Dapagliflozin Monotherapy in Type 2 Diabetic Patients With Inadequate Glycemic Control by Diet and Exercise

A randomized, double-blind, placebo-controlled, phase 3 trial

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OBJECTIVE — Dapagliflozin, a highly selective inhibitor of the renal sodium-glucose cotransporter-2, increases urinary excretion of glucose and lowers plasma glucose levels in an insulin-independent manner. We evaluated the efficacy and safety of dapagliflozin in treatment-naive patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS — This was a 24-week parallel-group, double-blind, placebo-controlled phase 3 trial. Patients with A1C 7.0–10% ($n = 485$) were randomly assigned to one of seven arms to receive once-daily placebo or 2.5, 5, or 10 mg dapagliflozin once daily in the morning (main cohort) or evening (exploratory cohort). Patients with A1C 10.1–12% (high-A1C exploratory cohort; $n = 73$) were randomly assigned 1:1 to receive blinded treatment with a morning dose of 5 or 10 mg/day dapagliflozin. The primary end point was change from baseline in A1C in the main cohort, statistically tested using an ANCOVA.

RESULTS — In the main cohort, mean A1C changes from baseline at week 24 were −0.23% with placebo and −0.58, −0.77 ($P = 0.0005$ vs. placebo), and −0.89% ($P < 0.0001$ vs. placebo) with 2.5, 5, and 10 mg dapagliflozin, respectively. Signs, symptoms, and other reports suggestive of urinary tract infections and genital infection were more frequently noted in the dapagliflozin arms. There were no major episodes of hypoglycemia. Data from exploratory cohorts were consistent with these results.

CONCLUSIONS — Dapagliflozin lowered hyperglycemia in treatment-naive patients with newly diagnosed type 2 diabetes. The near absence of hypoglycemia and an insulin-independent mechanism of action make dapagliflozin a unique addition to existing treatment options for type 2 diabetes.

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The need for optimal management of glycemia in patients with type 2 diabetes has long been recognized, owing to the well-established association between sustained hyperglycemia and serious microvascular complications including retinopathy, neuropathy, and nephropathy (1). However, because metabolic risk factors frequently occur as a cluster, it is difficult to control glycemia in patients with type 2 diabetes without negatively affecting one or more of the associated risk factors of hypertension, obesity, and hyperlipidemia. This fact is exemplified by the treatment-limiting side effects of many available antidiabetes agents, particularly in patients with a longer duration of disease (2–5). Sulfonylureas, thiazolidinediones, and insulin are all associated with weight gain in patients with diabetes (6,7). Negative effects on associated metabolic risk factors are not limited to antidiabetes agents; as an example, treatment of hypertension with thiazides is associated with increased uric acid levels and a worsening of hyperglycemia (8–10). In addition to the deleterious effect on metabolic comorbidities and for some agents an increased risk of hypoglycemia, treatment with most antidiabetes agents is further confounded by a loss of efficacy over time, in part due to the progressive worsening of diabetes characterized by insulin resistance and impaired glucose-stimulated insulin secretion (11).

An on-going effort to identify new treatment strategies for diabetes has led to the development of dapagliflozin, the first in a class of compounds referred to as sodium-glucose cotransporter 2 (SGLT2) inhibitors. SGLT2 is located almost exclusively in the kidney proximal tubules where it reabsorbs most of the ~180 g of glucose that is filtered through the glomeruli each day. Dapagliflozin is a highly selective and reversible inhibitor of SGLT2. A prolonged pharmacokinetic half-life due to the *C*-aryl glucoside-derived chemical structure, as well as a nearly 3,000-fold selectivity for SGLT2 versus SGLT1, make it possible for dapagliflozin to be administered in an unmodified oral form without affecting SGLT1-mediated glucose transport in other tissues (12–14). Dapagliflozin can inhibit up to one-half of the filtered glucose from being reabsorbed by the kidney, resulting in a dose-dependent increase in urinary glucose excretion and, ultimately, improvement in glycemic parameters (15–18). Also relevant here are observations that the renal reabsorptive capacity for glucose may be increased in patients with diabetes (19,20). On the basis of these findings, we conducted a phase 3 trial of dapagliflozin, administered as monotherapy for 24 weeks to treatment-naive

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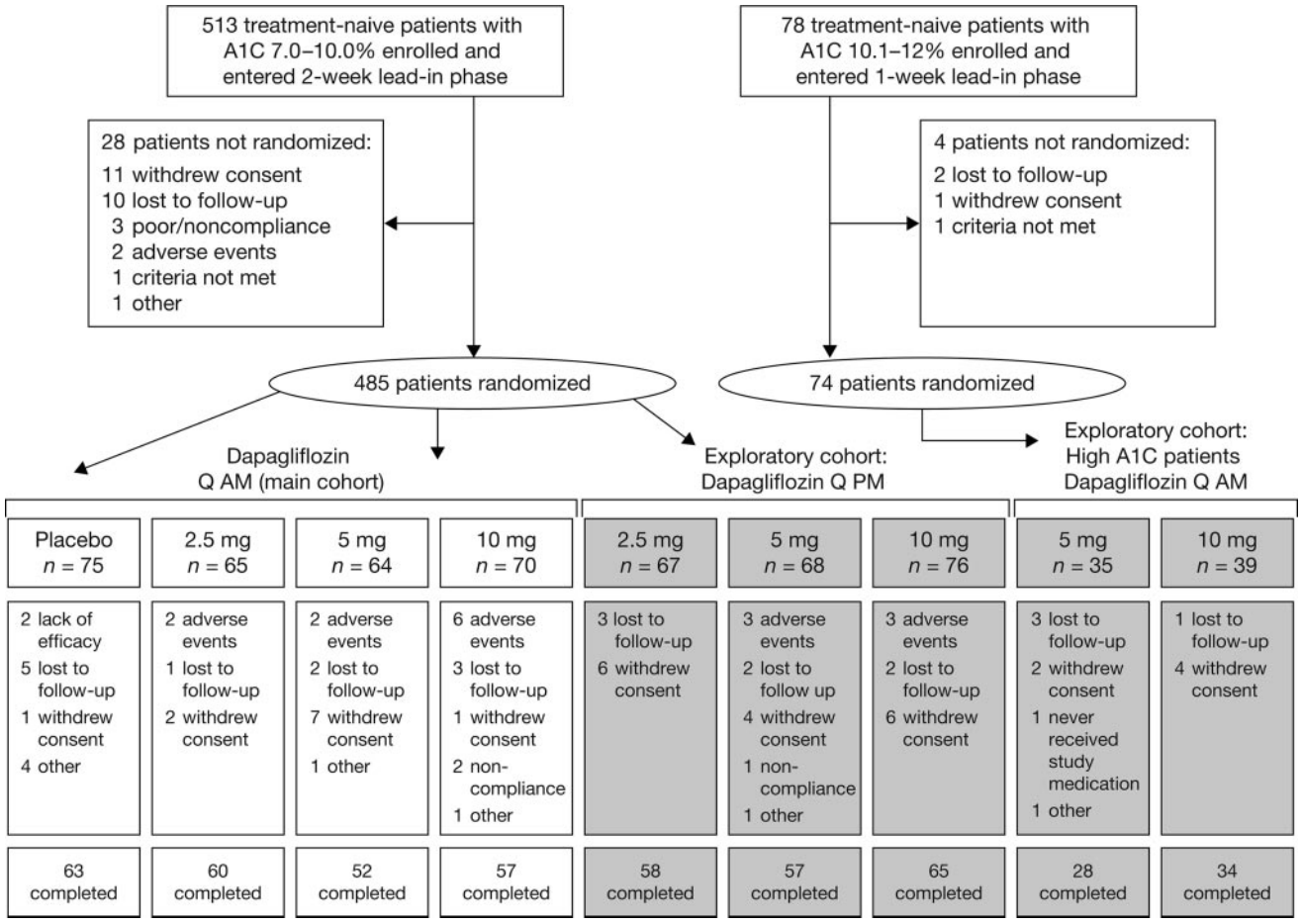

Figure 1—*Patient disposition.*

patients with type 2 diabetes. Here we report results from the study.

RESEARCH DESIGN AND METHODS

— Men and women with type 2 diabetes, aged 18–77 years, were enrolled between September 2007 and July 2008 at 85 sites in the U.S., Canada, Mexico, and Russia. Eligible patients were treatment-naive subjects whose hyperglycemia was inadequately controlled with diet and exercise alone. Entry criteria included BMI ≤45 kg/m^2 and fasting C-peptide ≥1.0 ng/ml. Patients were excluded if they had a history of type 1 diabetes, serum creatinine ≥133 μmol/l (men) or ≥124 μmol/l (women), urine albumin-to-creatinine ratio >200 mg/mmol, aspartate transaminase and/or alanine transaminase >3 times the upper limits of normal, creatine kinase ≥3 times the upper limit of normal, symptoms of severely uncontrolled diabetes (including marked polyuria and polydipsia with >10% weight loss during the last 3 months before enrollment); significant renal, hepatic, hematological, oncological, endocrine, psychiatric, or rheumatic diseases, a cardiovascular event (including New York Heart Association class III/IV congestive heart failure) within 6 months of enrollment, and severe uncontrolled blood pressure (systolic blood pressure ≥180 mmHg and/or diastolic blood pressure ≥110 mmHg).

This was a 24-week randomized, parallel-group, double-blind, placebo-controlled phase 3 trial with a 2-week diet/exercise placebo lead-in (1 week for patients with enrollment A1C 10.1–12.0%). The respective institutional review board or independent ethics committee approved the study protocol, and all patients gave informed consent. Patients with A1C 7.0–10% were randomly assigned equally to one of seven arms to receive once-daily placebo or 2.5, 5, or 10 mg dapagliflozin, administered once daily either in the morning (main cohort) or evening (exploratory cohort) for 24 weeks. Patients with A1C 10.1–12% (high-A1C exploratory cohort) were assigned randomly in a 1:1 ratio to receive blinded treatment with a morning dose of 5 or 10 mg/day dapagliflozin (a placebo group was not included because of the high A1C levels). Patients with fasting plasma glucose (FPG) >270 mg/dl at week 4, >240 mg/dl at week 8, or >200 mg/dl at weeks 12–24 were eligible for open-label rescue medication (500 mg metformin, titrated as needed up to 2,000 mg). Patients with A1C >8.0% for 12 weeks despite a maximum tolerated metformin dose were discontinued. Throughout the study, patients received diet/exercise counseling per American Diabetes Association recommendations.

End points and assessments

The primary efficacy end point was change from baseline in A1C at week 24 in the main patient cohort. Secondary efficacy measures included change from baseline at week 24 in FPG and body weight. Efficacy measures assessed in the exploratory evening dose and high-A1C cohorts included change from baseline at

week 24 in A1C, FPG, and body weight. For patients requiring rescue medication, data obtained after rescue were excluded from efficacy analyses. Fractional renal glucose excretion was calculated as the ratio of urine to plasma glucose multiplied by the ratio of plasma to urine creatinine.

Safety assessments included vital signs, laboratory measurements, and adverse events (coded using preferred terms of the Medical Dictionary for Regulatory Activites [MedDRA version 11.1]). In addition, at each visit, patients were actively monitored for clinical signs and symptoms suggestive of urinary tract infections (UTIs) and genital infections. UTIs and genital infections are reported here as an adverse event of special interest and include any of the prospectively defined 20 preferred terms relating to possible upper UTI events, 44 preferred terms relating to possible non–upper UTI events, and 49 preferred terms relating to possible genital infections (including bacterial and mycotic infections). Patients were instructed to self-monitor their blood glucose daily and to report any unusually high or low blood glucose event or any symptoms suggestive of hypoglycemia.

Statistical analysis

Analyses of change from baseline in A1C, FPG, and body weight were performed using an ANCOVA with treatment group as effect and baseline value as covariate. Point estimates and 95% CI were calculated for the mean change from baseline within each treatment group as well as for the difference in mean change from baseline between treatment groups. Per the study design, no *P* values were generated for end points in exploratory cohorts.

RESULTS — A total of 485 patients were randomly assigned to the main morning dose and exploratory evening dose cohorts (Fig. 1). In addition, 74 patients were randomly assigned to the exploratory, high-A1C cohort, of which 73 patients took at least one dose of study medication. Demographic and baseline characteristics are shown in Table 1.

In the main cohort, mean A1C reductions were dose ordered and apparent by week 4 and maintained thereafter (Fig. 2*A*). Mean A1C reductions from baseline at week 24 in the main cohort ranged from −0.58 to −0.89% with dapagliflozin compared with −0.23% with pla-

Table 1—*Demographics and baseline characteristics*

	Primary cohort				Exploratory cohorts					
		Dapagliflozin morning dose			Dapagliflozin evening dose			Dapagliflozin morning dose (A1C ≥ 10.1)		
	Placebo	2.5 mg	5 mg	10 mg	2.5 mg	5 mg	10 mg	5 mg	10 mg	
n	75	65	64	70	67	68	76	34	39	
Age (years)	52.7 ± 10.3	53.0 ± 11.7	52.6 ± 10.9	50.6 ± 9.97	54.3 ± 11.5	54.5 ± 11.0	50.7 ± 9.7	48.3 ± 9.3	47.9 ± 12.1	
Men	31 (41.3)	36 (55.4)	31 (48.4)	34 (48.6)	29 (43.3)	29 (42.6)	39 (51.3)	24 (70.6)	23 (59.0)	
Women	44 (58.7)	29 (44.6)	33 (51.6)	36 (51.4)	38 (56.7)	39 (57.4)	37 (48.7)	10 (29.4)	16 (41.0)	
A1C (%)	7.84 ± 0.87	7.92 ± 0.90	7.86 ± 0.94	8.01 ± 0.96	7.99 ± 0.99	7.82 ± 0.91	7.99 ± 1.05	10.82 ± 0.93	10.73 ± 0.85	
FPG (mg/dl)	159.9 ± 42.1	164.1 ± 48.0	162.2 ± 45.0	166.6 ± 41.5	160.6 ± 45.9	157.0 ± 50.9	168.1 ± 57.9	231.6 ± 65.1	241.2 ± 65.7	
Weight (kg)	88.8 ± 19.0	90.8 ± 22.8	87.6 ± 17.1	94.2 ± 18.7	88.3 ± 20.5	89.2 ± 20.5	92.1 ± 22.0	88.7 ± 19.2	87.5 ± 22.7	
BMI (kg/m^2)*	32.3 ± 5.5	32.6 ± 5.5	31.9 ± 4.8	33.6 ± 5.4	32.2 ± 5.3	32.8 ± 5.3	33.3 ± 5.6	32.6 ± 4.6	31.1 ± 5.9	
Diabetes duration (years)	0.50 (0.10, 3.40)	0.50 (0.1, 2.90)	0.25 (0.10, 1.40)	0.45 (0.10, 3.40)	0.20 (0.10, 1.20)	0.50 (0.15, 2.20)	0.40 (0.10, 2.45)	0.65 (0.20, 2.50)	1.40 (0.20, 3.50)	

Data are means ± SD, *n* (%), or median (quartile 1, quartile 3). *Mean baseline value for patients who have at least one postbaseline BMI measurement.

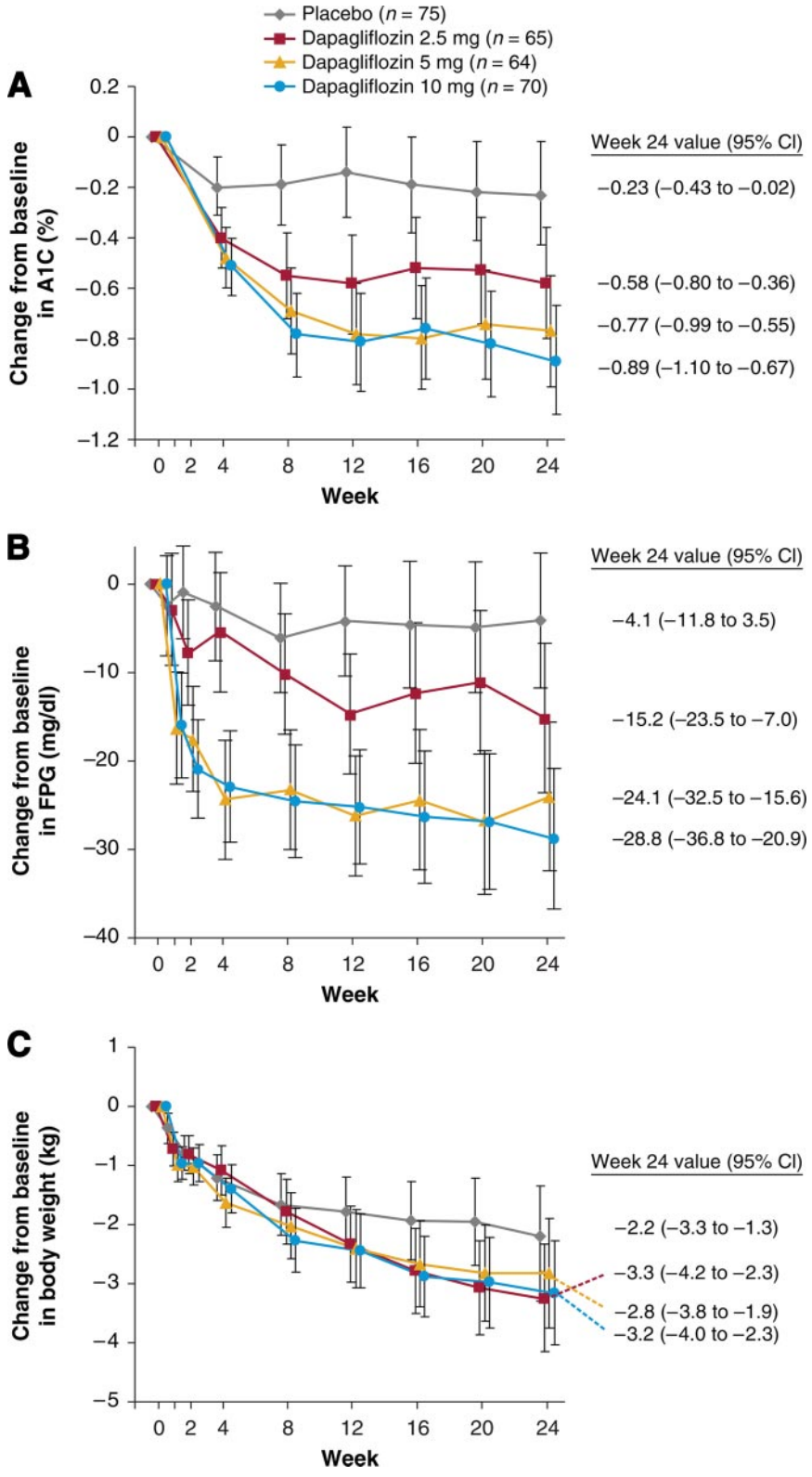

Figure 2—*Changes in glycemic parameters over time.* A*: Mean change from baseline in A1C after adjustment for baseline value.* B*: Mean change from baseline in FPG after adjustment for baseline value.* C*: Mean change from baseline in body weight after adjustment for baseline value. Error bars represent 95% CIs.*

cebo. The reductions were statistically significant with 5 and 10 mg dapagliflozin ($P = 0.0005$ and $P < 0.0001$, respectively, vs. placebo). At the end of study, a higher proportion of patients in dapagliflozin arms reached the American Diabetes Association/European Association for the Study of Diabetes target A1C of <7% (41, 44, and 51% with 2.5, 5, and 10 mg dapagliflozin, respectively, vs. 32% with placebo).

Reductions in FPG were apparent as early as week 1. Throughout the study, FPG reductions were more marked in 5 and 10 mg dapagliflozin arms and were statistically significant at week 24 (Fig. 2*B*, Table 2). Mean body weight decreases were greater with all dapagliflozin doses than with placebo, although they did not reach statistical significance (Fig. 3*C*, Table 2).

In the exploratory evening dose cohort, changes from baseline in A1C, FPG, and body weight at week 24 were similar to those seen in the main patient cohort (Table 2). In the exploratory high-A1C cohort (10.1–12% at enrollment), treatment with dapagliflozin for 24 weeks led to numerically greater reductions in mean A1C and FPG from baseline than those observed in other cohorts (Table 2). Subgroup analyses of the main patient cohort by baseline A1C were consistent with the ability of dapagliflozin to cause greater A1C reductions in patients with high baseline A1C. In patients with baseline A1C ≥9%, changes in mean A1C from baseline at week 24 were −1.23 ± 0.98, −1.98 ± 0.90, and −1.90 ± 0.79% with 2.5, 5, and 10 mg dapagliflozin groups, respectively, compared with 0.16 ± 2.50% with placebo.

Treatment with dapagliflozin did not result in any clinically meaningful changes from baseline in serum electrolytes including serum sodium (Table 2). There were no clinically relevant changes in any renal function parameter including serum creatinine, blood urea nitrogen, or cystatin C. In addition, there were no clinically relevant changes in mean serum albumin with dapagliflozin treatment. Small, numerical decreases from baseline in high-sensitivity C-reactive protein (placebo-subtracted adjusted mean change from baseline value [SE] ranged from −1.53 [1.06] to −2.67 [1.10] mg/l) and serum uric acid were observed in most dapagliflozin arms. Small, dose-ordered mean increases in hematocrit (up to 2.4%) were observed with dapagliflozin. A decrease in mean seated blood

Table 2—*Changes from baseline at week 24 in efficacy parameters, vital signs, and laboratory values*

		Primary cohort			Exploratory cohorts				
		Dapagliflozin morning dose			Dapagliflozin evening dose			Dapagliflozin morning dose (A1C ≥10.1)	
	Placebo	2.5 mg	5 mg	10 mg	2.5 mg	5 mg	10 mg	5 mg	10 mg
n	75	65	64	70	67	68	76	34	39
A1C (%)*†	−0.23 ± 0.10	−0.58 ± 0.11	−0.77 ± 0.11¶	−0.89 ± 0.11#	−0.83 ± 0.11	−0.79 ± 0.11	−0.79 ± 0.10	−2.88 ± 1.41‡	−2.66 ± 1.26‡
FPG (mg/dl)*†	−4.1 ± 3.9	−15.2 ± 4.2	−24.1 ± 4.3¶	−28.8 ± 4.0#	−25.6 ± 4.1	−27.3 ± 4.2	−29.6 ± 4.0	−77.1 ± 53.4‡	−84.3 ± 61.0‡
Weight (kg)*†	−2.2 ± 0.4	−3.3 ± 0.5	−2.8 ± 0.5	−3.2 ± 0.5	−3.8 ± 0.5	−3.6 ± 0.5	−3.1 ± 0.4	−2.1 ± 3.4‡	−1.9 ± 3.5‡
Urinary glucose: creatinine (g/g)§‖	0.96 ± 2.87	12.12 ± 2.98	17.68 ± 3.28	33.80 ± 3.08	24.24 ± 3.07	38.00 ± 3.09	45.80 ± 2.86	NA	NA
Vital signs									
Seated systolic blood pressure (mmHg)§	−0.9 ± 1.8	−4.6 ± 1.8	−2.3 ± 1.9	−3.6 ± 1.9	−4.0 ± 2.3	−5.2 ± 1.7	−2.3 ± 1.4	−5.7 ± 2.1	−2.5 ± 2.1
Seated diastolic blood pressure (mmHg)§	−0.7 ± 1.0	−2.8 ± 1.1	−1.7 ± 1.1	−2.0 ± 1.1	−3.2 ± 1.2	−2.0 ± 1.1	−1.0 ± 1.0	−3.3 ± 1.6	−2.9 ± 1.5
Laboratory values									
Serum creatinine (μmol/l)§	−0.4 ± 0.9	−0.6 ± 1.3	−2.0 ± 1.4	−1.1 ± 1.0	−0.5 ± 0.9	1.8 ± 0.9	−1.9 ± 1.7	0.0 ± 1.2	0.6 ± 1.4
Serum albumin (g/l)§	−0.1 ± 0.3	0.6 ± 0.4	0.3 ± 0.4	0.9 ± 0.3	0.0 ± 0.3	1.0 ± 0.4	1.3 ± 0.3	0.4 ± 0.5	0.7 ± 0.4
Cystatin C (mg/l)§	−0.014 ± 0.012	−0.009 ± 0.014	0.005 ± 0.014	−0.003 ± 0.016	0.014 ± 0.012	0.024 ± 0.009	−0.015 ± 0.026	0.070 ± 0.025	−0.045 ± 0.063
Hematocrit (%)§	−0.38 ± 0.25	1.60 ± 0.33	1.74 ± 0.40	2.38 ± 0.44	1.23 ± 0.26	1.92 ± 0.30	2.41 ± 0.30	0.77 ± 0.57	1.88 ± 0.42
Serum uric acid (μmol/l)†§	−11.9 ± 5.6	−39.3 ± 6.0	−50.6 ± 6.1	−51.7 ± 5.8	−59.5 ± 5.9	−43.4 ± 6.0	−49.4 ± 5.6	NA	NA
Blood urea nitrogen (mmol/l)§	0.2 ± 0.2	0.6 ± 0.2	0.6 ± 0.2	0.4 ± 0.2	0.6 ± 0.2	0.7 ± 0.2	0.4 ± 0.2	0.6 ± 0.2	0.9 ± 0.3
Serum electrolytes§									
Sodium (mmol/l)	−0.1 ± 0.3	−0.1 ± 0.3	−0.9 ± 0.4	−0.4 ± 0.4	−0.1 ± 0.3	−0.2 ± 0.3	0.1 ± 0.3	1.7 ± 0.6	0.5 ± 0.5
Potassium (mmol/l)	−0.03 ± 0.06	−0.05 ± 0.05	0 ± 0.05	−0.01 ± 0.06	−0.03 ± 0.06	−0.09 ± 0.05	−0.08 ± 0.06	−0.05 ± 0.08	−0.02 ± 0.06
Calcium (mmol/l)	0.01 ± 0.01	0.03 ± 0.02	0.00 ± 0.02	0.03 ± 0.01	0.01 ± 0.01	0.04 ± 0.02	0.04 ± 0.02	NA	NA
Magnesium (mmol/l)	−0.25 ± 0.18	0 ± 0.20	0.50 ± 0.26	0 ± 0.26	0 ± 0.25	0.15 ± 0.22	−0.20 ± 0.27	NA	NA
Inorganic phosphorus (mmol/l)	−0.01 ± 0.02	0.01 ± 0.02	0.04 ± 0.03	0.05 ± 0.02	0.04 ± 0.02	0.08 ± 0.02	0.06 ± 0.02	0.04 ± 0.03	0.07 ± 0.02

Data are means ± SEM unless otherwise indicated. NA, not assessed. *Assessed in patients without missing baseline and week 24 values with last observation carried forward. †Mean value after adjustment for baseline value. ‡Data are means ± SD. §Assessed in patients without missing baseline and week 24 values. ‖Ratio from morning fasting spot urine test. ¶$P < 0.001$; #$P < 0.0001$ ($\alpha = 0.019$ [two-sided] applying Dunnett adjustment; secondary end points were tested using a sequential procedure).

Table 3—*Adverse events*

	Primary cohort				Exploratory cohorts				
		Dapagliflozin morning dose			Dapagliflozin evening dose			Dapagliflozin morning dose (A1C ≥10.1)#	
	Placebo	2.5 mg	5 mg	10 mg	2.5 mg	5 mg	10 mg	5 mg	10 mg
n	75	65	64	70	67	68	76	34	39
AEs									
At least one AE	45 (60.0)	41 (63.1)	37 (57.8)	48 (68.6)	45 (67.2)	44 (64.7)	45 (59.2)	27 (79.4)	28 (71.8)
At least one serious AE	3 (4.0)	0	1 (1.6)	1 (1.4)	1 (1.5)	1 (1.5)	1 (1.3)	0	0
Discontinuation for AE	1 (1.3)	2 (3.1)	3 (4.7)	5 (7.1)	0	4 (5.9)	3 (3.9)	0	0
Discontinuation for serious AE	0	0	1 (1.6)	0	0	1 (1.5)	1 (1.3)	0	0
Most common AEs (≥10% in any group) by MedDRA preferred term*									
Nasopharyngitis	4 (5.3)	7 (10.8)	3 (4.7)	2 (2.9)	7 (10.4)	5 (7.4)	4 (5.3)	4 (11.8)	4 (10.3)
Diarrhea	1 (1.3)	4 (6.2)	1 (1.6)	1 (1.4)	3 (4.5)	7 (10.3)	3 (3.9)	2 (5.9)	1 (2.6)
Headache	5 (6.7)	5 (7.7)	3 (4.7)	4 (5.7)	3 (4.5)	9 (13.2)	9 (11.8)	5 (14.7)	6 (15.4)
Events by special interest category									
Hypoglycemia†	2 (2.7)	1 (1.5)	0	2 (2.9)	1 (1.5)	0	1 (1.3)	1 (2.9)	0
Events suggestive of UTIs‡	3 (4.0)	3 (4.6)	8 (12.5)	4 (5.7)	5 (7.5)	8 (11.8)	5 (6.6)	3 (8.8)	6 (15.4)
Events suggestive of genital infections§	1 (1.3)	5 (7.7)	5 (7.8)	9 (12.9)	6 (9.0)	3 (4.4)	2 (2.6)	2 (5.9)	7 (17.9)
Hypotensive events	1 (1.3)	0	0	1 (1.4)	3 (4.5)	0	0	1 (2.9)	1 (2.6)

Data are *n* (%) and include data after rescue. *Additional adverse events (AEs) with ≥5% incidence in any of the primary cohort and exploratory evening dose arms were arthralgia, pharyngitis, upper respiratory infection, UTI, back pain, dizziness, constipation, influenza, myalgia, peripheral edema, pain in extremity, and insomnia. †None of the hypoglycemic events led to discontinuation from the study, and none was a major episode, defined as a symptomatic episode requiring third-party assistance due to severe impairment in consciousness or behavior, with a capillary or plasma glucose value <54 mg/dl, and prompt recovery after glucose or glucagon administration. ‡These events included signs, symptoms, and other reports suggestive of UTIs. §These events included signs, symptoms, and other reports suggestive of genital infections. #Not placebo controlled.

pressure with no notable increase in orthostatic hypotension was observed in the dapagliflozin arms (Table 2). Rates of hypotension/dehydration/hypovolemia were similar among placebo and dapagliflozin arms. Treatment with dapagliflozin did not alter the lipid profile of patients, although small numerical increases in HDL cholesterol were noted in all dapagliflozin arms (placebo-subtracted adjusted mean change from baseline value [SE] ranged from 0.02 [0.07] to 0.17 [0.08] mmol/l).

Glucose-to-creatinine ratios were higher with dapagliflozin than with placebo (Table 2). Higher values with the evening dose presumably reflect the pharmacokinetic half-life of dapagliflozin. In pooled data from the morning and evening cohorts, changes from baseline in fractional renal glucose excretion at week 24 were significantly related ($r = -0.13$, $P = 0.008$) with the corresponding changes in body weight, such that across all study arms greater renal glucose losses were associated with larger decrements in body weight. A similar trend was found for changes in glucose excretion and changes in A1C ($P = 0.11$).

Adverse events are summarized in Table 3. There was one death due to a motor vehicle accident in the 10 mg dapagliflozin group. There were no major episodes of hypoglycemia in this study, and none of the patients discontinued the study medication due to hypoglycemia. An increased incidence in signs and symptoms and other reports suggestive of UTIs and genital infections was noted with dapagliflozin treatment. Safety data in the exploratory evening dose cohort were similar to those in the morning dose cohort. A small number of patients ($n = 6$) experienced nocturia with the evening dose (one, two, and three patients in the 2.5, 5 or 10 mg dapagliflozin evening dose arms, respectively, and none with the morning dose). There were no other notable differences in the number or type of adverse events reported with the evening dose.

CONCLUSIONS — Administration of dapagliflozin as monotherapy to treatment-naive patients with type 2 diabetes resulted in clinically meaningful decreases in A1C and FPG, along with favorable effects on weight, blood pressure, and other metabolic parameters. Although the decrease in body weight in our study did not reach statistical significance compared with placebo, dapagliflozin treatment did lead to increased renal glucose excretion. This glucose excretion persisted for the full 24-week study period and was consistent with the urinary loss of ~200–300 calories/day as reported previously (17). A factor that may have lessened the effect of dapagliflozin on weight was the large placebo effect in this study, which was probably due to a greater impact of diet/exercise counseling on motivated patients with newly diagnosed diabetes in a clinical trial setting. It should also be noted that the progressive decrease in weight over time had not reached a plateau by the end of study; thus, long-term studies are needed to more precisely gauge the effect of dapagliflozin on weight in the monotherapy setting. Furthermore, in exploratory analysis of pooled data greater increments in fractional renal glucose excretion were associated with greater decrements in body weight, suggesting a link between the mechanism of action of dapagliflozin and clinical outcome.

Data from the high-A1C cohort are of particular relevance given the mechanism

of action of dapagliflozin as an SGLT2 inhibitor. Patients with high A1C at enrollment are likely already to present with glycosuria as their filtered glucose load may exceed the absorption capacity of the kidney. However, dapagliflozin was able to elicit a considerable improvement in glycemia in the exploratory high-A1C cohort. Results from subgroup analysis of patients with baseline A1C ≥9% were also consistent with the observation that dapagliflozin continues to be efficacious in patients who present with higher A1C levels.

There were no major episodes of hypoglycemia in this study. After prospectively defined monitoring (see RESEARCH DESIGN AND METHODS), signs and symptoms suggestive of UTIs and genital infections were more frequently reported in the dapagliflozin arms. The reported signs/symptoms/events of UTIs and genital infections resolved with standard care and rarely led to discontinuation.

The decrease in mean systolic and diastolic blood pressure noted in this study is in keeping with the diuretic effect of dapagliflozin. Also consistent with this effect is the increase in hematocrit levels noted in the dapagliflozin arms. In addition to blood pressure, favorable, albeit small, effects were also noted in several other clinical parameters including HDL cholesterol, uric acid, and high-sensitivity C-reactive protein. Although effects on weight, blood pressure, and other metabolic risk factors were small, they may have a cumulative benefit in the long term.

Most notably, lowering of plasma glucose with dapagliflozin is accompanied by a urinary loss of calories, suggesting a shift toward negative net energy balance. This effect of dapagliflozin is unlike that of other antidiabetic agents, which often cause weight gain as they lower plasma glucose concentrations. Given its effect on net energy balance and its insulin-independent mechanism, dapagliflozin is likely to have beneficial effects in a wide spectrum of patients with diabetes (17,18).

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E.F. analyzed and interpreted data, contributed to writing of the manuscript, and reviewed/edited the manuscript. S.J.R. obtained data and reviewed the manuscript. A.S. designed the study, acquired data, analyzed and interpreted data, contributed to writing of the manuscript, and reviewed/edited the manuscript. W.T. analyzed and interpreted data, performed statistical analysis and verified data, contributed to writing of the manuscript, and reviewed/edited the manuscript. J.F.L. designed the study, analyzed and interpreted data, contributed to writing of the manuscript, and reviewed/edited the manuscript.

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