COMMENTARY

SGLT Inhibitors for Type 1 Diabetes: An Obvious Choice or Too Good to Be True?

Matthew C. Riddle[1] *and William T. Cefalu*[2]

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In the recent past we have been fortunate to find new treatments based on entirely new mechanisms . . . or is that really so? The sodium–glucose cotransporter inhibitors (SGLTi) offer an instructive case in point. These apparently "new" agents were preceded by phlorizin, a naturally occurring compound that has been used for physiologic studies for over 100 years (1). Given orally it interferes with intestinal absorption of carbohydrates and causes glucosuria. Studies in animal models of diabetes have provided useful insights, such as evidence that reduction of hyperglycemia can restore insulin sensitivity toward normal (2). However, phlorizin was considered unsuited for use by humans due to undesirable side effects. Recently its mechanism of action has been traced to effects on sodium–glucose cotransporters (SGLT) in the intestinal mucosa and the renal proximal tubule (3), and drugs with more nuanced effects on these transporters have been developed (4,5). These newer agents have greater affinity for SGLT2, which is expressed mainly in the kidney, and less for SGLT1, which facilitates intestinal absorption of glucose. Clinical effects of the newer SGLTi drugs in type 2 diabetes (T2D) include modest reductions of plasma glucose and A1C, weight, and blood pressure and are mediated in large part by glucosuria and sodium diuresis. These agents are taken once daily by mouth and do not require dose titration. Symptomatic side effects—mostly urinary or genital irritation or infections—are common but tolerated by most patients.

Importantly, the new SGLTi drugs have highly desirable—and somewhat unexpected—cardiac and renal protective effects, as least in selected cohorts. Large trials of empagliflozin and canagliflozin, aiming to demonstrate safety in patients with T2D and high cardiovascular risk, have shown favorable effects on heart failure, cardiovascular death, and progression of albuminuria (6–9). Unwanted effects have been reported as well, including dehydration, lower-extremity amputations, and diabetic ketoacidosis (DKA), but they are relatively uncommon.

Although their underlying mechanisms are not fully understood, the cardiovascular and renal benefits have led to great enthusiasm for the SGLTi drugs and increasing clinical use. Consideration of their use immediately after metformin is advised for patients with T2D with established cardiovascular disease (10), and questions have arisen about other groups of patients. We need to know whether these agents can be as effective for patients with T2D not accompanied by overt cardiovascular or renal disease, or for cardiac patients without diabetes, and studies are exploring these questions. But what about prescribing these agents along with basal-bolus insulin for type 1 diabetes (T1D) (11)?

Supplementing earlier small studies of combining an SGLTi with basal-bolus insulin for T1D, six reports of larger studies have now been published (12–17), two of them in this issue (16,18) and three in the September issue of *Diabetes Care* (14,15,17). These studies were designed to determine whether this form of combination therapy can improve glycemic control without unacceptable risk of hypoglycemia, DKA, or other immediately apparent adverse effects in this population. Their main features and results are summarized in Table 1. Canagliflozin was the drug used in one study, sotagliflozin in three, dapagliflozin in two, and empagliflozin in one. The designs of these studies were similar. All were two- or three-arm, randomized, placebo-controlled studies with duration between 18 and 52 weeks. The mean age of participants was between 41 and 46 years, mean BMI between 27 and 30 kg/m^2, and mean baseline A1C between 7.6 and 8.5%. Outcomes reported at the end of the studies were also similar. The mean placebo-adjusted improvement of A1C associated with use of the SGLTi ranged between 0.25 and

[1]*Division of Endocrinology, Diabetes, & Clinical Nutrition, Oregon Health & Science University, Portland, OR*
[2]*American Diabetes Association, Arlington, VA*

Corresponding author: Matthew C. Riddle, riddlem@ohsu.edu.

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Table 1—Design features and main outcomes of large randomized clinical trials evaluating efficacy and safety of SGLTi in T1D

Drug tested	Participants (*N*)	Study duration (weeks)	Age (years)	BMI (kg/m^2)	A1C at baseline [%]	A1C change vs. placebo (%)	Weight change vs. placebo (kg)	DKA events (% incidence)
Canagliflozin 100 mg	351	18	42	28.1	7.9	−0.29	−2.8	4.3
Canagliflozin 300 mg						−0.25	−4.4	6.0
Placebo								0
(Henry et al. [12])								
Sotagliflozin 400 mg	1,402	24	43	28.2	8.2	−0.46	−3.0	3.0
Placebo								0.6
(Garg et al. [13])								
Sotagliflozin 200 mg	793	52	46	29.7	7.6	−0.25	−3.1	3.4
Sotagliflozin 400 mg						−0.31	−4.3	4.2
Placebo								0.4
(Buse et al. [14])								
Sotagliflozin 200 mg	782	52	41	27.8	7.75	−0.21	−2.2	2.3
Sotagliflozin 400 mg						−0.32	−2.9	3.4
Placebo								0
(Danne et al. [15])								
Dapagliflozin 5 mg	833	52	42	28.3	8.5	−0.33	−2.95	4.0
Dapagliflozin 10 mg						−0.36	−4.5	3.4
Placebo								1.9
(Dandona et al. [16])								
Dapagliflozin 5 mg	813	24	43	27.6	8.4	−0.37	−3.2	2.6
Dapagliflozin 10 mg						−0.42	−3.7	2.2
Placebo								0
(Mathieu et al. [17])								
Empagliflozin 10 mg EASE-2	723	26	45	29.2	8.1	−0.39	−2.7	4.3*
Empagliflozin 25 mg EASE-2						−0.45	−3.3	3.3*
Placebo EASE-2						–	–	1.2
Empagliflozin 2.5 mg EASE-3	961	52	43	28.2	8.1	−0.28	−1.8	0.8
Empagliflozin 10 mg EASE-3						−0.45	−3.0	4.3*
Empagliflozin 25 mg EASE-3						−0.52	−3.4	3.3*
Placebo EASE-3						–	–	1.2
(Rosenstock et al. [18])								

Mean values are shown where appropriate. EASE, Empagliflozin as Adjunctive to Insulin Therapy Program. *Participants taking 10 and 25 mg of empagliflozin in the two components of the EASE program were pooled for this analysis.

0.52%, with little difference between lower and higher doses in the studies that included this comparison. Changes of weight relative to placebo averaged between −2.2 and −4.4 kg, with a tendency toward greater reductions at the higher doses. Of note was the incidence of DKA, which ranged between 1.5 and 6.0% greater with active treatment than with placebo. Other than DKA, no notable adverse effects beyond the urogenital symptoms previously observed in T2D appeared in these short-term studies.

How can we interpret these results? On the positive side, the reduction of A1C by about 0.3–0.4% (1.5–2.0 mmol/mol) is at a level generally considered clinically significant. If sustained over time, this improvement would likely reduce the risk of microvascular complications. Better overall control was obtained without increasing the risk of hypoglycemia. The modest but consistent reduction of weight might also be important for some patients and could limit later cardiovascular risk. These considerations are naturally appealing to patients and providers who are frustrated when glycemic targets cannot be attained and concerned about weight and other cardiovascular risk factors.

Unfortunately, there are also limitations. The increased frequency of DKA is the main cause for concern. The incidence of confirmed DKA averaging close to 3% during these studies lasting no longer than a year is not a trivial problem. This risk might be even greater under conditions in routine clinical settings where monitoring of patients may be less close than in clinical trials. Experience in populations of patients considered to have T2D has shown that treatment with an SGLTi can be associated with DKA accompanied by no more than moderate hyperglycemia and nonspecific symptoms (19–21). In many cases the event is preceded by an illness or procedure or by an inappropriate reduction of insulin dosage. The correct diagnosis may be delayed by lack of marked hyperglycemia. Some patients affected clearly have T2D, but many appear to be individuals with unrecognized T1D. Thus, the consistently increased frequency of DKA in recent studies of SGLTi in T1D is not very surprising. If SGLTi drugs are to be approved and prescribed for T1D, heightened awareness about this complication must be emphasized. This is

also true for patients thought to have T2D who actually have T1D and are already being prescribed SGLTi, especially given recent reports of increasingly frequent hospital admissions for DKA generally (22,23). Education and support of both patients and medical providers to prevent euglycemic DKA are key clinical strategies and must be improved. They should include advice on ketone testing as well as recognition of atypical symptoms (nausea, vomiting, malaise) in the absence of significant hyperglycemia (24).

Moreover, even if we are able to limit the risk of DKA, there are other questions to address. Is the excess of fractures found in the canagliflozin development studies in T2D (25), posing the possibility of a class effect of SGLTi on bone integrity, a real concern? No such effect has yet been seen with empagliflozin and dapagliflozin (26,27), but physiologic studies of bone metabolism provide some support for this hypothesis (28–30). In addition to altered handling of calcium and phosphorus in the kidney, ongoing mobilization of gluconeogenic substrates provoked by fasting glucosuria and accompanying hormonal changes might lead to a long-term effect on bone matrix. Weight loss due to caloric restriction is known to be associated with loss of bone mineral and fractures (31–33), and women with anorexia nervosa have greatly reduced bone mineral content at an early age (34,35). Whether long-term use of SGLTi drugs by younger T1D patients could have effects on bone like those induced by voluntary dietary restriction cannot be determined by short-term studies. We need to weigh known short-term clinical benefits against potential long-term risks such as this one.

These observations on the efficacy and safety of SGLTi have important clinical implications. Balancing benefits versus risks of SGLTi will require thoughtful decisions by regulatory and professional groups, care providers, and also people with diabetes. The most obvious responsibility falls upon regulators and groups creating guidance for clinical care. Does the evidence provided by these short-term studies justify approval of these agents for use in T1D? If so, what tactics for mitigation of risks are needed? Are we at a stage where we can stratify individual patients according to benefits versus risks so as to allow appropriate use of these new drugs by selected cohorts? We can expect a vigorous discussion of these questions. To support such decisions, we need more information. Of particular interest is whether a direct renal effect limiting progression of nephropathy—beyond that provided by improved control of A1C and blood pressure—can be demonstrated in T1D, and the present studies do not address this question. Also, confirmation of the short-term risk of DKA in T1D reminds us that long-term risks also need further evaluation in both T1D and T2D. As suggested in earlier commentaries (36–38), drugs in this class should be prescribed cautiously until longer-term, prospectively collected experience with them is available.

The story that began with phlorizin is still in progress. The newer SGLTi drugs offer a greatly improved balance of benefits versus risks, and their use in T1D is clearly an exciting possibility. It would offer the first adjunctive oral therapy for this important cohort of patients. But we do need more information to personalize the use of these powerful new agents in T1D. So, is use of SGLTi agents in T1D "an obvious choice," or are the promises of this approach "too good to be true"? The key lies in precise identification of which patients will obtain the greatest benefit with the least risk.

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References

1. Ehernkranz JRL, Lewis NG, Kahn CR, Roth J. Phlorizin: a review. Diabetes Metab Res Rev 2005;21:31–38
2. Rossetti L, Smith D, Shulman GI, Papachristou D, DeFronzo RA. Correction of hyperglycemia with phlorizin normalizes tissue sensitivity to insulin in diabetic rats. J Clin Invest 1987;79:1510–1515
3. Ferrannini E. Sodium-glucose co-transporters and their inhibition: clinical physiology. Cell Metab 2017;26:27–38
4. Chao EC, Henry RR. SGLT2 inhibition–a novel strategy for diabetes treatment. Nat Rev Drug Discov 2010;9:551–559
5. Scheen AJ. Pharmacodynamics, efficacy and safety of sodium-glucose co-transporter type 2 (SGLT2) inhibitors for the treatment of type 2 diabetes mellitus. Drugs 2015;75:33–59
6. Zinman B, Wanner C, Lachin JM, et al.; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117–2128
7. Neal B, Perkovic V, Mahaffey KW, et al.; CANVAS Program Collaborative Group. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017;377:644–657
8. Abdul-Ghani M, Del Prato S, Chilton R, DeFronzo RA. SGLT2 inhibitors and cardiovascular risk: lessons learned from the EMPA-REG OUTCOME trial. Diabetes Care 2016;39:717–725
9. Heerspink HJL, Kosiborod M, Inzucchi SE, Cherney DZI. Renoprotective effects of sodium-glucose cotransporter-2 inhibitors. Kidney Int 2018;94:26–39
10. American Diabetes Association. 8. Pharmacologic approaches to glycemic treatment: *Standards of Medical Care in Diabetes—2018*. Diabetes Care 2018;41(Suppl. 1):S73–S85
11. Dellepiane S, Ben Nasr M, Assi E, et al. Sodium glucose cotransporters inhibitors in type 1 diabetes. Pharmacol Res 2018;133:1–8
12. 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 2 diabetes. Diabetes Care 2015;38:2258–2265
13. Garg SK, Henry RR, Banks P, et al. Effects of sotagliflozin added to insulin in patients with type 1 diabetes. N Engl J Med 2017;377:2337–2348
14. Buse JB, Garg SK, Rosenstock J, et al. Sotagliflozin in combination with optimized insulin therapy in adults with type 1 diabetes: the North American inTandem1 study. Diabetes Care 2018;41:1970–1980
15. Danne T, Cariou B, Banks P, et al. HbA_{1c} and hypoglycemia reductions at 24 and 52 weeks with sotagliflozin in combination with insulin in adults with type 1 diabetes: the European inTandem study. Diabetes Care 2018;41:1981–1990
16. Dandona P, Mathieu C, Phillip M, et al.; DEPICT-1 Investigators. Efficacy and safety of dapagliflozin in patients with inadequately controlled type 1 diabetes: the DEPICT-1 52-week study. Diabetes Care 2018;41:2552–2559
17. Mathieu C, Dandona P, Gillard P, et al.; DEPICT-2 Investigators. Efficacy and safety of dapagliflozin in patients with inadequately controlled type 1 diabetes (the DEPICT-2 study): 24-week results from a randomized controlled trial. Diabetes Care 2018;41:1938–1946
18. Rosenstock J, Marquard J, Laffel LM, et al. Empagliflozin as adjunctive to insulin therapy in type 1 diabetes: the EASE trials. Diabetes Care 2018;41:2560–2569

19. Taylor SI, Blau JE, Rother KI. SGLT2 inhibitors may predispose to ketoacidosis. J Clin Endocrinol Metab 2015;100:2849–2852
20. 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
21. Meyer EJ, Gabb G, Jesudason D. SGLT2 inhibitor–associated euglycemic diabetic ketoacidosis: a South Australian clinical case series and spontaneous adverse event notifications. Diabetes Care 2018;41:e47–e49
22. Zhong VW, Juhaeri J, Mayer-Davis EJ. Trends in hospital admission for diabetic ketoacidosis in adults with type 1 and type 2 diabetes in England, 1998–2013: a retrospective cohort study. Diabetes Care 2018;41:1870–1877
23. Vellanki P, Umpierrez GE. Increasing hospitalizations for DKA: a need for prevention programs. Diabetes Care 2018;41:1839–1841
24. Rosenstock J, Ferrannini E. Euglycemic diabetic ketoacidosis: a predictable, detactable, and preventable safety concern with SGLT2 inhibitors. Diabetes Care 2015;38:1638–1642
25. Watts NB, Bilezikian JP, Usiskin K, et al. Effects of canagliflozin on fracture risk in patients with type 2 diabetes mellitus. J Clin Endocrinol Metab 2016;101:157–166
26. Kohler S, Kaspers S, Salsali A, Zeller C, Woerle HJ. Analysis of fractures in patients with type 2 diabetes treated with empagliflozin in pooled data from placebo-controlled trials and a head-to-head study versus glimepiride. Diabetes Care 2018;41:1809–1816
27. Jabbour S, Seufert J, Scheen A, Bailey CJ, Karup C, Langkilde AM. Dapagliflozin in patients with type 2 diabetes mellitus: a pooled analysis of safety data from phase IIb/III clinical trials. Diabetes Obes Metab 2018;20:620–628
28. Thrailkill KM, Nyman JS, Bunn RC, et al. The impact of SGLT2 inhibitors, compared with insulin, on diabetic bone disease in a mouse model of type 1 diabetes. Bone 2017;94:141–151
29. Blau JE, Bauman V, Conway EM, et al. Canagliflozin triggers the FGF23/1,25-dihydroxyvitamin D/PTH axis in healthy volunteers in a randomized crossover study. JCI Insight 2018;3:e99123
30. 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 2016;101:44–51
31. Crandall CJ, Yildiz VO, Wactawski-Wende J, et al. Postmenopausal weight change and incidence of fracture: post hoc findings from Women's Health Initiative Observational Study and Clinical Trials. BMJ 2015;350:h25
32. Villareal DT, Fontana L, Weiss EP, et al. Bone mineral density response to caloric restriction-induced weight loss or exercise-induced weight loss: a randomized controlled trial. Arch Intern Med 2006;166:2502–2510
33. Villareal DT, Fontana L, Das SK, et al.; CALERIE Study Group. Effect of two-year caloric restriction on bone metabolism and bone mineral density in non-obese younger adults: a randomized clinical trial. J Bone Miner Res 2016;31:40–51
34. Bachrach LK, Guido D, Katzman D, Litt IF, Marcus R. Decreased bone density in adolescent girls with anorexia nervosa. Pediatrics 1990;86:440–447
35. Misra M, Aggarwal A, Miller KK, et al. Effects of anorexia nervosa on clinical, hematologic, biochemical, and bone density parameters in community-dwelling adolescent girls. Pediatrics 2004;114:1574–1583
36. Cefalu WT, Riddle MC. SGLT2 inhibitors: the latest "new kids on the block"! Diabetes Care 2015;38:352–354
37. Nathan DM. Adjunctive treatments for type 1 diabetes. N Engl J Med 2017;377:2390–2391
38. McCrimmon RJ, Henry RR. AGLT inhibitor adjunct therapy in type 1 diabetes. Diabetologia 2018;61:2126–2133