

Sodium-Glucose Cotransport Inhibition With Dapagliflozin in Type 2 Diabetes

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OBJECTIVE— Dapagliflozin, a novel inhibitor of renal sodium-glucose cotransporter 2, allows an insulin-independent approach to improve type 2 diabetes hyperglycemia. In this multiple-dose study we evaluated the safety and efficacy of dapagliflozin in type 2 diabetic patients.

RESEARCH DESIGN AND METHODS— Type 2 diabetic patients were randomly assigned to one of five dapagliflozin doses, metformin XR, or placebo for 12 weeks. The primary objective was to compare mean change from baseline in A1C. Other objectives included comparison of changes in fasting plasma glucose (FPG), weight, adverse events, and laboratory measurements.

RESULTS— After 12 weeks, dapagliflozin induced moderate glucosuria (52–85 g urinary glucose/day) and demonstrated significant glycemic improvements versus placebo (Δ A1C -0.55 to -0.90% and Δ FPG -16 to -31 mg/dl). Weight loss change versus placebo was -1.3 to -2.0 kg. There was no change in renal function. Serum uric acid decreased, serum magnesium increased, serum phosphate increased at higher doses, and dose-related 24-h urine volume and hematocrit increased, all of small magnitude. Treatment-emergent adverse events were similar across all groups.

CONCLUSIONS— Dapagliflozin improved hyperglycemia and facilitates weight loss in type 2 diabetic patients by inducing controlled glucosuria with urinary loss of ~ 200 – 300 kcal/day. Dapagliflozin treatment demonstrated no persistent, clinically significant osmolarity, volume, or renal status changes.

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Type 2 diabetes is characterized by hyperglycemia, which contributes to micro- and macrovascular complications including retinopathy, nephropathy, neuropathy, and accelerated cardiovascular disease (1–4). Excess hyperglycemia promotes glucotoxicity through increased insulin resistance and interference with β -cell function (5,6). Despite various therapeutic options, many patients demonstrate inadequate glycemic control and remain at risk for chronic complications (7).

Dapagliflozin is the first in a new class of oral selective sodium-glucose cotransporter 2 (SGLT2) inhibitors designed for

treating type 2 diabetes (8,9). Dapagliflozin improves hyperglycemia by inhibiting renal glucose reabsorption through SGLT2. SGLT2 is a sodium-solute cotransport protein located in the kidney proximal tubule that reabsorbs the majority of glomerular-filtered glucose (10–13).

Both phlorizin, an O-glucoside, non-specific renal glucose reabsorption inhibitor, and individuals with SGLT2 genetic mutations provided early insight into the potential value of this therapeutic approach. Phlorizin was shown to reduce hyperglycemia by inhibiting glucose reabsorption (14,15); however, clinical ap-

plication was limited by glucosidase degradation and lack of SGLT2 selectivity. Dapagliflozin is highly SGLT2 selective and contains a C-glucoside for increased in vivo stability, characteristics that prolong half-life and produce consistent pharmacodynamic activity (9). Dapagliflozin induces steady rates of glucosuria in healthy volunteers and type 2 diabetic patients, amounting to ~ 70 g glucose excreted daily (16). Individuals with familial renal glycosuria, a condition caused by genetic mutations in SGLT2, have been characterized as having largely benign phenotypes with normal life expectancies and no long-term renal deterioration or known health consequences (17,18).

This dose-ranging monotherapy study describes efficacy, safety, and laboratory data for dapagliflozin treatment over 12 weeks. The results support application of SGLT2 inhibition as a unique insulin-independent approach to improve hyperglycemia and weight status in type 2 diabetic patients.

RESEARCH DESIGN AND METHODS

From December 2005 to September 2006, drug-naïve type 2 diabetic patients, aged 18–79 years, with A1C $\geq 7\%$ and $\leq 10\%$, were recruited at 98 clinical centers in the U.S., 24 in Canada, 8 in Mexico, and 3 in Puerto Rico. Inclusion criteria included fasting C-peptide >1.0 ng/ml, BMI ≤ 40 kg/m², and renal status as follows: glomerular filtration rate >60 ml/min per 1.73 m², serum creatinine <1.5 mg/dl (men)/ <1.4 mg/dl (women), and urine microalbumin/creatinine ratio ≤ 300 mg/g.

This was a prospective, 12-week, randomized, parallel-group, double-blind, placebo-controlled study, with a 2-week diet/exercise placebo lead-in and 4-week follow-up (Fig. 1). Patients were randomly assigned equally to once-daily dapagliflozin (2.5, 5, 10, 20, or 50 mg), metformin XR (750 mg force-titrated at week 2 to 1,500 mg) (therapeutic benchmark), or placebo. Safety and efficacy were assessed at all study visits. Patients with fasting plasma glucose (FPG) >240 mg/dl at weeks 4 and 6, >220 mg/dl at week 8, or >200 mg/dl at week 10 were discontinued from the study and were el-

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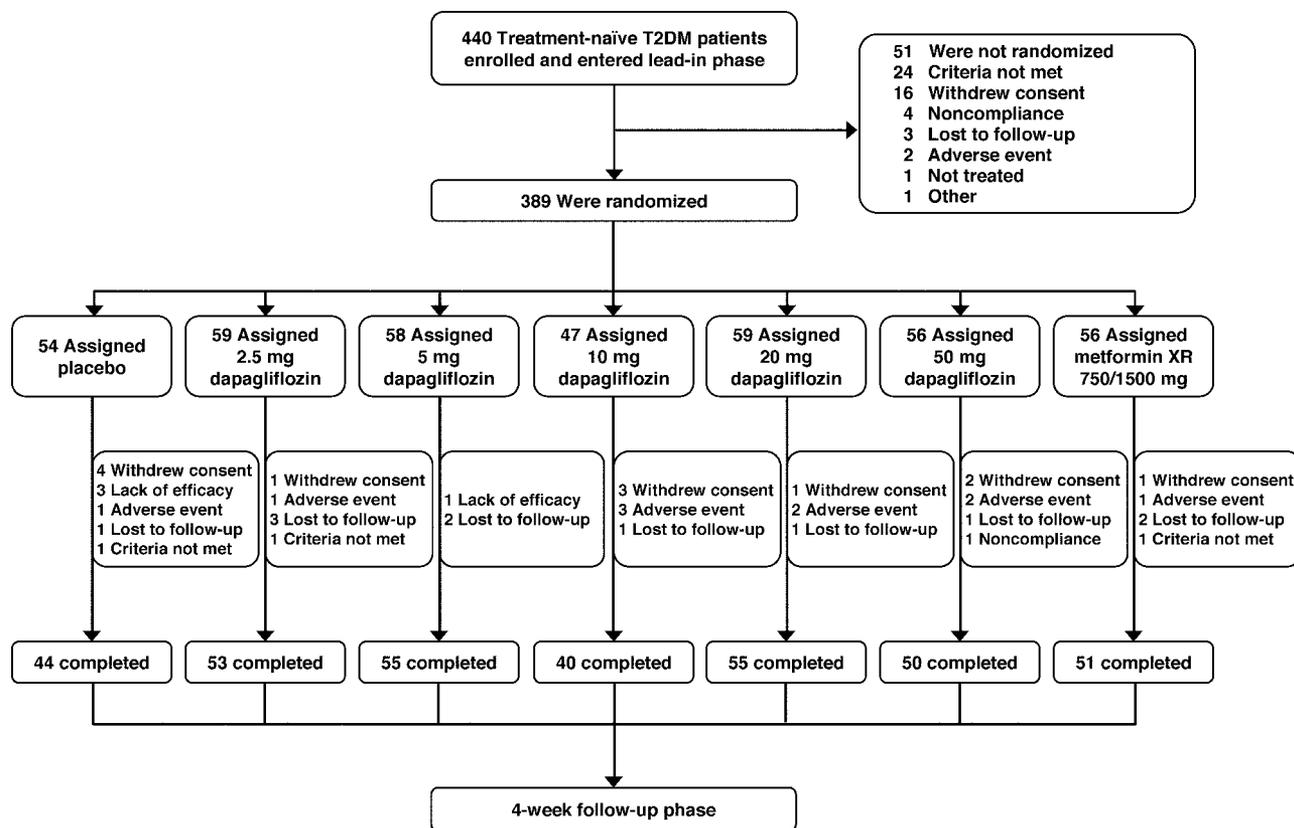


Figure 1—Patient disposition and study design. T2DM, type 2 diabetic.

igible to receive additional antidiabetic agents. The study was conducted pursuant to the Declaration of Helsinki and was approved by institutional review boards/independent ethics committees at participating sites. Patients provided written informed consent before enrollment.

The primary objective was to compare mean A1C change from baseline for each dapagliflozin group versus placebo after 12 weeks. Secondary objectives were comparisons of dapagliflozin versus placebo for FPG change from baseline, dose-dependent trends in glycemic efficacy, proportion of patients achieving A1C <7%, and change in 24-h urinary glucose-to-creatinine ratio.

Measurements

Study visits occurred at screening; days –14 and 1; weeks 1, 2, 4, 6, 8, 10, and 12; and follow-up weeks 14 and 16. Fasting blood and urine samples were collected after a minimum 10-h fast. During oral glucose tolerance testing, blood was drawn at 0, 30, 60, 120, and 180 min after an oral glucose challenge (75 g). Samples were centrally assessed (Quintiles Laboratories, Smyrna, GA). Glucose area under the curve (AUC) was calculated by trape-

zoidal methodology. Vital signs, brief physical examination, and adverse event assessment were performed at each visit. Complete physical examination and electrocardiograms were performed at lead-in and week 12.

Adverse events were summarized by preferred term (Medical Dictionary for Regulatory Activities [MedDRA], version 10). Safety topics of special interest were summarized by interest categories.

Statistical analyses

Fifty patients per treatment group provided 82% power to detect a mean 0.7% difference in A1C between dapagliflozin groups and placebo, assuming 1% SD. Comparisons between dapagliflozin and placebo were performed at the 0.012 level using Dunnett's adjustment so that overall type 1 error rate was controlled at 0.05 significance. Statistical analyses were performed on all randomly assigned and treated patients. Missing values were imputed by last observation carried forward (LOCF). Week 12 primary and secondary efficacy analyses for A1C, FPG, and 24-h urinary glucose-to-creatinine ratio were performed by ANCOVA with treatment group as the effect and baseline value as

covariate. Linear trend tests were performed to assess dose-response relationships among dapagliflozin groups for A1C change from baseline after 12 weeks. Fisher's exact test was used to compare the proportion of subjects achieving A1C <7.0% between dapagliflozin groups and placebo.

RESULTS— A total of 389 patients were randomly assigned to receive dapagliflozin, metformin, or placebo (Fig. 1); 348 completed week 12, and 41 discontinued. The most common reason for discontinuation was withdrawal of consent (12 patients). Baseline demographics and disease characteristics were similar among all groups (Table 1).

At week 12, all dapagliflozin groups achieved significant reductions in mean A1C change from baseline versus placebo (Fig. 2A and Table 2). Adjusted mean reductions ranged from –0.55 to –0.90% (dapagliflozin), –0.18% (placebo), and –0.73% (metformin). No log-linear dose-response relationship was demonstrated ($P_{\text{trend}} = 0.41$).

FPG reductions were apparent by week 1 in all dapagliflozin groups. By week 12, adjusted mean FPG reductions

Table 1—Baseline patient characteristics

	Dapagliflozin dose					Metformin
	2.5 mg	5 mg	10 mg	20 mg	50 mg	
Age (years)	55 ± 11	55 ± 12	54 ± 9	55 ± 10	53 ± 10	53 ± 11
Sex						
Male (%)	29 (49)	28 (48)	25 (53)	32 (54)	25 (45)	27 (48)
Female (%)	30 (51)	30 (52)	22 (47)	27 (46)	31 (55)	29 (52)
A1C (%)	7.6 ± 0.7	8.0 ± 0.9	8.0 ± 0.8	7.7 ± 0.9	7.8 ± 1.0	7.9 ± 0.9
FPG (mg/dl)	145 ± 34	153 ± 48	148 ± 38	149 ± 41	153 ± 42	150 ± 46
PPG (mg · min/dl)	42,225 ± 9,733	44,416 ± 9,885	44,283 ± 12,071	42,625 ± 7,426	44,822 ± 10,244	43,867 ± 12,832
24-h urinary glucose (g/24 h)	6 ± 16	6 ± 14	11 ± 31	10 ± 35	8 ± 25	7 ± 21
24-h urinary glucose/creatinine (g/g)	4.8 ± 12	6.3 ± 20	6.1 ± 14	6.7 ± 24	7.6 ± 23	6.9 ± 26
24-h urine volume (liters)	2.2 ± 0.9	1.9 ± 0.8	1.9 ± 0.9	1.8 ± 0.8	1.8 ± 0.8	2.0 ± 1.0
Weight (kg)	90 ± 20	89 ± 17	86 ± 17	88 ± 18	92 ± 19	89 ± 18
BMI (kg/m ²)	32 ± 5	32 ± 5	31 ± 5	31 ± 5	32 ± 4	32 ± 5
sBP (mmHg)	127 ± 14	126 ± 13	127 ± 16	127 ± 15	126 ± 16	126 ± 16
dBp (mmHg)	78 ± 8	76 ± 8	77 ± 8	77 ± 8	77 ± 9	77 ± 8
Heart rate (beats/min)	71 ± 10	70 ± 10	69 ± 8	68 ± 10	70 ± 10	72 ± 11
Creatinine (mg/dl)	0.85 ± 0.15	0.83 ± 0.19	0.85 ± 0.17	0.88 ± 0.19	0.84 ± 0.2	0.85 ± 0.19
BUN (mg/dl)	15.3 ± 4.2	14.6 ± 4.1	14.3 ± 3.6	15.6 ± 4.2	14.6 ± 4.6	14.5 ± 3.2
Sodium (mEq/l)	137.6 ± 2.5	137.7 ± 2.8	137.6 ± 1.9	137.8 ± 2.5	138.0 ± 2.6	137.8 ± 2.7
Potassium (mEq/l)	4.2 ± 0.4	4.1 ± 0.4	4.1 ± 0.3	4.2 ± 0.3	4.1 ± 0.5	4.1 ± 0.4
Calcium (mg/dl)	9.3 ± 0.4	9.2 ± 0.4	9.3 ± 0.4	9.3 ± 0.4	9.2 ± 0.5	9.3 ± 0.4
Magnesium (mEq/l)	1.7 ± 0.1	1.7 ± 0.2	1.7 ± 0.2	1.7 ± 0.1	1.6 ± 0.2	1.7 ± 0.2
Phosphate (mg/dl)	3.8 ± 0.6	3.7 ± 0.6	3.6 ± 0.6	3.8 ± 0.4	3.7 ± 0.6	3.7 ± 0.5
Uric acid (mg/dl)	5.5 ± 1.2	5.2 ± 1.3	5.5 ± 1.2	5.3 ± 1.3	5.6 ± 1.4	5.5 ± 1.4

Data are means ± SD.

were -16 to -31 mg/dl (dapagliflozin), -6 mg/dl (placebo), and -18 mg/dl (metformin), demonstrating dose-related FPG decreases and statistically significant reductions in the 5- to 50-mg dapagliflozin groups versus placebo (Fig. 2B). Adjusted mean postprandial plasma glucose (PPG) AUC reductions from baseline were $-7,053$ to $-10,149$ mg · min⁻¹ · dl⁻¹ (dapagliflozin), $-3,182$ mg · min⁻¹ · dl⁻¹ (placebo), and $-5,891$ mg · min⁻¹ · dl⁻¹ (metformin) (Fig. 2C and Table 2).

Proportions of patients achieving A1C <7% at week 12 ranged from 40 to 59% (dapagliflozin), 32% (placebo), and 54% (metformin). The comparison versus placebo was statistically significant only for the 50-mg group ($P < 0.01$).

Urinary glucose excretion increased in all dapagliflozin groups. Adjusted mean changes in 24-h urinary glucose-to-creatinine ratios at week 12 were 32–65 g/g versus -0.2 g/g for placebo ($P < 0.001$ for each dapagliflozin group) (Fig. 2D and Table 2). Total mean urinary glucose excreted per 24 h at week 12 ranged from 52 to 85 g with dapagliflozin (Table 2).

Total body weight reductions occurred in all groups (Fig. 3A). Mean percent reductions at week 12 were -2.5 to -3.4% (dapagliflozin), -1.2% (placebo), and -1.7% (metformin) (Fig. 3B and Table 2). More patients achieved >5% reductions with dapagliflozin (range 15.3–29.1%) than with placebo (7.7%); the proportion with metformin was 16.1%. Mean percent changes in waist circumference were -1.6 to -3.5% (dapagliflozin), -1.2% (placebo), and -2.2% (metformin).

Generally, adverse events were reported at similar frequencies across all groups (Table 2). No deaths or drug-related serious adverse events occurred. Hypoglycemic events were reported in 6–10% of dapagliflozin-treated patients with no dose relationship, in 4% of placebo-treated patients, and in 9% of metformin-treated patients (Table 2). There were no symptomatic hypoglycemic events with a fingerstick glucose ≤ 50 mg/dl.

Relevant adverse events were grouped into special interest categories. Events relating to each category were pooled (e.g., preferred terms “urinary tract infection” and “cystitis” were pooled as “infections of the urinary tract”) (Table 2). Infections of the urinary tract were seen in 5–12% of dapagliflozin-treated patients with no clear dose relationship versus 6% of

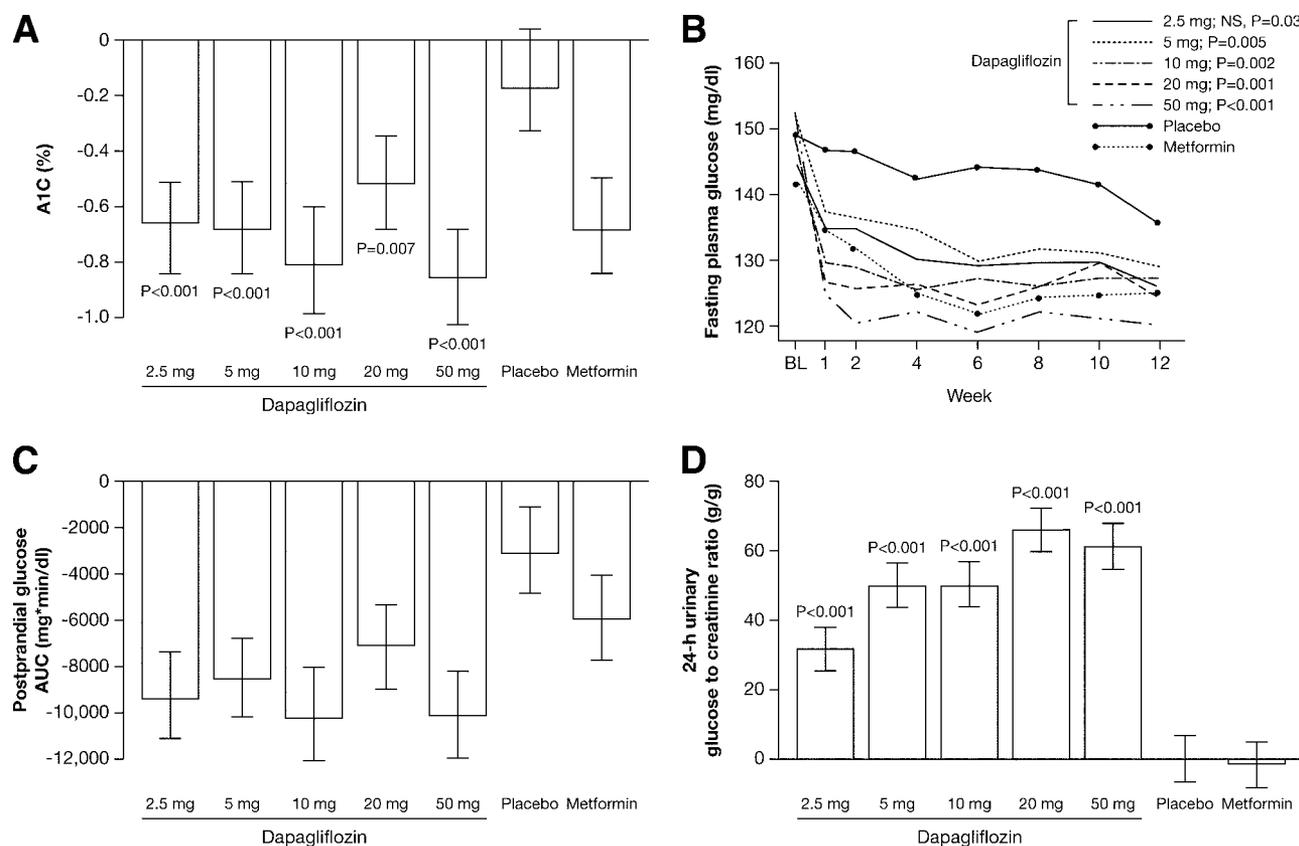


Figure 2—Changes in glycemic parameters. A: Adjusted mean change from baseline in A1C at week 12 (LOCF). B: Mean change in FPG over time (observed values). C: Adjusted mean change from baseline in postprandial glucose area under the curve (AUC) during a 75-g oral glucose tolerance test at week 12 (LOCF). D: Change from baseline in 24-h urinary glucose (grams) normalized for urinary creatinine (grams) at week 12 (LOCF). Displayed are means and 95% CIs (A, B, and D). When statistical significance was achieved with dapagliflozin groups compared with placebo, Dunnett's multiplicity adjustment was used. P values versus placebo at week 12.

placebo-treated patients and 9% of metformin-treated patients. Genital infections were seen in 2–7% of dapagliflozin-treated patients, 0% of placebo-treated patients, and 2% of metformin-treated patients.

Hypotensive events were seen in 0–2% of dapagliflozin-treated patients versus 2% of placebo-treated patients and 4% of metformin-treated patients. Decreased blood pressure was observed in all dapagliflozin groups (Table 2). Mean changes from baseline in supine systolic blood pressure (sBP) at week 12 ranged from -2.6 to -6.4 mmHg with no clear dose relationship. Similar changes occurred for standing sBP. Changes in diastolic blood pressure (dBp) and heart rate were small and inconsistent across dapagliflozin groups.

The diuretic effect of dapagliflozin was assessed by 24-h urine volume, hematocrit, and serum blood urea nitrogen (BUN) and creatinine (Table 2). Small dose-related increases in 24-h urine volumes (range 107–470 ml above baseline

of 1.8–2.2 l) were demonstrated at week 12. Increases in hematocrit were also dose-related (range 1.5–2.9%). There were small changes from baseline in serum BUN and no change in serum creatinine at week 12 across dapagliflozin doses. Mean percent increases at week 12 in the BUN-to-creatinine ratio ranged from 10.4 to 18.3%, with no apparent dose relationship. Changes in urine volume, hematocrit, and BUN-to-creatinine ratio returned toward baseline during follow-up. There was no clinically meaningful change in estimated glomerular filtration rate (Modification of Diet in Renal Disease formula) (19) in any group. All groups experienced a small decrease in 24-h creatinine clearance.

A small increase of ~ 0.1 mEq/l above the baseline mean (1.7 mEq/l) in serum magnesium and a larger relative decrease of ~ 1.0 mg/dl below the baseline mean (5.5 mg/dl) in serum uric acid were observed, returning toward baseline after discontinuation of dapagliflozin. Serum phosphate increased in a dose-related

manner for doses ≥ 5 mg (range -0.01 to $+0.24$ mg/dl from baseline of 3.6–3.8 mg/dl), although these changes were not statistically different from placebo (0.08 mg/dl) (Table 2). There were no clinically relevant mean changes from baseline in serum sodium, potassium, and calcium (Table 2).

With respect to bone metabolism, serum 1,25-dihydroxyvitamin D and 25-hydroxyvitamin D values were unchanged from baseline. Mean changes in the 24-h urinary calcium-to-creatinine ratio were similar to those with placebo. Small increases in mean parathyroid hormone concentrations (range 0.6–7.0 pg/ml above baseline of 31.1–35.0 pg/ml) were noted, which were generally greater than the 0.8 pg/ml increase for placebo. There was no clear treatment effect of dapagliflozin on fasting lipid parameters in this 12-week study.

CONCLUSIONS— Glucose reabsorption by the kidney is necessary from an evolutionary standpoint to retain calo-

Table 2—Efficacy parameters, adverse events, vital signs, and laboratory parameters

	Dapagliflozin dose					Metformin
	2.5 mg	5 mg	10 mg	20 mg	50 mg	
Efficacy parameters						
AIC (%) ^{*†}	-0.71 ± 0.09	-0.72 ± 0.09	-0.85 ± 0.11	-0.55 ± 0.09	-0.90 ± 0.10	-0.73 ± 0.10
P value vs. placebo	<0.001 [‡]	<0.001 [‡]	<0.001 [‡]	0.007 [‡]	<0.001 [‡]	
FPG (mg/dl) ^{*†}	-16 ± 3	-19 ± 3	-21 ± 4	-24 ± 3	-31 ± 3	-18 ± 3
P value vs. placebo	0.03	0.005 [‡]	0.002 [‡]	<0.001 [‡]	<0.001 [‡]	
PPG AUC (mg · min ⁻¹ · dl ⁻¹) ^{*†}	-9,382	-8,478	-10,149	-7,053	-10,093	-5891
95% CI	-11,420 to -7,344	-10,200 to -6,756	-12,215 to -8,082	-8,913 to -5,194	-12,024 to -8,162	-7,775 to -4,008
Proportion with AIC <7.0% [§]	26 (46)	23 (40)	23 (52)	26 (46)	31 (59)	29 (54)
P value vs. placebo	0.17	0.43	0.06	0.17	0.01 [‡]	
24-h urinary glucose/creatinine (g/g) ^{*†}	32 ± 3	49 ± 3	51 ± 3	65 ± 3	60 ± 3	-1.4 ± 3
P value vs. placebo	<0.001 [‡]					
Body weight reduction (%) [*]	-2.7	-2.5	-2.7	-3.4	-3.4	-1.7
95% CI	-3.4 to -1.9	-3.3 to -1.8	-3.5 to -1.8	-4.1 to -2.6	-4.1 to -2.6	-2.4 to -0.9
Total 24-h urinary glucose (g/24 h) [§]	52 ± 39	64 ± 34	68 ± 38	85 ± 43	82 ± 38	6 ± 21
Adverse events (double-blind period)						
Total subjects with an adverse event	35 (59)	35 (60)	32 (68)	40 (68)	35 (63)	38 (68)
Serious adverse events	1 (2)	0	1 (2)	1 (2)	1 (2)	1 (2)
Discontinuation for adverse events	1 (2)	0	3 (6)	2 (3)	2 (4)	1 (2)
Most common adverse events (≥10% in any group) by MedDRA preferred term						
Urinary tract infection	3 (5)	5 (9)	5 (11)	4 (7)	4 (7)	4 (7)
Nausea	3 (5)	4 (7)	3 (6)	2 (3)	3 (5)	6 (11)
Headache	4 (7)	3 (5)	2 (4)	3 (5)	1 (2)	2 (4)
Diarrhea	1 (2)	1 (2)	1 (2)	4 (7)	1 (2)	7 (13)
Events by special interest category						
Hypoglycemic events	4 (7)	6 (10)	3 (6)	4 (7)	4 (7)	5 (9)
Infections of the urinary tract	3 (5)	5 (9)	5 (11)	7 (12)	5 (9)	5 (9)

Table 2—Continued

	Dapagliflozin dose						Metformin
	2.5 mg	5 mg	10 mg	20 mg	50 mg	Placebo	
Genital infections [§]	2 (3)	1 (2)	1 (2)	4 (7)	4 (7)	0 (0)	1 (2)
Urinary tract or genital infection	4 (6.8)	6 (10.3)	5 (10.6)	10 (16.9)	9 (16.1)	3 (5.6)	6 (10.7)
Hypotensive events [#]	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	1 (2)	2 (4)
Vital signs**							
sBP (mmHg)	-3.1 ± 10.7	-2.9 ± 12.7	-6.4 ± 11.4	-4.3 ± 12.3	-2.6 ± 13.1	2.4 ± 11.1	-0.4 ± 12.4
P value vs. placebo	0.02	0.04	0.001	0.008	0.056		
dBp (mmHg)	0.8 ± 6.4	-0.3 ± 7.0	-2.6 ± 7.7	-0.5 ± 7.1	0.1 ± 8.0	0.3 ± 5.7	-0.6 ± 8.0
P value vs. placebo	0.67	0.66	0.07	0.56	0.89		
Heart rate (beats/min)	-1.4 ± 8.0	-1.0 ± 8.9	-0.03 ± 8.9	1.9 ± 11.2	0.1 ± 7.1	-2.3 ± 7.8	1.1 ± 9.6
P value vs. placebo	0.58	0.45	0.21	0.04	0.12		
Urine output (ml/24h)**	106.6 ± 606.9	340.0 ± 551.3	374.5 ± 741.6	374.9 ± 723.1	470.3 ± 797.5	-111.5 ± 655.4	-95.8 ± 75.4
P value vs. placebo	0.09	<0.001	0.002	<0.001	<0.001		
Laboratory parameters**							
Creatinine (mg/dl)	-0.01 ± 0.10	-0.00 ± 0.10	-0.02 ± 0.08	-0.01 ± 0.09	0.02 ± 0.11	-0.00 ± 0.10	-0.02 ± 0.12
P value vs. placebo	0.73	0.98	0.34	0.90	0.22		
BUN (mg/dl)	1.07 ± 3.96	0.71 ± 3.07	2.03 ± 3.72	0.87 ± 3.37	1.32 ± 3.61	-0.96 ± 2.81	-0.18 ± 2.67
P value vs. placebo	0.004	0.006	<0.001	0.005	0.001		
Sodium (mEq/l)	0.28 ± 2.90	0.56 ± 2.62	-0.15 ± 2.06	0.56 ± 2.28	0.50 ± 3.51	0.93 ± 2.83	-0.06 ± 2.35
P value vs. placebo	0.26	0.50	0.05	0.46	0.51		
Potassium (mEq/l)	-0.04 ± 0.34	0.02 ± 0.36	0.00 ± 0.32	-0.03 ± 0.29	0.00 ± 0.45	-0.01 ± 0.44	-0.04 ± 0.53
P value vs. placebo	0.76	0.71	0.88	0.84	0.88		
Calcium (mg/dl)	-0.11 ± 0.35	-0.04 ± 0.47	-0.12 ± 0.44	-0.11 ± 0.37	0.01 ± 0.48	-0.10 ± 0.48	-0.09 ± 0.55
P value vs. placebo	0.90	0.50	0.86	0.95	0.25		
Magnesium (mEq/l)	0.07 ± 0.14	0.10 ± 0.13	0.12 ± 0.19	0.14 ± 0.12	0.18 ± 0.16	0.04 ± 0.16	-0.03 ± 0.16
P value vs. placebo	0.30	0.04	0.03	0.001	<0.001		
Phosphate (mg/dl)	-0.01 ± 0.50	0.07 ± 0.50	0.12 ± 0.58	0.20 ± 0.43	0.24 ± 0.60	0.08 ± 0.47	-0.08 ± 0.54
P value vs. placebo	0.35	0.92 SD	0.73	0.17	0.15		
Uric acid (mg/dl)	-1.03 ± 0.81	-1.12 ± 0.84	-0.98 ± 0.66	-1.13 ± 0.78	-1.14 ± 1.15	-0.16 ± 0.75	0.18 ± 0.53
P value vs. placebo	<0.001	<0.001	<0.001	<0.001	<0.001		
Hematocrit (%)	1.51 ± 2.12	2.03 ± 2.36	1.95 ± 2.19	2.57 ± 2.44	2.86 ± 2.75	-0.08 ± 2.16	-1.12 ± 2.62
P value vs. placebo	0.001	<0.001	<0.001	<0.001	<0.001		

Data are means ± SD or n (%). *Change from baseline at week 12, LOCF. Missing data imputed by LOCF ranged from 5.2 to 13.6% (AIC), 11.5 to 26.0% (FPG), 5.2 to 13.6% (proportion with AIC <7.0%), and 2.0 to 8.2% (24-h urinary glucose/creatinine). †AIC, FPG, PPG, and 24-h urinary glucose/creatinine represent adjusted mean changes. ‡Between-group comparisons significant at $\alpha = 0.012$, applying Dunnett's adjustment. §Absolute week 12 value. ¶Infections of the urinary tract were events of urinary tract infection, cystitis, *Escherichia coli* urinary tract infection, urinary tract infection fungal, and fungal infection (verbatim investigator term "yeast infection [in urine]"). ¶¶Genital infections were events of vulvovaginal mycotic infection, vaginal infection, genital herpes, genital infection fungal, penile infection, vaginitis bacterial, and vulvitis. ##Hypotensive events were events of hypotension, orthostatic hypotension, and syncope. **Change from baseline at week 12.

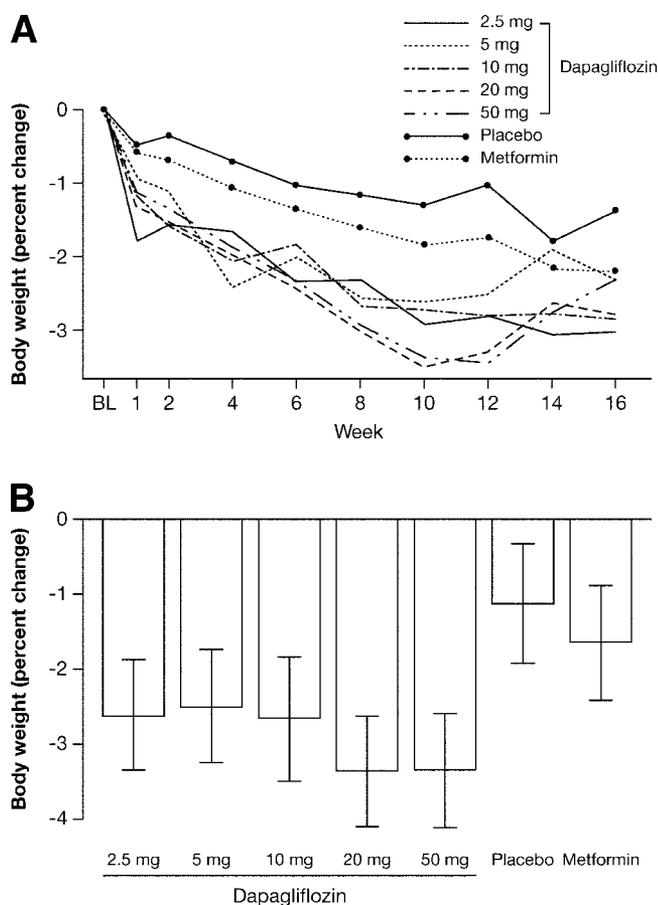


Figure 3—Percent changes in weight. A: Percent change from baseline in weight over the 12-week treatment period and 4-week follow-up period (observed values). B: Adjusted mean percent change from baseline in weight after 12 weeks of treatment (LOCF). Displayed are means and 95% CIs.

ries but becomes detrimental in type 2 diabetes by contributing to perpetuation of hyperglycemia and caloric excess. Paradoxically, the glucose resorptive capacity of the kidney may increase in type 2 diabetes (20). Therefore, limiting renal glucose reabsorption through the inhibition of SGLT2 represents a new approach to treating hyperglycemia in type 2 diabetic patients.

This study provides evidence that inducing controlled glucosuria through selective SGLT2 inhibition improves hyperglycemia consistently over 12 weeks of treatment in type 2 diabetic patients. Dapagliflozin produced decreases in A1C, FPG, and PPG after 12 weeks, with reductions in FPG apparent by week 1. Changes in FPG were dose-related; however, there was little evidence of a dose response for either PPG or A1C. These observations apparently reflect an intrinsic property of dapagliflozin as an SGLT2 inhibitor. The impact of SGLT2 inhibition was relatively greater on PPG than on FPG, with renal glucose excretion

acting as a relief valve to blunt postprandial hyperglycemia. Even the lowest dapagliflozin dose (2.5 mg) produced a near-maximal effect on PPG, consistent with reductions observed in a clinical ward study (16). In contrast, the effect on FPG, measured at the trough drug concentration, was dose-ordered and corresponded to expected residual trough pharmacodynamic activity (16).

Dapagliflozin exhibited a diuretic effect, with small dose-dependent increases in urine volume equivalent to ~0.3–1.5 voids/day, small increases in BUN, and small dose-dependent increases in hematocrit. No clinical safety signals for dehydration were observed. The observed decrease in sBP was consistent with a diuretic action. The relevance of this diuresis in type 2 diabetic patients, who often require diuretics for controlling hypertension (21), warrants further investigation. Although no effect on renal function was observed, longer-term studies and exploratory renal biomarker assessments are being undertaken.

Dapagliflozin-treated patients experienced total body weight reductions. Veterinary literature suggests that chronic administration of phlorizin in lactating cows induces lipolysis (22), and dapagliflozin in obese rats induces reduced adiposity (23). During treatment, all doses induced progressive weight reductions, consistent with steady caloric loss through glucosuria. Weight loss was more pronounced during week 1 with dapagliflozin, particularly at higher doses. This observation, coupled with a rapid partial rebound in weight after discontinuation of higher doses, suggests that diuresis may contribute to some weight loss. Overall, it appears likely that acute weight reduction during week 1 represents fluid loss, which may also result in lower sBP, whereas continued gradual weight loss represents decreased fat mass. Longer-term clinical and body composition studies will help to establish the relative contribution of diuresis versus adiposity reduction to total weight loss.

Daily dapagliflozin was well tolerated with no major difference in adverse events across treatment groups. The hypoglycemia experience supports the potential for dapagliflozin to achieve meaningful glycemic efficacy with relatively low hypoglycemic risk. The number of reported urinary tract infections was similar among dapagliflozin, metformin, and placebo groups and is consistent with rates reported in type 2 diabetic patients (24). The incidence of genital infections was higher with dapagliflozin versus placebo, especially at higher doses, but without statistical significance for comparison. Of note is the lower rate of genital infections reported for placebo group patients than previously reported for type 2 diabetic patients (25).

Dapagliflozin increased serum phosphate at higher doses, and all arms including placebo and metformin demonstrated increased serum parathyroid hormone. Additional data are needed to understand the long-term effects of chronic glucosuria and dapagliflozin treatment on skeletal metabolism.

This study demonstrated the clinical efficacy of inhibiting renal glucose reabsorption with dapagliflozin in type 2 diabetic patients and relative safety across numerous doses. Our results suggest that dapagliflozin, as the first in a new class of SGLT inhibitors, can improve glycemic and weight status of type 2 diabetic patients. Although we evaluated monotherapy, the insulin-independent mecha-

nism of dapagliflozin may complement other type 2 diabetes agents that act through insulin signaling pathways and thus enhance combination therapy. Although human genetic case reports are reassuring, the chronic effects of pharmacologically induced glucosuria are unknown and require long-term assessment. On the basis of evidence to date, further clinical study of dapagliflozin is warranted to develop a more definitive benefit/risk profile for this novel therapeutic agent.

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