT2 with dapagliflozin in pancreatic alpha cells triggers glucagon secretion. Nat Med 2015;21:512–517

52. Venkatesh B, Moore G, Gill D, Kelly W. Diabetic ketoacidosis precipitated by therapy with antidiabetic agents SGLT2 inhibitors: two cases. Crit Care Resusc 2015;17:280–282

53. Storgaard H, Bagger JI, Knop FK, Vilsbøll T, Rungby J. Diabetic ketoacidosis in a patient with type 2 diabetes after initiation of sodium-glucose cotransporter 2 inhibitor treatment. Basic Clin Pharmacol Toxicol 2016;118:168–170

54. Hayami T, Kato Y, Kamiya H, et al. Case of ketoacidosis by a sodium-glucose cotransporter 2 inhibitor in a diabetic patient with a low-carbohydrate diet. J Diabetes Investig 2015;6:587–590

55. Roach P, Skierczynski P. Euglycemic diabetic ketoacidosis in a patient with type 2 diabetes after treatment with empagliflozin. Diabetes Care 2016;39:e3

56. 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;38:1687–1693

57. Erondu N, Desai M, Ways K, Meininger G. Diabetic ketoacidosis and related events in the canagliflozin type 2 diabetes clinical program. Diabetes Care 2015;38:1680–1686

58. 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