# Effects of Dapagliflozin, an SGLT2 Inhibitor, on $HbA_{1c}$, Body Weight, and Hypoglycemia Risk in Patients With Type 2 Diabetes Inadequately Controlled on Pioglitazone Monotherapy

Julio Rosenstock, MD[1]
Marisa Vico, MD[2]
Li Wei, PHD[3]
Afshin Salsali, MD[4]
James F. List, MA, MD, PHD[4]

**OBJECTIVE**—To examine the safety and efficacy of dapagliflozin, a sodium-glucose cotransporter-2 inhibitor, added on to pioglitazone in type 2 diabetes inadequately controlled on pioglitazone.

**RESEARCH DESIGN AND METHODS**—Treatment-naive patients or those receiving metformin, sulfonylurea, or thiazolidinedione entered a 10-week pioglitazone dose-optimization period with only pioglitazone. They were then randomized, along with patients previously receiving pioglitazone ≥30 mg, to 48 weeks of double-blind dapagliflozin 5 ($n$ = 141) or 10 mg ($n$ = 140) or placebo ($n$ = 139) every day plus open-label pioglitazone. The primary objective compared $HbA_{1c}$ change from baseline with dapagliflozin plus pioglitazone versus placebo plus pioglitazone at week 24. Primary analysis was based on ANCOVA model using last observation carried forward; all remaining analyses used repeated-measures analysis.

**RESULTS**—At week 24, the mean reduction from baseline in $HbA_{1c}$ was −0.42% for placebo versus −0.82 and −0.97% for dapagliflozin 5 and 10 mg groups, respectively ($P$ = 0.0007 and $P < 0.0001$ versus placebo). Patients receiving pioglitazone alone had greater weight gain (3 kg) than those receiving dapagliflozin plus pioglitazone (0.7–1.4 kg) at week 48. Through 48 weeks: hypoglycemia was rare; more events suggestive of genital infection were reported with dapagliflozin (8.6–9.2%) than placebo (2.9%); events suggestive of urinary tract infection showed no clear drug effect (5.0–8.5% for dapagliflozin and 7.9% for placebo); dapagliflozin plus pioglitazone groups had less edema (2.1–4.3%) compared with placebo plus pioglitazone (6.5%); and congestive heart failure and fractures were rare.

**CONCLUSIONS**—In patients with type 2 diabetes inadequately controlled on pioglitazone, the addition of dapagliflozin further reduced $HbA_{1c}$ levels and mitigated the pioglitazone-related weight gain without increasing hypoglycemia risk.

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Inhibition of sodium-glucose cotransporter-2 (SGLT2) represents a novel mechanism that reduces hyperglycemia independent of insulin secretion or action (1). In addition, this inhibitory action can induce mild osmotic diuresis and increase urinary excretion of glucose with modest caloric elimination leading to weight loss (2,3). Dapagliflozin, an SGLT2 inhibitor (4), has been shown to improve glycemic control in patients with type 2 diabetes as monotherapy (5) and in combination with metformin (6), sulfonylurea (7), or insulin (8), but not yet with a thiazolidinedione.

Some patients with type 2 diabetes use pioglitazone (9), which lowers glucose by altering gene transcription enhancing insulin sensitivity. However, safety concerns of fluid retention, weight gain, congestive heart failure, bone fractures, and, more recently, concerns about bladder cancer has limited its use as second line therapy when metformin is not tolerated or as triple oral therapy (10–14).

The safety hypothesis for a trial combining pioglitazone with dapagliflozin would not be anticipated to worsen the pioglitazone-related side effects and, because dapagliflozin causes glucosuria, which drives diuresis and caloric loss, it may mitigate the concerns of weight gain and fluid retention/edema. This is the first clinical study to examine additive effects of an SGLT2 inhibitor administered in combination with pioglitazone.

## RESEARCH DESIGN AND METHODS

This randomized, double-blind, placebo-controlled, parallel group, 24-week study with a subsequent 24-week extension enrolled male and female patients with type 2 diabetes between 29 July 2008 and 4 July 2009. The study took place at 105 sites in Argentina, Canada, India, Mexico, Peru, Philippines, Taiwan, and United States and was completed on 15 June 2010. Institutional review boards or independent ethics committees approved this protocol, and each patient provided written informed consent.

Patients ≥18 years old having fasting C-peptide ≥1.0 ng/mL and BMI ≤45.0 kg/m$^2$ entered group A or B. Group A patients had received ≥12 weeks of pioglitazone 30 or 45 mg/day and had $HbA_{1c}$ ≥7.0 and ≤10.5%. Group B patients were drug naive for the previous 10 weeks with $HbA_{1c}$ ≥8.0 and ≤11.0% or had received pioglitazone 15 mg/day or any dose of rosiglitazone with $HbA_{1c}$ ≥8.0 and

From the [1]Dallas Diabetes and Endocrine Center at Medical City, Dallas, Texas; the [2]Instituto de Investigaciones Clinicas Zarate, Buenos Aires, Argentina; [3]Bristol-Myers Squibb, Hopewell, New Jersey; and [4]Bristol-Myers Squibb, Princeton, New Jersey.
Corresponding author: Julio Rosenstock, juliorosenstock@dallasdiabetes.com.
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≤11.0% or had received ≥8 weeks of metformin ≤1700 mg/day or sulfonylurea less than or equal to half the maximal dose with $HbA_{1c}$ ≥7.0 and ≤11.0%. Group B patients could not be on >1 oral antidiabetic medication, and patients on more than half the maximum dose of sulfonylurea or metformin were excluded. Group B patients underwent a 10-week dose-optimization period in which their initial therapy was discontinued, and pioglitazone 30 mg/day was started and increased to 45 mg/day if possible. Group B patients were discontinued if their fasting plasma glucose (FPG) was >270 mg/dL (15.0 mmol/L) after 3 weeks or after 6 weeks with $HbA_{1c}$ <7.0 or >11.0%. Exclusion criteria included aspartate or alanine aminotransferases >2.5 times the upper limit of normal, total bilirubin >2.0 mg/dL, serum creatinine ≥2.0 mg/dL, urine albumin/creatinine ratio >1,800 mg/g, calculated creatinine clearance <50 mL/min, and congestive heart failure class III and IV.

Patients with prerandomization $HbA_{1c}$ ≥7.0 and ≤10.5% entered the 2-week, single-blind lead-in period and received diet and exercise counseling. Randomized patients received double-blind dapagliflozin 5 or 10 mg or placebo every day (oral administration) with open-label pioglitazone 30 or 45 mg/day, stratified by pre-enrollment diabetes treatment group A and B. To ensure adequate representation from group A, randomization was set to recruit at least one-third of the patients from this group.

The primary objective compared the change at 24 weeks from baseline in $HbA_{1c}$ with each dose of dapagliflozin plus pioglitazone versus placebo plus pioglitazone. Secondary objectives included change from baseline in FPG, postprandial glucose (PPG) measured by 120-min postchallenge response to an oral glucose tolerance test, and total body weight.

If FPG was >270 mg/dL (15.0 mmol/L) (week 4–8), >240 mg/dL (13.3 mmol/L) (week 8–12), or >200 mg/dL (11.1 mmol/L) (week 12–24), then patients were eligible to receive open-label rescue medication (metformin or sulfonylurea). Patients completing the first 24 weeks of the study were eligible for an additional 24 weeks. During weeks 24 to 48, if $HbA_{1c}$ was >8.0 (week 25–36) or >7.5% (week 36–47), patients were eligible to receive open-label rescue medication. Data obtained after rescue were excluded from the efficacy analysis but included in safety analysis.

Adverse events, laboratory abnormalities, and vital signs were assessed for the safety and tolerability of treatment. Hypoglycemia definitions are in the Supplementary Appendix and were documented for any event the investigator considered to be a hypoglycemic event, regardless of blood glucose measurement. Signs, symptoms, and events suggestive of urinary tract infection (UTI) and genital infection were solicited at every visit. Preferred term lists included a broad spectrum of signs and symptoms of UTIs and genital infections in addition to specific diagnoses. Seated blood pressure was determined after 5 min of rest followed by the orthostatic blood pressure measurements. Average blood pressure was determined from three replicate measurements taken at least 1 min apart in each position (seated, supine, and standing).

### Statistical analyses

Statistical analyses at week 24 (last observation carried forward) including changes from baseline in $HbA_{1c}$, FPG, PPG, and body weight were performed using ANCOVA with treatment group as an effect and baseline value and strata based on pre-enrollment antidiabetic therapy as covariates in the model. Secondary end points were tested for significance sequentially.

At week 48, analyses of change from baseline in $HbA_{1c}$, FPG, PPG, and body weight were performed using longitudinal repeated-measures analysis over time including the fixed categorical effects of strata based on pre-enrollment antidiabetic therapy, treatment, week, and treatment-by-week interaction as well as the continuous fixed covariates of baseline measurement and baseline measurement-by-week interaction. No statistical testing was performed for the 48-week long-term period. Rescue was added as an additional effect to the mixed model when the analysis was performed on data regardless of rescue.

**RESULTS**—Of the 972 enrolled patients, 558 met the entrance criteria, and 480 entered the lead-in phase with pioglitazone. Almost equal numbers of patients came from group A (48%, 200 out of 420) and group B (52%, 220 out of 420) (Supplementary Fig. 1). Demographics and baseline characteristics are shown in Table 1. The proportion of patients who were discontinued or rescued for lack of glycemic control was less with dapagliflozin (11–18%) than with placebo (34%).

Treatment with dapagliflozin 5 and 10 mg added on to pioglitazone resulted in statistically significant mean reductions in $HbA_{1c}$, FPG, and PPG when compared with placebo at week 24 (Table 2) and were maintained through week 48 (Table 2). The mean reduction from baseline in $HbA_{1c}$ with dapagliflozin plus pioglitazone

**Table 1**—*Demographics and baseline characteristics*

| | Placebo + pioglitazone ≥30 mg | Dapagliflozin 5 mg + pioglitazone ≥30 mg | Dapagliflozin 10 mg + pioglitazone ≥30 mg |
|---|---|---|---|
| *n* | 139 | 141 | 140 |
| Age (years) | 53.5 ± 11.4 | 53.2 ± 10.9 | 53.8 ± 10.4 |
| Men | 71 (51.1) | 78 (55.3) | 59 (42.1) |
| Women | 68 (48.9) | 63 (44.7) | 81 (57.9) |
| Race | | | |
| White | 102 (74.3) | 102 (72.3) | 101 (72.1) |
| African American | 6 (4.3) | 9 (6.4) | 7 (5.0) |
| Asian | 24 (17.3) | 26 (18.4) | 21 (15.0) |
| Other | 7 (5.0) | 4 (2.8) | 11 (7.9) |
| $HbA_{1c}$ (%) | 8.34 ± 1.00 | 8.40 ± 1.03 | 8.37 ± 0.96 |
| FPG (mg/dL) | 160.7 ± 47.0 | 168.6 ± 52.1 | 164.9 ± 46.3 |
| FPG (mmol/L) | 8.92 ± 2.61 | 9.36 ± 2.89 | 9.15 ± 2.57 |
| 120-min PPG (mg/dL) | 294 ± 81 | 285 ± 99 | 308 ± 93 |
| 120-min PPG (mmol/L) | 16.3 ± 4.50 | 15.8 ± 5.49 | 17.1 ± 5.17 |
| Weight (kg) | 86.4 ± 21.3 | 87.8 ± 20.7 | 84.8 ± 22.2 |
| BMI | | | |
| ≥30 kg/m$^2$ | 85 (61.2) | 87 (61.7) | 72 (51.4) |
| ≥25 kg/m$^2$ | 122 (87.8) | 122 (86.5) | 130 (92.9) |
| Duration of diabetes (years) | 5.07 ± 5.05 | 5.64 ± 5.36 | 5.75 ± 6.44 |

Data are means ± SD or *n* (%).

ranged from −0.82 to −0.97% compared with −0.42% with the placebo plus pioglitazone at week 24 ($P = 0.0007$ and $P < 0.0001$ for dapagliflozin 5- and 10-mg groups, respectively.) At 48 weeks, the mean reductions in $HbA_{1c}$ were maintained, and dapagliflozin groups ranged from −0.95 to −1.21% compared with −0.54% with the placebo plus pioglitazone. These reductions were dose-dependent (Fig. 1*A*) and similar between groups A and B over time (data not shown). Rapid decreases in FPG were observed at week 1 (Fig. 1*B*) in the dapagliflozin groups and significant at week 24 (Table 2). At week 48, a greater reduction in mean change from baseline in PPG was observed with dapagliflozin plus pioglitazone (−60.4 to −80.9 mg/dL [−3.35 to −4.49 mmol/L]) than with placebo plus pioglitazone (−25.4 mg/dL [1.41 mmol/L]) (Table 2).

The increase in mean urinary glucose to creatinine ratio from baseline was maintained in the dapagliflozin groups over time (Fig. 1*C*). The placebo group experienced a mean increase in body weight of 3.0 kg through week 48. Dapagliflozin groups had a slight weight reduction initially, followed by gradual weight gain toward the baseline values at week 24 and gains of 1.4 and 0.7 kg for 5 and 10 mg, respectively, at week 48 (Table 2 and Fig. 1*D*). These changes for the dapagliflozin groups were significant at week 24 compared with placebo, maintained throughout 48 weeks (Table 2), and appeared to be dose-dependent over time (Fig. 1*D*).

The placebo group experienced a mean increase in seated blood pressure at weeks 24 and 48, whereas both dapagliflozin groups experienced mean decreases (Table 2). Small mean increases in hematocrit occurred in both dapagliflozin treatment groups (1.36–2.04%), whereas the placebo showed −0.44% change at week 48. Small changes were observed on mean fasting LDL cholesterol (1.1–3.4% for dapagliflozin and 4.5% for placebo), total cholesterol (0.0–2.0% for dapagliflozin and 1.9% for placebo), triglycerides (3.7–4.2% for dapagliflozin and 13.5% for placebo), and HDL cholesterol (4.1–7.2% for dapagliflozin and 1.3% for placebo) at week 48.

No clinically relevant changes in calcium, magnesium, phosphorous, or serum 25 hydroxyvitamin D concentrations were apparent in any treatment group throughout the study (data not shown). There were small increases within the normal limits for parathyroid hormone

**Table 2—*Change from baseline at weeks 24 and 48 in efficacy parameters, vital signs, and laboratory values***

| | Week 24 | | | Week 48 | | |
|---|---|---|---|---|---|---|
| | Placebo + pioglitazone ≥30 mg | Dapagliflozin 5 mg + pioglitazone ≥30 mg | Dapagliflozin 10 mg + pioglitazone ≥30 mg | Placebo + pioglitazone ≥30 mg | Dapagliflozin 5 mg + pioglitazone ≥30 mg | Dapagliflozin 10 mg + pioglitazone ≥30 mg |
| *n* | 139 | 141 | 140 | 139 | 141 | 140 |
| $HbA_{1c}$ (%)*† | −0.42 ± 0.08 | −0.82 ± 0.08‡ | −0.97 ± 0.08§ | −0.54 ± 0.08 | −0.95 ± 0.08 | −1.21 ± 0.07 |
| FPG (mg/dL)*† | −5.5 ± 2.9 | −24.9 ± 2.9§ | −29.6 ± 2.9§ | −13.1 ± 3.6 | −22.8 ± 3.2 | −33.1 ± 3.0 |
| FPG (mmol/L)*† | −0.31 ± 0.16 | −1.38 ± 0.16§ | −1.64 ± 0.16§ | −0.73 ± 0.20 | −1.27 ± 0.18 | −1.84 ± 0.17 |
| 120 min PPG (mg/dL)*‖ | −14.1 ± 6.4 | −65.1 ± 6.3§ | −67.5 ± 6.4§ | −25.4 ± 7.1 | −60.4 ± 5.9 | −80.9 ± 5.7 |
| 120 min PPG (mmol/L)*‖ | −0.78 ± 0.36 | −3.61 ± 0.35§ | −3.75 ± 0.36§ | −1.41 ± 0.39 | −3.35 ± 0.33 | −4.49 ± 0.32 |
| Weight (kg)*† | 1.64 ± 0.28 | 0.09 ± 0.28§ | −0.14 ± 0.28§ | 2.99 ± 0.41 | 1.35 ± 0.38 | 0.69 ± 0.36 |
| Seated systolic blood pressure (mmHg) | 1.3 ± 1.2 | −0.8 ± 1.2 | −3.4 ± 1.2 | 2.0 ± 1.2 | −1.0 ± 1.1 | −2.2 ± 1.2 |
| Seated diastolic blood pressure (mmHg) | 0.7 ± 0.8 | −1.0 ± 0.7 | −3.1 ± 0.8 | 0.4 ± 0.9 | −0.7 ± 0.7 | −2.4 ± 0.7 |
| Urinary glucose/creatinine ratio¶ | 1.56 ± 22.1 | 35.7 ± 32.4 | 43.7 ± 37.1 | −1.74 ± 10.6 | 30.4 ± 28.7 | 38.4 ± 28.6 |
| Serum creatinine (μmol/L) | −0.44 ± 0.68 | −1.24 ± 0.72 | 1.24 ± 0.83 | 0.62 ± 1.10 | 0.62 ± 1.04 | 2.12 ± 0.86 |
| Serum uric acid (μmol/L) | 11.3 ± 3.90 | −19.6 ± 5.46 | −26.2 ± 4.70 | — | — | — |
| Blood urea nitrogen (mmol/L) | −0.088 ± 0.12 | 0.46 ± 0.14 | 0.46 ± 0.13 | −0.37 ± 0.14 | 0.40 ± 0.16 | 0.35 ± 0.16 |
| Sodium (mmol/L) | −0.2 ± 0.2 | 0.4 ± 0.2 | 0.7 ± 0.2 | 0.2 ± 0.2 | 0.7 ± 0.3 | 1.4 ± 0.2 |
| Potassium (mmol/L) | 0.02 ± 0.04 | −0.05 ± 0.03 | 0.01 ± 0.04 | 0.05 ± 0.03 | −0.05 ± 0.04 | −0.02 ± 0.03 |
| Parathyroid hormone (pg/mL) | 0.4 ± 1.2 | 4.6 ± 1.2 | 4.2 ± 1.4 | 2.7 ± 1.5 | 10.6 ± 6.7 | 7.3 ± 1.4 |
| Serum albumin (g/dL) | −0.02 ± 0.02 | 0.02 ± 0.02 | −0.01 ± 0.02 | −0.06 ± 0.03 | −0.01 ± 0.03 | 0.01 ± 0.03 |

Data are mean change from baseline ± SE unless otherwise indicated and excludes data after rescue except serum uric acid, which included data after rescue. *Adjusted mean change from baseline. †Weeks 24 and 48 were based on ANCOVA model using last observation carried forward and repeated-measures analysis, respectively. ‡$P = 0.0007$ versus placebo. §$P < 0.0001$ versus placebo. ‖Measured by 120-min postchallenge response to an oral glucose tolerance test. ¶Mean change from baseline ± SD.

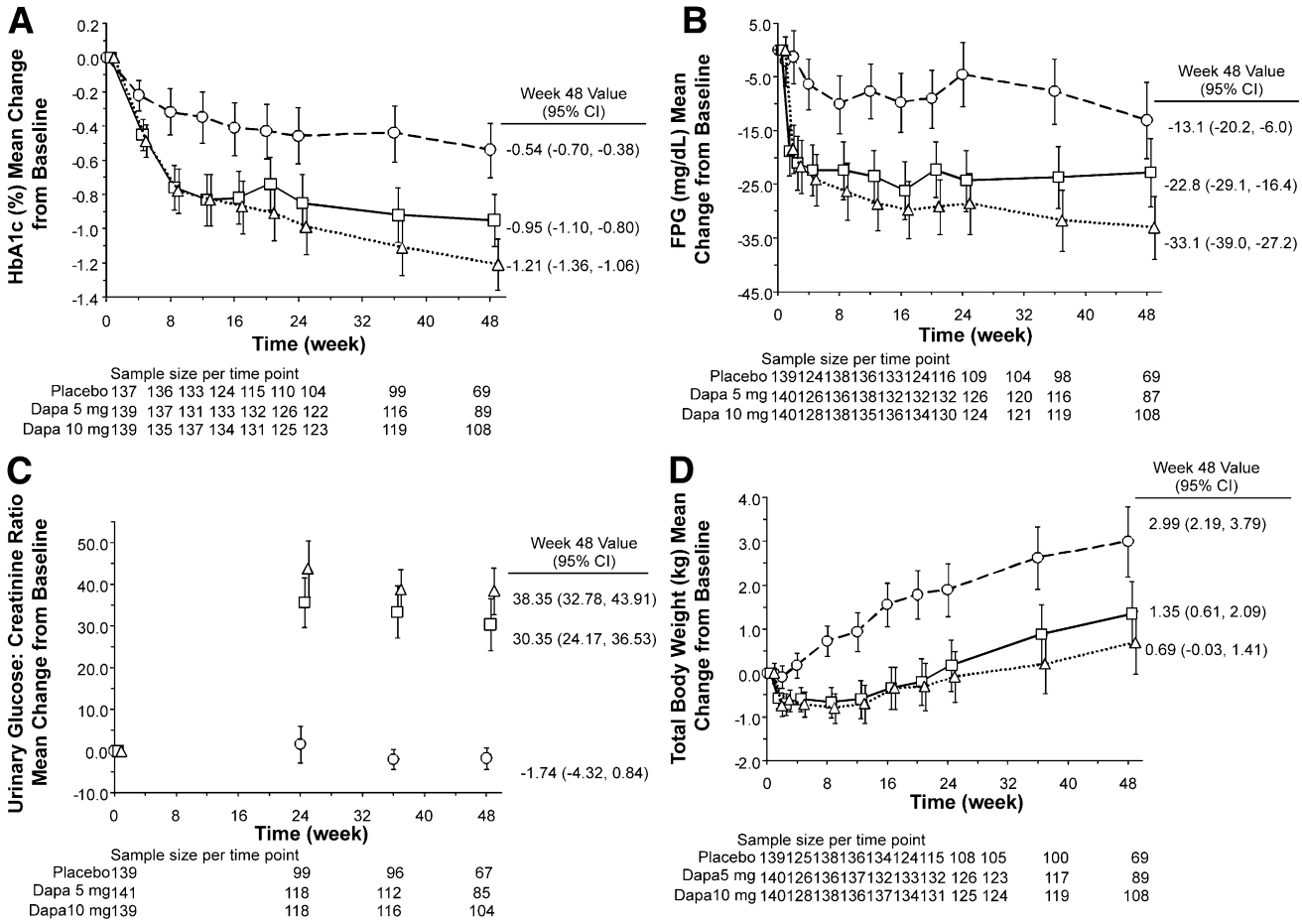


**Figure 1**—*Changes in glycemic parameters for placebo (circles), dapagliflozin 5 mg (squares), and dapagliflozin 10 mg (triangles) all plus pioglitazone ≥30 mg.* A: *Mean change from baseline in $HbA_{1c}$ after adjustment for baseline value over time.* B: *Mean change from baseline in FPG after adjustment for baseline value over time.* C: *Mean urinary glucose to creatinine ratio change from baseline over time.* D: *Mean change from baseline in total body weight after adjustment for baseline value over time. Includes patients who took at least one dose of double-blind study medication. Error bars represent 95% CIs. Treatment symbols shifted horizontally to prevent error bars from overlapping.*

and small mean changes in bone markers (serum procollagen type 1 *N*-propeptide, COOH-terminal telopeptide of type 1 collagen, *N*-terminal telopeptide of type 1 collagen, and osteocalcin) compared with placebo, which were unlikely to be clinically significant.

Table 3 describes the adverse events through week 48. The proportion of patients who reported at least one adverse event was similar for dapagliflozin (68.1–70.7%) and placebo (66.9%) through week 48. One death due to septic shock was reported on day 117 in the dapagliflozin 5-mg group within 2 days of presenting with acute cholecystitis. Discontinuations were low and similar between the dapagliflozin and the placebo groups, none due to hypoglycemia. No major episodes of hypoglycemia occurred during the 48-week study.

All of the renal events listed in Table 3 occurred during the first 24-week period, and no additional events occurred during the second 24-week period. They included serum creatinine increase (four events), creatinine renal clearance decrease (one event), glomerular filtration rate decrease (one event), and abnormal renal function test (one event). The proportion of patients with an event suggestive of UTI was 7.9, 8.5, and 5.0% with placebo, dapagliflozin 5 mg, and 10 mg, respectively, through week 48. Signs, symptoms, and other events suggestive of genital infection were more common in both dapagliflozin treatment groups (8.6–9.2%) than in the placebo group (2.9%) through week 48. Most events suggestive of UTI or genital infection were of mild or moderate intensity; none of these events were serious or led to withdrawal from the study except for one patient (dapagliflozin 5 mg) with recurrent UTIs.

Patients treated with pioglitazone plus dapagliflozin 5 or 10 mg had a lower rate of peripheral edema (4.3 and 2.1%, respectively) compared with pioglitazone plus placebo (6.5%) (Table 3). Two patients (one female and one male) from the dapagliflozin 5-mg group experienced limb fractures (one foot and one hand, respectively) during the first 24-week period. One patient on placebo had an event of heart failure, and one patient on dapagliflozin 5 mg had urothelial bladder cancer detected on day 144.

**CONCLUSIONS**—In this study, the addition of dapagliflozin to pioglitazone lowered $HbA_{1c}$ levels and attenuated the pioglitazone-related weight gain in patients with type 2 diabetes inadequately controlled on pioglitazone alone. Dapagliflozin acts in the kidney by inhibiting the reabsorption of glucose (15,16) and is not only capable of reducing FPG but also reabsorption of higher glucose load postprandially as shown in this study. These beneficial effects of dapagliflozin on hyperglycemia were

**Table 3—*Adverse and special interest events through week 48***

| | Placebo + pioglitazone ≥30 mg | Dapagliflozin 5 mg + pioglitazone ≥30 mg | Dapagliflozin 10 mg + pioglitazone ≥30 mg |
|---|---|---|---|
| *n* | 139 | 141 | 140 |
| At least one adverse event | 93 (66.9) | 96 (68.1) | 99 (70.7) |
| At least one serious adverse event | 4 (2.9) | 6 (4.3) | 2 (1.4) |
| Adverse event leading to discontinuation of study medication | 5 (3.6) | 5 (3.5) | 3 (2.1) |
| Most common adverse events (>5% in any treatment group) | | | |
| Dyslipidemia | 9 (6.5) | 11 (7.8) | 16 (11.4) |
| Nasopharyngitis | 7 (5.0) | 7 (5.0) | 11 (7.9) |
| Diarrhea | 6 (4.3) | 5 (3.5) | 9 (6.4) |
| Back pain | 4 (2.9) | 5 (3.5) | 8 (5.7) |
| Upper respiratory tract infection | 10 (7.2) | 10 (7.1) | 7 (5.0) |
| Headache | 10 (7.2) | 3 (2.1) | 4 (2.9) |
| Pain in extremity | 1 (0.7) | 10 (7.1) | 4 (2.9) |
| Edema peripheral | 9 (6.5) | 6 (4.3) | 3 (2.1) |
| Adverse events of special interest | | | |
| Suggestive of urinary tract infection | 11 (7.9) | 12 (8.5) | 7 (5.0) |
| Suggestive of genital infection | 4 (2.9) | 13 (9.2) | 12 (8.6) |
| Mycotic genital infection | 1 (0.7) | 8 (5.7) | 6 (4.3) |
| Decreased renal function | 1 (0.7) | 2 (1.4) | 2 (1.4) |
| Fracture | 0 | 2 (1.4) | 0 |
| Total patients with hypoglycemia | 1 (0.7) | 3 (2.1) | 0 |
| Major episode of hypoglycemia* | 0 | 0 | 0 |
| Congestive heart failure | 1 (0.7) | 0 | 0 |
| Bladder cancer† | 0 | 1 (0.7) | 0 |

Data are *n* (%). *Major episode defined as a symptomatic episode requiring external assistance due to severe impairment in consciousness or behavior with a capillary or plasma glucose value <54 mg/dL (<3.0 mmol/L) and prompt recovery after glucose or glucagon administration. Minor episodes defined as either a symptomatic episode with a capillary or plasma glucose measurement <63 mg/dL (3.5 mmol/L) regardless of need for external assistance or an asymptomatic capillary or plasma glucose measurement <63 mg/dL (3.5 mmol/L), which does not qualify as a major episode. Other episodes defined as episodes reported by the investigator that are suggestive of hypoglycemia but do not meet the above criteria. †Urothelial bladder carcinoma.

maintained for almost 1 year and were consistent with sustained pharmacodynamic activity on glycosuria.

The glucosuria induced by SGLT-2 inhibition might be suspected to lead to hypoglycemia, UTIs, and genital infections. However, hypoglycemia events were rare in this study. No clear relationship to dapagliflozin was observed for events suggestive of UTIs, although one patient withdrew from the trial due to recurring UTIs. Consistent with previous reports (5,6,8), events suggestive of genital infections were higher in patients on dapagliflozin than on placebo. None of these genital infections were serious, and all responded to antimicrobial treatment.

Urinary excretion of glucose also leads to caloric loss and the addition of dapagliflozin to pioglitazone can potentially mitigate weight gain due to pioglitazone. The differences between placebo and dapagliflozin-treated groups in weight were mainly driven by continuous weight gain in the placebo group, reflecting probably that pioglitazone was initiated or optimized during the prerandomization period, whereas no meaningful changes from baseline occurred in dapagliflozin groups. Dapagliflozin, acting as a mild diuretic, may also mitigate the fluid retaining effects of pioglitazone as evidenced by fewer reports of edema.

Some studies suggest that pioglitazone may modestly lower blood pressure (17), a beneficial effect for patients with diabetes. When dapagliflozin was used as monotherapy (5) or in combination therapy (6,8), there was also some suggestive mild lowering of blood pressure. In this study, addition of dapagliflozin to pioglitazone was associated with a modest further decrease in blood pressure beyond the effect of pioglitazone alone in the absence of any ill effects such as hypotensive events or measured orthostatic hypotension. Thus, along with effects on weight, dapagliflozin may add to the blood pressure benefit of pioglitazone.

Congestive heart failure, bladder cancer, or bone fractures, known side effects of long-term use of pioglitazone, were rare events; too rare at this stage to infer any effect on the risk of these events with the addition of dapagliflozin (13,14,18). Two fractures did occur in the dapagliflozin 5-mg group, but all patients received pioglitazone, and thiazolidinediones are known to increase the risk of fractures (19).

Dapagliflozin added on to pioglitazone resulted in sustained glycemic benefits in both fasting and postprandial plasma glucose concentrations. As a possible mild diuretic and consistent glucouretic, dapagliflozin mitigated the weight gain and fluid retention due to pioglitazone. Even though more genital infections occurred with dapagliflozin than placebo, dapagliflozin added on to pioglitazone was effective and well-tolerated. The direct removal of glucose by dapagliflozin complements the insulin-sensitizing action of pioglitazone, providing a potential combination that balances well the benefits and risks of therapy for some patients with type 2 diabetes.

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conflicts of interest relevant to this article were reported.

J.R., M.V., L.W., and A.S. analyzed and interpreted data, contributed to the discussion, and reviewed/edited the manuscript. J.F.L. analyzed and interpreted data, contributed to the discussion, reviewed/edited the manuscript, and wrote the manuscript. J.F.L. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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