

# Sodium Glucose Cotransport Inhibition in Type 2 Diabetes Treatment

Dapagliflozin selectively inhibits renal glucose reabsorption, lowers hyperglycemia, and leads to weight loss among type 2 diabetes patients.

BY CONNI BERGMANN KOURY, EDITOR IN CHIEF

Intensive glycemic control has been associated with a marked decrease in the risk of *microvascular* complications associated with type 2 diabetes.<sup>1-5</sup> Data from the UKPDS (United Kingdom Prospective Diabetes Study) also revealed a trend toward a reduction in *macrovascular* complications associated with intensive glycemic control.<sup>3</sup> Subsequent long-term follow-up of the UKPDS cohort confirmed the reduction in microvascular risk and risk of myocardial infarction.<sup>4</sup> Then the ADVANCE (Action in Diabetes and Vascular Disease)<sup>2</sup> and ACCORD (Action to Control Cardiovascular Risk in Diabetes) studies,<sup>1</sup> however, failed to demonstrate macrovascular benefits in patients assigned to intensive glycemic control.

It has been suggested that the use of sulfonylureas may have obviated any benefit of achieving A1C levels of 6.5% in ADVANCE, based on a greater risk of mortality observed with these agents.<sup>6</sup> Experts now believe that the failure of achieving benefit by aiming for goal A1C <6.0% in ACCORD was likely due to a failure of the *process* of control in these patients, which resulted in weight gain and a three- to four-fold increase in hypoglycemia.<sup>7</sup> This issue continues to be studied.

Based on the pathophysiology of hyperglycemia, the current guidelines of the American Diabetes Association<sup>8</sup> and the European Association for the Study of Diabetes (EASD)<sup>9</sup> have set a goal of achieving near-normal levels of A1C while managing the risks of hypoglycemia. Based on this evidence for reduced A1C targets and tighter glycemic control, development of new therapeutic strategies that achieve significant reductions in A1C while minimizing risk of therapeutic complications—such as hypoglycemia and weight gain—remains a priority.

## SGLT2 INHIBITION

A novel approach that shows promise in achieving these goals are agents that induce renal glycosuria by selectively blocking sodium glucose cotransporter 2 (SGLT2).<sup>10-14</sup> According to preclinical models, SGLT2 inhibition lowers blood glucose independently of insulin. Kipnes<sup>15</sup> reported that inhibition of SGLT2 by new agents, such as dapagliflozin (joint development by Bristol-Myers Squibb Company and AstraZeneca), has the potential to reduce hyperglycemia by inhibiting glucose reabsorption in the kidney. Preclinical trials demonstrated that dapagliflozin is indeed a potent and selective inhibitor of SGLT2. It has shown linear pharmacokinetics over the dose range of 2.5 to 5.0 mg/day, it is not significantly influenced when taken with food, and is primarily eliminated via urinary excretion. Clinical trials have shown that dapagliflozin treatment induces glucosuria and improves glycemic parameters in patients with type 2 diabetes.

Bakris et al<sup>16</sup> discussed the importance of the kidneys' role in regulating glucose. The group also reported that evidence has suggested selective inhibition of SGLT2 induces glucosuria in a dose-dependent manner and may have beneficial effects on glucose regulation in individuals with type 2 diabetes. Preclinical data on dapagliflozin and sergliflozin, confirm that these compounds are highly selective inhibitors for SGLT2, have beneficial effects on the glucose utilization rate, and reduce hyperglycemia while having no hypoglycemic adverse effects. These compounds represent a very promising approach for the treatment of diabetes, investigators concluded.

## PHASE 3 TRIAL

Results from a 24-week study presented at the 45th EASD Annual Meeting<sup>17</sup> revealed that dapagliflozin—

added to metformin— was associated with significant mean reductions in the primary endpoint, A1C, and in the secondary endpoint, fasting plasma glucose (FPG), in patients with type 2 diabetes who were inadequately controlled with metformin alone, as compared with placebo plus metformin.

Dapagliflozin is currently in phase 3 trials.<sup>18</sup> The study also showed that individuals receiving dapagliflozin had statistically greater mean reductions in body weight compared with individuals taking placebo. According to the company, these 24-week data represent the first public presentation of dapagliflozin phase 3 results.

“Given the continued rising prevalence of type 2 diabetes, development of novel treatments such as SGLT2 inhibitors are needed to help improve glycemic control. The preliminary data on weight loss and blood pressure may be important adjuvants to glycemic control,” said Cliff Bailey, Professor of Clinical Science and Head of Diabetes Research at Aston University, Birmingham, UK, in a news release from the drug’s manufacturers. “We look forward to additional data from pivotal dapagliflozin studies which will explore the potential benefits of this new class of medicine for type 2 diabetes patients.”

**Study design.** A group of 546 type 2 diabetes patients aged 18 to 77 years were included in this randomized, double-blind, placebo-controlled investigation. At baseline, patients’ A1C was  $\geq 7\%$  and  $\leq 10\%$ . Following a 2-week lead-in phase, patients were randomized to one of four separate treatment arms: dapagliflozin 2.5 mg (n=137), dapagliflozin 5 mg (n=137), dapagliflozin 10 mg (n=135), or placebo (n=137). Patients in all arms were also receiving metformin ( $\geq 1,500$  mg/d). The primary endpoint of the study compared mean A1C change from baseline for each dapagliflozin treatment arm versus placebo after 24 weeks. Secondary endpoints included change from baseline in FPG and body weight at week 24 versus placebo, and adjusted percentage of individuals treated with dapagliflozin who achieved A1C  $< 7\%$  at 24 weeks. Additional exploratory endpoints included body weight decrease of  $\geq 5\%$  or  $\geq 10\%$  as well as body weight percent change from baseline. The study includes an extension phase for a total duration of 2 years.

**Study results.** After 24 weeks, individuals receiving dapagliflozin 2.5, 5, and 10 mg plus metformin demonstrated a statistically significant adjusted mean change in A1C from baseline of -0.67%, -0.70%, and -0.84%, respectively, compared with -0.30% for placebo ( $P < .0005$  for all treatment arms). Individuals treated with dapagliflozin demonstrated a statistically significant adjusted mean change in FPG, from baseline at week 24: -17.8 mg/dL for dapagliflozin 2.5 mg, -21.5 mg/dL for dapagliflozin 5 mg, and -23.5 mg/dL for dapagliflozin 10 mg, compared with

-6.0 mg/dL for placebo ( $P < .005$  for all treatment arms). The adjusted percentage of patients treated with dapagliflozin who achieved A1C  $< 7\%$  at 24 weeks, a secondary endpoint, was 33% for dapagliflozin 2.5 mg ( $P = \text{NS}$ ), 37.5% for dapagliflozin 5 mg, and 40.6% for dapagliflozin 10 mg (both  $P < .05$ ) versus 25.9% for placebo.

The study also evaluated the potential impact of dapagliflozin on weight loss. These findings included data measuring changes in total body weight over the 24-week study period. At 24 weeks, the change in total body weight in kilograms, a secondary endpoint, was -2.21 kg for dapagliflozin 2.5 mg, -3.04 kg for dapagliflozin 5 mg, and -2.86 kg for dapagliflozin 10 mg, compared with -0.89 kg for placebo ( $P < .0001$ ). Overall, more patients taking dapagliflozin achieved weight losses  $\geq 5\%$  versus placebo, an exploratory endpoint (24% for dapagliflozin 2.5 mg, 25.4% for dapagliflozin 5 mg, 28.0% for dapagliflozin 10 mg vs 5.9% for placebo).

Adverse events were generally balanced across all groups. Overall, the number of individuals reporting at least one adverse event for dapagliflozin 2.5 mg, dapagliflozin 5 mg, dapagliflozin 10 mg, and placebo were 89, 95, 98, and 88, respectively. Rates of urinary tract infections were similar for dapagliflozin 2.5 mg, 5 mg, 10 mg and placebo (4.4%, 7.3%, 8.1%, and 8.0%, respectively). Rates of genital infections were higher for the 2.5-mg, 5-mg, and 10-mg dapagliflozin treatment arms versus placebo (8.0%, 13.1%, 8.9%, and 5.1%, respectively). The investigators reported that genital tract infections were mild or moderate in nature and did not lead to discontinuation from the study. There were no clinically meaningful changes in markers for renal impairment, increases in mean serum creatinine, or increases in electrolyte abnormalities associated with dapagliflozin therapy.

The number of reported hypoglycemic events was similar across all treatment arms: 2.2% for dapagliflozin 2.5 mg, 3.6% for dapagliflozin 5 mg, 3.7% for dapagliflozin 10 mg, and 2.9% for placebo. There was no occurrence of hypoglycemia that led to discontinuation of the study. Reductions in blood pressure were observed without associated signs of hypotension. Changes in blood pressure at week 24 ranged from -3.1 to -5.9 systolic/-2.1 to -2.7 diastolic mm Hg with dapagliflozin, compared with -0.3 systolic/-0.4 diastolic mm Hg with placebo. A similar proportion of patients across all treatment arms, including placebo, had measured orthostatic hypotension.

## DAPAGLIFLOZIN PLUS INSULIN, INSULIN SENSITIZERS

Wilding et al<sup>20</sup> sought to determine whether dapagliflozin would lower hyperglycemia in patients with type 2 diabetes that is poorly controlled with high insulin

doses plus oral antidiabetic agents (OADs). They found that, in patients receiving high insulin doses plus insulin sensitizers who had their baseline insulin reduced by 50%, dapagliflozin decreased A1C, produced better FPG and postprandial glucose (PPG) levels, and lowered weight more than placebo.

**Study design.** This randomized, double-blind, three-arm parallel-group, placebo-controlled, trial was conducted in 26 centers in the United States and Canada. Investigators wrote that, based on data from an insulin dose-adjustment setting cohort (n=4), patients in the treatment cohort (n=71) were randomized in a 1:1:1 fashion to placebo, 10 or 20 mg dapagliflozin, plus OAD(s) and 50% of their daily insulin dose. The primary outcome studied was a change from baseline in A1C at week 12 (dapagliflozin vs. placebo, last observation carried forward [LOCF]).

Included patients had type 2 diabetes, were aged 18 to 75 years, had body mass index  $\leq 45$  kg/m<sup>2</sup>, and A1C 7.5% to 10%. They were receiving stable-dose insulin sensitizer therapy (metformin  $\geq 1,000$  mg and/or pioglitazone [Actos, Takeda]  $\geq 30$  mg or rosiglitazone [Avandia, GlaxoSmithKline] 4 mg) for  $\geq 6$  weeks and insulin therapy for  $\geq 12$  weeks before enrollment (insulin dose must have been  $\geq 50$  units of U-100 daily and stable for  $\geq 6$  weeks).

**Study results.** At week 12 (LOCF), patients assigned to the 10- and 20-mg dapagliflozin groups had -0.70 and -0.78% mean differences in A1C change from baseline versus placebo. In both dapagliflozin groups, 65.2% of patients achieved a decrease from baseline in A1C  $\geq 0.5\%$  compared with 15.8% in the placebo group. Mean changes from baseline in FPG were +17.8, +2.4, and -9.6 mg/dL (placebo, 10, and 20 mg dapagliflozin, respectively). PPG reductions with dapagliflozin also showed dose dependence, the investigators found. Mean changes in total body weight were -1.9, -4.5, and -4.3 kg (placebo, 10, and 20 mg dapagliflozin). Overall, adverse events were balanced across all groups, although more genital infections occurred in the 20-mg dapagliflozin group than in the placebo group.

## CONCLUSIONS

The progression of type 2 diabetes is defined by a cycle of deteriorating glycemic control due to declining beta-cell function. It is known that therapies that employ insulin supplementation or secretion carry with them hypoglycemia risk, weight gain, decreased insulin sensitivity, and an eventual loss of effectiveness. Wilding et al wrote that this “frustrating clinical setting is exemplified most dramatically by patients with late-stage type 2 diabetes who require escalating insulin doses, often with oral agents such as metformin and/or thiazolidinediones, to

maintain glycemic control.” More than 25% of patients are ultimately treated with insulin-based regimens, often in combination with OADs. A novel strategy for controlling glycemia independently of insulin involves limiting glucose reabsorption in the proximal tubule of the kidney, where glucose is reabsorbed via SGLT2 receptors. Dapagliflozin selectively inhibits SGLT2, thereby limiting glucose reabsorption.

Recent results with dapagliflozin establish that SGLT2 inhibition can improve glycemic control and weight in patients with diabetes that is poorly controlled with metformin, as well as among those who are poorly controlled with high insulin doses and oral insulin sensitizer therapy. Additionally, this therapeutic approach may lend itself to reducing the weight gain that often occurs when insulin therapy is intensified in this population. ■

1. Action to Control Cardiovascular Risk in Diabetes Study Group, Gerstein HC, Miller ME, et al. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med.* 2008;358:2545–2559.
2. ADVANCE Collaborative Group, Patel A, MacMahon S, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med.* 2008;358:2560–2572.
3. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 (UKPDS 33). *Lancet* 1998;352:837–853.
4. Stratton IM, Adler AT, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ.* 2000;321:405–412.
5. Holman RR, Paul SK, Bethel MA, et al. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med.* 2008;359:1577–1589.
6. Simpson SH, Majumdar SR, Tsuyuki RT, et al. Dose-response relation between sulphonylurea drugs and mortality in type 2 diabetes mellitus: a population-based cohort study. *CMAJ.* 2006;174:169–74.
7. Havas S. The ACCORD trial and control of blood glucose level in type 2 diabetes mellitus. Time to challenge conventional wisdom. *Arch Intern Med.* 2009;169:150–154.
8. ADA Clinical Practice Recommendations. *Diabetes Care.* 2009;32:S1–S2.
9. Nathan DM, Buse JB, Davidson MB, et al. Medical management of hyperglycaemia in type 2 diabetes mellitus: a consensus algorithm for the initiation and adjustment of therapy. *Diabetologia.* 2009;52:17–30.
10. Jabbar SA, Goldstein BJ. Sodium glucose co-transporter 2 inhibitors: blocking renal tubular reabsorption of glucose to improve glycaemic control in patients with diabetes. *Int J Clin Pract.* 2008;62:1279–1284.
11. Abdul-Ghani MA, DeFronzo RA. Inhibition of renal glucose reabsorption: a novel strategy for achieving glucose control in type 2 diabetes mellitus. *Endocr Pract.* 2008;14:782–790.
12. Wanciewicz EV, Siwkowski A, Meibohm B, et al. Long term safety and efficacy of ISIS 388626, an optimized SGLT2 antisense inhibitor, in multiple diabetic and euglycemic species. Program and abstracts of the 68th Scientific Sessions of the American Diabetes Association; June 6–10, 2008; San Francisco, California. Abstract 334-OR.
13. List JF, Woo VC, Villegas EM, et al. Efficacy and safety of dapagliflozin in a dose-ranging monotherapy study of treatment-naïve patients with type 2 diabetes. Program and abstracts of the 68th Scientific Sessions of the American Diabetes Association; June 6–10, 2008; San Francisco, California. Abstract 329-OR.
14. Fujimori Y, Katsuno K, Nakashima I, Ishikawa-Takemura Y, Fujikura H, Isaji M. Remogliflozin etabonate, in a novel category of selective low-affinity sodium glucose cotransporter (SGLT2) inhibitors, exhibits antidiabetic efficacy in rodent models. *J Pharmacol Exp Ther.* 2008;327:268–276.
15. Kipnes M. Dapagliflozin: an emerging treatment option in type 2 diabetes. *Expert Opin Investig Drugs.* 2009;18:327–334.
16. Bakris GL, Fonseca VA, Sharma K, Wright EM. Renal sodium-glucose transport: role in diabetes mellitus and potential clinical implications. *Kidney Int.* 2009;Apr 8. [Epub ahead of print]
17. Bailey C. Dapagliflozin as an add-on to metformin lowers hyperglycaemia in type 2 diabetes patients inadequately controlled with metformin alone. *Diabetologia.* 2009;52:S76.
18. Dapagliflozin study demonstrated significantly improved glycemic control and weight reduction in type 2 diabetes patients inadequately controlled with metformin. [www.businesswire.com/portal/site/bms/?ndmViewId=news\\_view&newsId=20091002005099&newsLang=en](http://www.businesswire.com/portal/site/bms/?ndmViewId=news_view&newsId=20091002005099&newsLang=en). Accessed Nov. 19, 2009.
19. Wilding JPH, Norwood P, Tjoen C, et al. A study of dapagliflozin in patients with type 2 diabetes receiving high doses of insulin plus insulin sensitizers: Applicability of a novel insulin-independent treatment. *Diabetes Care.* 2009;32:1656–1662.