SGLT2 Inhibitors: The Latest "New Kids on the Block"!

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Everything in the world of diabetes is moving fast these days. Over the last few months, we have received extensive new information regarding the burden of diabetes and suggested changes in treatment strategies. Specifically, in the December 2014 issue of *Diabetes Care*, we reported startling new statistics about the rising costs associated with diabetes and prediabetes (1). The economic burden associated with diagnosed and undiagnosed diabetes, gestational diabetes mellitus, and prediabetes was estimated to be 48% higher than that reported in 2007. For 2012, the estimated total burden exceeded $322 billion, comprising $244 billion in excess medical costs and $78 billion in reduced productivity (1). Following the release of these economic statistics there came further proposals regarding strategies for managing diabetes. In the January 2015 issue of *Diabetes Care*, and coordinated with a release in *Diabetologia*, there was an update to the 2012 position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) on the management of hyperglycemia (2).

A prominent change with respect to treatment options since publication of the 2012 statement concerned the sodium–glucose cotransporter (SGLT) 2 inhibitors. Metformin remains the preferred drug for monotherapy, but based on a rapid accumulation of new information about SGLT2 inhibitors, this new class of agents is included as a reasonable choice for second-line or third-line therapy in the updated statement. Because *Diabetes Care* has recently received many submissions reporting new data and evolving clinical strategies for SGLT2 blockers, our editorial team has elected to feature this class of agents in this issue of *Diabetes Care*. The articles presented in this issue describe research related to novel combinations with a dipeptidyl peptidase-4 inhibitor or with insulin, favorable effects on blood pressure and weight as well as glycemic control, and new agents that inhibit both SGLT1 and SGLT2 (3–13).

As outlined with the new recommendations from the ADA/EASD and as provided in Fig. 2 of the update (2), there is the suggested option of adding SGLT2 inhibitors to the background of metformin or sulfonylurea plus metformin if glycemic goals are not met. In this issue, we provide two articles that provide additional information that this option offers added benefit by addressing "unmet" clinical needs, such as weight loss, lipid and blood pressure control, and durability (3,4). In the first study, Leiter et al. (3) assessed the efficacy and safety of canagliflozin at doses of 100 or 300 mg/day, compared with glimepiride, in an extension study of 104 weeks in patients with type 2 diabetes inadequately controlled with metformin. Both doses of canagliflozin and glimepiride reduced A1C significantly from baseline. Durability analyses showed sustained lowering of A1C with both canagliflozin doses, and reductions in body weight and systolic blood pressure compared with glimepiride. The study by Matthaei et al. (4) evaluated the efficacy and safety of 10 mg/day of dapagliflozin added to background metformin and sulfonylurea over a 24-week period in patients with type 2 diabetes who had inadequate glycemic control. As would be expected, significant improvements in glucose and A1C were reported with the addition of dapagliflozin. In addition, body weight and systolic blood pressure were significantly reduced from baseline over the study period. Patients receiving dapagliflozin showed placebo-subtracted increases in total, LDL, and HDL cholesterol with no change in LDL/HDL cholesterol ratio or triglycerides. In these studies evaluating canagliflozin and dapagliflozin, the adverse events reported (e.g., genital mycotic infections, urinary tract infections) seemed consistent with prior reports and both agents appeared to be well tolerated.

The concept of triple oral therapy is supported by the progressive nature of type 2 diabetes and also the new statement from the ADA/EASD. Inclusion of the SGLT2 inhibitors in such combinations is logical and may reasonably be

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considered very early in treatment. Because the pathogenesis of type 2 diabetes is complex and involves multiple metabolic defects, Dr. Abdul-Ghani (5), in this issue of *Diabetes Care*, provides comments on the use of combination therapy with antidiabetes drugs with different mechanisms of action and states that this approach has the advantage of preventing compensatory mechanisms and the potential of producing an additive reduction in A1C. As proposed, the combination of an SGLT2 inhibitor plus a dipeptidyl peptidase-4 inhibitor produced a robust reduction in A1C in two studies reported in this issue evaluating dapagliflozin with saxagliptin (6) and empagliflozin with linagliptin (7). Rosenstock et al. (6) compared the efficacy and safety of dual add-on of saxagliptin plus dapagliflozin versus saxagliptin and dapagliflozin added on alone in patients with type 2 diabetes poorly controlled with metformin. The authors report that the proportion of patients achieving A1C $<$7% (53 mmol/mol) was 41% with triple therapy versus 18% with saxagliptin plus metformin and 22% with dapagliflozin plus metformin. The authors concluded that greater improvements in glycemic control were obtained with triple therapy of saxagliptin and dapagliflozin together than with dual therapy of saxagliptin or dapagliflozin alone in patients poorly controlled with metformin. In a similarly conceived study using empagliflozin plus linagliptin as second-line therapy in subjects with type 2 diabetes inadequately controlled on metformin, DeFronzo et al. (7) concluded that reductions in A1C with empagliflozin plus linagliptin were superior to those with empagliflozin or linagliptin alone as add-ons to metformin. In addition, the proportion of subjects with adverse events was similar across treatment arms with no hypoglycemic events requiring assistance. Thus, a clinical strategy that combined empagliflozin plus linagliptin as second-line therapy for 52 weeks significantly reduced A1C compared with the individual components and was reported to be well tolerated. One additional study reported in this issue of *Diabetes Care* aimed to evaluate the efficacy and safety of the initial combination of empagliflozin plus linagliptin in subjects with type 2 diabetes not receiving antidiabetes therapy for greater than 12 weeks (8). The reported reductions from baseline in A1C with empagliflozin plus linagliptin were significantly different versus linagliptin and empagliflozin 10 mg but not versus empagliflozin 25 mg.

One of the more exciting aspects of SGLT2 inhibition is that its metabolic effects do not depend on an insulin-dependent mechanism. As outlined above, these agents appear to be effective when used with other agents and can be proposed for use throughout the natural history of type 2 diabetes, including in combination with insulin therapy. Given the mechanism of action, there is also the potential for use as an adjunct to insulin therapy in type 1 diabetes. In this issue, we provide two articles exploring the potential use of SGLT2 inhibitors in both insulin-treated type 2 diabetes and type 1 diabetes (9,10). Neal et al. (9) report a substudy within a large, randomized, double-blind, placebo-controlled trial (Canagliflozin Cardiovascular Assessment Study [CANVAS]) to define the effects of canagliflozin (when used in addition to insulin at a dose of $\geq$20 IU/day) on a range of efficacy, safety, and tolerability outcomes in patients with type 2 diabetes with inadequate glycemic control. They reported significant falls in fasting plasma glucose, body weight, and blood pressure and a greater incidence of hypoglycemia, genital mycotic infections, and hypovolemia with both canagliflozin doses. They concluded that canagliflozin added to insulin therapy improved glycemic control and decreased body weight. They also reported that there was a greater frequency of several anticipated side effects, although few led to discontinuation of treatment. In a very novel evaluation of SGLT2 inhibitors in adults with type 1 diabetes, Henry et al. (10) performed a 2-week, dose-ranging, randomized, double-blind, placebo-controlled proof-of-concept study with dapagliflozin. The primary objective was to assess short-term safety, and secondary objectives included pharmacokinetic, pharmacodynamic, and efficacy measurements. The authors reported that this exploratory study of dapagliflozin in type 1 diabetes demonstrated acceptable short-term tolerability and expected pharmacokinetic profiles and increases in urinary glucose excretion. However, reductions in 24-h glucose, glycemic variability, and insulin dose were only suggested with the SGLT2 inhibitor. They concluded that these findings suggest that SGLT2 inhibition may prove in larger randomized controlled trials to be efficacious in reducing hyperglycemia in type 1 diabetes.

It is clear there are additional clinical benefits of using SGLT2 inhibitors in subjects with type 2 diabetes, and a reduction of blood pressure appears to be another such benefit. In this issue, we also report a study that was designed mainly to investigate the efficacy, safety, and tolerability of empagliflozin (10 or 25 mg) in patients with type 2 diabetes and hypertension (11). In addition to showing the expected changes in A1C, it was demonstrated that empagliflozin was associated with significant and clinically meaningful reductions in blood pressure. The exact mechanism of blood pressure lowering with these agents is not completely understood, but a discussion of possible mechanisms is provided in a commentary on this article by Majewski and Bakris (12).

Finally, a novel approach to SGLT inhibition involves not only actions on SGLT2 but also blockade of SGLT1, the primary transporter for glucose uptake from intestinal lumen. The main effect of SGLT1 inhibition is expected to be a reduction in postprandial glucose. Concerning this possibility, Rosenstock et al. (13) present data on a novel dual inhibitor of SGLT1 and SGLT2 (LX4211) in type 2 diabetes. People with type 2 diabetes inadequately controlled on metformin were randomly assigned to LX4211 in doses of 75 mg q.i.d., 200 mg q.i.d., 400 mg q.i.d., or 200 mg b.i.d. or to placebo. The new drug markedly significantly reduced A1C in a dose-dependent manner. Greater A1C reductions were produced by 400 mg q.i.d. than 200 mg q.i.d. of LX4211 without higher urinary glucose excretion, suggesting a contribution of SGLT1 inhibition. Significant reductions were also seen for body weight and systolic blood pressure. It was concluded that dual inhibition of SGLT1 and SGLT2 with LX4211 produced a significant dose-related improvement in glucose control that was not correlated with glycosuria and was associated with reductions in weight and systolic blood pressure.

What does all this new information about the SGLT2 drugs do to help us today? First, it holds the promise of new ways to individualize treatment of diabetes. This class of drugs has a novel mode of action that appears capable of adding a further glucose-lowering effect

in combination with many other classes. This effect, typically in the range of 0.5 to 1.0% A1C, is clinically relevant although perhaps less than that of some other agents. By itself, it does not cause hypoglycemia. By causing loss of glucose in the urine, the SGLT2 agents favor weight loss, and by increasing clearance of sodium, they may assist in control of edema and hypertension. All these are desirable qualities, making them a welcome addition to our clinical resources. Thus, the studies reported in this issue of *Diabetes Care* provide a rich source of detailed information on the use of this new class of drugs in various clinical situations.

All the data presented thus far on SGLT2 inhibition are very encouraging, but there is still reason for caution (14,15). Because these drugs are so new and the duration of studies available at present is so limited, the balance of benefits versus risks is still not well understood and it will take time to fully evaluate this issue. The most important symptomatic side effects are genitourinary, including frequent urination, discomfort with urination, and vaginal or penile mycotic infections. When these related symptoms are considered collectively, up to 20–30% of women may be affected, with lower proportions of men. How much these symptoms will affect long-term adherence to treatment remains unclear, although the reports from the randomized studies suggest that in most cases the symptoms did not lead to discontinuation. Less common but also important is the potential for postural hypotension due to sodium depletion, especially in the context of diuretic therapy. Whether this effect will prove a serious risk for ill and older patients is also unknown. In one recently reported study of dapagliflozin, over 44% of the participants were older than 65 and 7% over 75 years of age. The study did suggest that when added to a usual background regimen in an older population with advanced type 2 diabetes and preexisting cardiovascular disease the SGLT2 inhibitor improved glycemic control without an increase in hypoglycemic risk, promoted weight loss, and was reported to be well tolerated (16). However, metabolic consequences of altered balance of other electrolytes and nutrients—including calcium, magnesium, phosphate, and others—are not yet fully understood. And finally, when glycosuria reduces plasma glucose in the presence of insulin deficiency, as in type 1 diabetes, could a high rate of gluconeogenesis from muscle-derived amino acids potentially occur and be associated with ketogenesis or even ketoacidosis? And these are just the immediately apparent potential limitations of this class of agents. Ongoing and future studies will surely help us understand how frequent and serious these problems may be, if at all, and how to minimize them if they do occur.

The editorial team at *Diabetes Care* is proud to present this collection of high-quality studies of this promising new class of glucose-lowering agents. As further experience with the new kids on the block becomes available we will continue to update the diabetes community on their benefits and risks and the clinical settings where they may be most helpful. Considering the new information on rising costs of both treating and not adequately treating diabetes, we hope these studies will clarify to some degree the ways these new drugs may best assist personalization of therapy. The goal of course will be to attain the best possible medical outcomes while minimizing both the human and economic burdens of this effort.

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References

1. Dall TM, Yang W, Halder P, et al. The economic burden of elevated blood glucose levels in 2012: diagnosed and undiagnosed diabetes, gestational diabetes mellitus, and prediabetes. Diabetes Care 2014;37:3172–3179
2. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2015;38:140–149
3. Leiter LA, Yoon K-H, Arias P, et al. Canagliflozin provides durable glycemic improvements and body weight reduction over 104 weeks versus glimepiride in patients with type 2 diabetes on metformin: a randomized, double-blind, phase 3 study. Diabetes Care 2015;38:355–364
4. Matthaei S, Bowering K, Rohwedder K, Grohl A, Parikh S; Study 05 Group. Dapagliflozin improves glycemic control and reduces body weight as add-on therapy to metformin plus sulfonylurea: a 24-week randomized, double-blind clinical trial. Diabetes Care 2015;38:365–372
5. Abdul-Ghani M. Where does combination therapy with an SGLT2 inhibitor plus a DPP-4 inhibitor fit in the management of type 2 diabetes? Diabetes Care 2015;38:373–375
6. Rosenstock J, Hansen L, Zee P, et al. Dual add-on therapy in type 2 diabetes poorly controlled with metformin monotherapy: a randomized double-blind trial of saxagliptin plus dapagliflozin addition versus single addition of saxagliptin or dapagliflozin to metformin. Diabetes Care 2015;38:376–383
7. DeFronzo RA, Lewin A, Patel S, et al. Combination of empagliflozin and linagliptin as second-line therapy in subjects with type 2 diabetes inadequately controlled on metformin. Diabetes Care 2015;38:384–393
8. Lewin A, DeFronzo R, Patel S, et al. Initial combination of empagliflozin and linagliptin in subjects with type 2 diabetes. Diabetes Care 2015;38:394–402
9. Neal B, Perkovic V, de Zeeuw D, et al.; CANVAS Trial Collaborative Group. Efficacy and safety of canagliflozin, an inhibitor of sodium–glucose cotransporter 2, when used in conjunction with insulin therapy in patients with type 2 diabetes. Diabetes Care 2015;38:403–411
10. Henry RR, Rosenstock J, Edelman S, et al. Exploring the potential of the SGLT2 inhibitor dapagliflozin in type 1 diabetes: a randomized, double-blind, placebo-controlled pilot study. Diabetes Care 2015;38:412–419
11. Tikkanen I, Narko K, Zeller C, et al.; EMPA-REG BP Investigators. Empagliflozin reduces blood pressure in patients with type 2 diabetes and hypertension. Diabetes Care 2015;38:420–428
12. Majewski C, Bakris GL. Blood pressure reduction: an added benefit of sodium–glucose cotransporter 2 inhibitors in patients with type 2 diabetes. Diabetes Care 2015;38:429–430
13. Rosenstock J, Cefalu WT, Lapuerta P, et al. Greater dose-ranging effects on A1C levels than on glucosuria with LX4211, a dual inhibitor of SGLT1 and SGLT2, in patients with type 2 diabetes on metformin monotherapy. Diabetes Care 2015;38:431–438
14. Ferrannini E, Solini A. SGLT2 inhibition in diabetes mellitus: rationale and clinical prospects. Nat Rev Endocrinol 2012;8:495–502
15. Riser Taylor S, Harris KB. The clinical efficacy and safety of sodium glucose cotransporter-2 inhibitors in adults with type 2 diabetes mellitus. Pharmacotherapy 2013;33:984–999
16. Leiter LA, Cefalu WT, de Bruin TW, Gause-Nilsson I, Sugg J, Parikh SJ. Dapagliflozin added to usual care in individuals with type 2 diabetes mellitus with preexisting cardiovascular disease: a 24-week, multicenter, randomized, double-blind, placebo-controlled study with a 28-week extension. J Am Geriatr Soc 2014;62:1252–1262