Dapagliflozin Versus Glipizide as Add-on Therapy in Patients With Type 2 Diabetes Who Have Inadequate Glycemic Control With Metformin

A randomized, 52-week, double-blind, active-controlled noninferiority trial

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OBJECTIVE—Although initially effective, sulfonylureas are associated with poor glycemic durability, weight gain, and hypoglycemia. Dapagliflozin, a selective inhibitor of sodium-glucose cotransporter 2 (SGLT2), reduces hyperglycemia by increasing urinary glucose excretion independent of insulin and may cause fewer of these adverse effects. We compared the efficacy, safety, and tolerability of dapagliflozin with the sulfonylurea glipizide in patients with type 2 diabetes inadequately controlled with metformin monotherapy.

RESEARCH DESIGN AND METHODS—This 52-week, double-blind, multicenter, active-controlled, noninferiority trial randomized patients with type 2 diabetes (baseline mean HbA_{1c}, 7.7%), who were receiving metformin monotherapy, to add-on dapagliflozin ($n = 406$) or glipizide ($n = 408$) up-titrated over 18 weeks, based on glycemic response and tolerability, to ≤10 or ≤20 mg/day, respectively.

RESULTS—The primary end point, adjusted mean HbA_{1c} reduction with dapagliflozin (−0.52%) compared with glipizide (−0.52%), was statistically noninferior at 52 weeks. Key secondary end points: dapagliflozin produced significant adjusted mean weight loss (−3.2 kg) versus weight gain (1.2 kg; $P < 0.0001$) with glipizide, significantly increased the proportion of patients achieving ≥5% body weight reduction (33.3%) versus glipizide (2.5%; $P < 0.0001$), and significantly decreased the proportion experiencing hypoglycemia (3.5%) versus glipizide (40.8%; $P < 0.0001$). Events suggestive of genital infections and lower urinary tract infections were reported more frequently with dapagliflozin compared with glipizide but responded to standard treatment and rarely led to study discontinuation.

CONCLUSIONS—Despite similar 52-week glycemic efficacy, dapagliflozin reduced weight and produced less hypoglycemia than glipizide in type 2 diabetes inadequately controlled with metformin. Long-term studies are required to further evaluate genital and urinary tract infections with SGLT2 inhibitors.

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Metformin is recommended as the initial oral antidiabetic drug (OAD) therapy for patients with type 2 diabetes (1–5), but the progressive nature of type 2 diabetes often requires treatment intensification to maintain glycemic control (6). A sulfonylurea or insulin is commonly added to metformin as a second step (1–5). Although initially effective, sulfonylurea treatment is associated with poor glycemic durability (6), weight gain, and hypoglycemia (7,8).

Dapagliflozin is the first in a novel class of glucose-lowering medications, the selective sodium-glucose cotransporter 2 (SGLT2) inhibitors (9). These agents reduce glucose reabsorption from the proximal tubule of the kidney, leading to increased urinary glucose excretion with resulting net caloric loss (10). This effect depends on baseline glycemic control and the renal filtration rate but is independent of insulin. Consequently, reduction in plasma glucose with dapagliflozin reduces the glucose load filtered by the kidney and limits further glucose excretion, suggesting that dapagliflozin may possess a low intrinsic propensity for hypoglycemia (11). Dapagliflozin might thus provide an alternative to existing add-on therapies by improving glycemic control without associated weight gain or hypoglycemic risk.

Recent placebo-controlled clinical trials of 24-weeks' duration have shown promise for dapagliflozin as monotherapy in patients with type 2 diabetes (12) and as add-on therapy in patients inadequately controlled with metformin (13), but longer-term head-to-head trials comparing dapagliflozin with established therapies are required. The current study directly tested the efficacy, safety, and tolerability of dapagliflozin against glipizide during a treatment period of 52 weeks in patients with type 2 diabetes inadequately controlled by metformin monotherapy.

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A complete list of study investigators can be found in the Supplementary Data online.

RESEARCH DESIGN AND METHODS

Study design

This was a 52-week randomized, double-blind, parallel-group, active-controlled, phase III, noninferiority trial with a 156-week extension period conducted from 31 March 2008 and ongoing at 95 sites in 10 countries: Argentina, 17 centers; France, 7; Germany, 16; U.K., 12; Italy, 3; Mexico, 4; the Netherlands, 10; South Africa, 10; Spain, 6; and Sweden, 10. Patient disposition is shown in Supplementary Fig. A1. The study complied with the Declaration of Helsinki and the International Conference on Harmonization/Good Clinical Practice Guidelines, was approved by institutional review boards and independent ethics committees for the participating centers, and is registered with ClinicalTrials.gov (NCT00660907). All participants provided informed consent before entering the study. Data from the 52-week double-blind treatment period are presented here.

Inclusion criteria

This study enrolled men and women aged ≥18 years with inadequately controlled type 2 diabetes (HbA_{1c} >6.5 and ≤10%) while receiving metformin or metformin and one other OAD administered up to half-maximal dose for at least 8 weeks before enrollment. A maximum of 25% of randomized patients had a baseline HbA_{1c} <7%. Further criteria included a fasting plasma glucose (FPG) ≤15 mmol/L and C-peptide concentration of ≥0.33 nmol/L. Exclusion criteria are listed in the Supplementary Data.

Treatments and interventions

Eligible patients receiving metformin monotherapy at a stable dose of <1,500 mg/day or at a variable dose, or combined with another OAD, entered an 8-week stabilization period during which other OADs were discontinued and the metformin dose was stabilized to 1,500–2,500 mg/day in all patients. Patients who were already receiving a stable dose of metformin monotherapy (1,500–2,500 mg/day) for at least 8 weeks before enrollment skipped the dose-stabilization period (Supplementary Table A1). Once patients were stabilized, no further changes in the metformin dose were allowed. All patients received dietary and lifestyle advice commencing from the start of the dose-stabilization period.

After a 2-week, single-blind, placebo lead-in period, patients were randomized in a 1:1 ratio to receive double-blind treatment with dapagliflozin or glipizide. All patients commenced treatment at dosage level 1, which was dapagliflozin at 2.5 mg or glipizide at 5 mg. During an 18-week period and at 21-day intervals, patients were up-titrated to the next dosage level if FPG was ≥6.1 mmol/L. Level 2 was dapagliflozin at 5 mg or glipizide at 10 mg, and level 3 was dapagliflozin at 10 mg or glipizide at 20 mg. Up-titration continued until the maximum tolerable dose level was reached. A 20-mg limit for glipizide was chosen because the glycemic benefits of sulfonylureas are virtually complete at half-maximal doses, and higher doses are generally not recommended (2).

After the 18-week titration period, patients entered a 34-week maintenance period, during which no further up-titration was allowed. However, patients could be down-titrated to the preceding level or potentially down to level 0 (placebo for both arms) in the event of recurrent hypoglycemia.

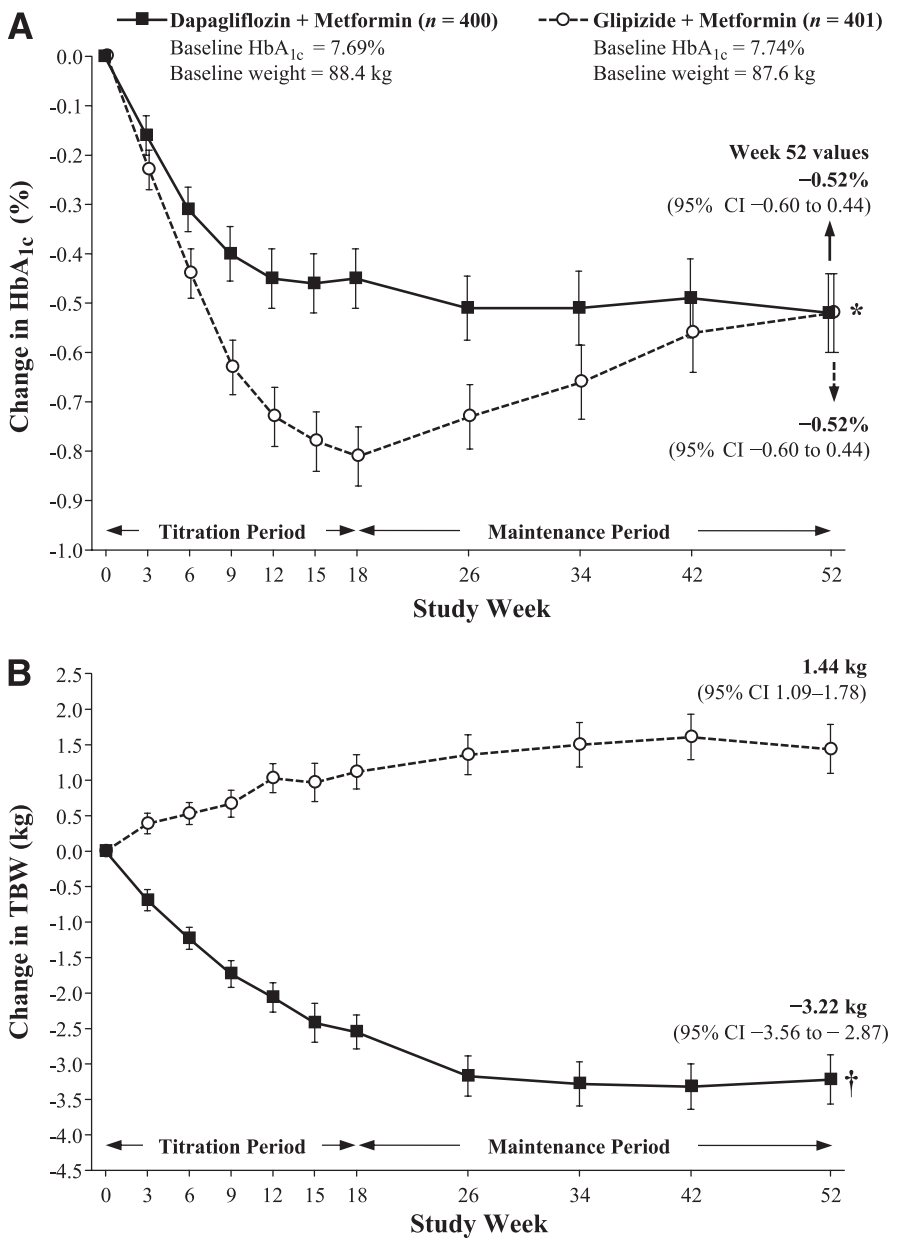

Figure 1—*Change in HbA_{1c} (%)* (A) *and TBW (kg)* (B) *during the 52-week double-blind treatment period. Data are adjusted mean change from baseline and 95% CI derived from ANCOVA using the full analysis set and LOCF values. *Dapagliflozin noninferior to glipizide; difference 0.00 (95% CI of difference −0.11 to 0.11). †Difference from glipizide −4.65 kg (95% CI of difference −5.14 to −4.17;* P < *0.0001).*

Patients with inadequate glycemic control during the 52-week double-blind treatment period were discontinued according to time-specific criteria. After having received a maximum titrated or tolerated dose for at least 2 weeks, patients were discontinued if their FPG was *1*) >15 mmol/L at weeks 3, 6, or 9; *2*) >13.3 mmol/L at weeks 12, 15, or 18; *3*) >12.2 mmol/L at weeks 26 or 34; or *4*) >11.1 mmol/L at week 42. Because metformin therapy is contraindicated with renal impairment, patients were also discontinued at any point in the study if the calculated creatinine clearance using the Cockcroft-Gault equation (14) was <60 mL/min.

Allocation concealment and blinding

Patients were randomized sequentially at study level according to a predefined computer-generated randomization scheme provided by AstraZeneca. Allocation of study treatments was performed via an Interactive Web Response System in balanced block sizes of 4 to ensure approximate balance among treatment groups. Blinding of patients and investigators to study treatment was achieved using a double-dummy technique. Metformin was administered as an open-label treatment throughout the study.

End points and safety assessments

The predefined primary end point was absolute change in HbA_{1c} from baseline to week 52. Key secondary end points were *1*) absolute change in total body weight (TBW) from baseline to week 52; *2*) proportion of patients reporting at least one episode of hypoglycemia ("major," "minor," or "other," episode) during the 52-week double-blind treatment period; and *3*) the proportion of patients achieving a TBW decrease ≥5% from baseline to week 52. Major hypoglycemia was defined as a symptomatic episode requiring external assistance due to severely impaired consciousness or behavior, with capillary or plasma glucose levels of 54 mg/dL (<3.0 mmol/L) and recovery after glucose or glucagon administration. Minor hypoglycemia was defined as a symptomatic episode with capillary or plasma glucose levels of 63 mg/dL (<3.5 mmol/L), irrespective of the need for external assistance, or an asymptomatic episode with capillary or plasma glucose levels of 63 mg/dL (<3.5 mmol/L) that did not qualify as a major episode. Other hypoglycemia was defined as an episode with symptoms suggestive of hypoglycemia but without measurement confirmation.

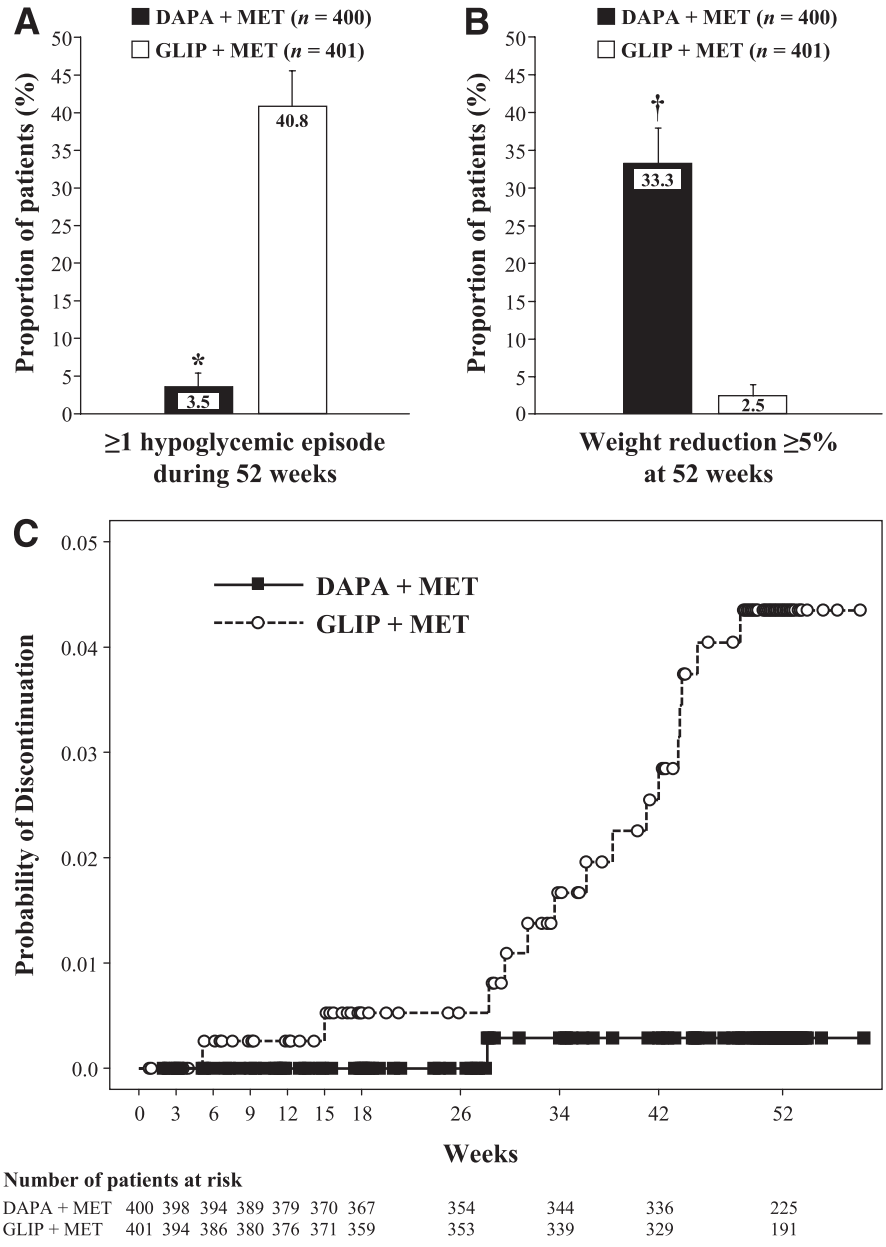

Figure 2—*Effect of treatments with dapagliflozin (DAPA) and glipizide (GLIP) with metformin (MET) on hypoglycemia, reduction in body weight, and time to study discontinuation due to lack of glycemic control at 52 weeks.* A*: Proportion of patients with at least one episode of hypoglycemia at 52 weeks. *Difference vs. GLIP + MET, −37.2% (95% CI of difference −42.3 to −21.2; P < 0.0001).* B*: Proportion of patients with ≥5% reduction in body weight at 52 weeks. †Difference vs. GLIP + MET, 30.8% (95% CI of difference 26.0–35.7; P < 0.0001). Data are adjusted proportions and 95% CI according to the methodology of Zhang et al. (15) using the full analysis set and LOCF values.* C*: Time to study discontinuation due to lack of glycemic control. Symbols represent censored observations. Week is not the scheduled visit week but the actual number of days from the first dose of double-blind study medication divided by 7. Number of patients at risk is the number of patients at risk at the beginning of the period.*

A number of exploratory end points were assessed, including change from baseline to week 52 for body weight in patients with a baseline BMI ≥30 kg/m^2 and in those with baseline BMI ≥27 kg/m^2, waist circumference, change in HbA_{1c} in patients with an HbA_{1c} of ≥7% at baseline, and FPG. The proportions of patients with HbA_{1c} <7% at week 52 in patients with baseline HbA_{1c} ≥7% and proportions of patients with HbA_{1c} ≤6.5% at week 52 were also assessed. Absolute changes from baseline to week 52 for seated systolic and diastolic blood pressure, and percent

changes from baseline to week 52 for total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, and free fatty acids were assessed.

Safety and tolerability was assessed by collating data on adverse events (AEs) using the Medical Dictionary for Regulatory Activities (MedDRA version 12.1), hypoglycemic events, laboratory tests, calculated creatinine clearance, urinary glucose/creatinine ratio, electrocardiographic and physical examinations, and vital signs. In addition, patients were actively questioned at each study visit to assess signs, symptoms, and reports suggestive of genital infections and urinary tract infections (UTIs). These responses, and those obtained spontaneously, were categorized in the database using a predefined list of MedDRA terms suggestive of genital infections and UTIs.

Statistical analysis

A hierarchic closed-testing procedure was used to control the type I error rate across the primary and key secondary end points at the 0.05 level (two-sided). Thus, if noninferiority was established for the primary end point at a one-sided 0.025 significance level, then key secondary end point testing for superiority could proceed in the sequence described previously. If the first key secondary end point was significant at a two-sided 0.05 significance level, then the second secondary end point could be evaluated, and so forth.

The primary and continuous key secondary and exploratory end points were evaluated using ANCOVA, with treatment as the fixed effect and baseline value as the covariate, to derive a least squares estimate of the treatment difference in mean change with corresponding two-sided 95% CI. Proportions were analyzed using logistic regression with adjustment for baseline values as described by Zhang et al. (15). Statistical noninferiority of dapagliflozin versus glipizide was established if the upper limit of the 95% CI for the treatment difference in mean HbA_{1c} change from baseline to week 52 was <0.35% (noninferiority margin). For graphic presentation of HbA_{1c} and TBW over the 52-week treatment period, the change from baseline (last observation carried forward [LOCF]) was analyzed at each interval using ANCOVA with treatment as the fixed effect and baseline value as the covariate. The Kaplan-Meier method was used to analyze time to onset of patient discontinuation because of poor glycemic control.

Table 1—*Overall summary of numbers of patients with an AE, numbers of AEs with frequency ≥3% in any group, and numbers of patients with AEs of special interest during the 52-week double-blind treatment period using the safety analysis set*

	Dapagliflozin + metformin *n* = 406	Glipizide + metformin *n* = 408
Overall summary of patients with an AE		
Patients with AE		
≥1	318 (78.3)	318 (77.9)
≥1 related to study treatment	110 (27.1)	110 (27.0)
Leading to discontinuation*	37 (9.1)	24 (5.9)
Patients with SAE		
≥1	35 (8.6)	46 (11.3)
≥1 related to study treatment	6 (1.5)	4 (1.0)
Leading to discontinuation	9 (2.2)	8 (2.0)
Deaths	0	3 (0.7)
Patients with AE with frequency ≥3% in any group†		
Nasopharyngitis	43 (10.6)	61 (15.0)
Hypertension	30 (7.4)	35 (8.6)
Influenza	30 (7.4)	30 (7.4)
UTI†	30 (7.4)	17 (4.2)
Upper respiratory tract infection	24 (5.9)	31 (7.6)
Headache	21 (5.2)	17 (4.2)
Back pain	19 (4.7)	20 (4.9)
Bronchitis	19 (4.7)	14 (3.4)
Diarrhea	19 (4.7)	26 (6.4)
Calculated creatinine renal clearance decreased*	17 (4.2)	7 (1.7)
Cough	15 (3.7)	20 (4.9)
Dizziness	15 (3.7)	37 (9.1)
Gastroenteritis	14 (3.4)	14 (3.4)
Nausea	14 (3.4)	15 (3.7)
Vulvovaginal candidiasis†	14 (3.4)	2 (0.5)
Arthralgia	11 (2.7)	21 (5.1)
Patients with special interest AE		
Hypoglycemic events‡		
Total	14 (3.4)§	162 (39.7)§
Major episode	0	3 (0.7)
Minor episode	7 (1.7)	147 (36.0)
Other episode	7 (1.7)	40 (9.8)
Leading to study discontinuation	0	6 (1.5)
Classified as a SAE	0	3 (0.7)
Signs and symptoms suggestive of genital infections‖		
Total	50/406 (12.3)	11/408 (2.7)
Male	12/226 (5.3)	1/223 (0.4)
1 event	7 (3.1)	1 (0.4)
2 or 3 events	4 (1.8)	0
>3 events	1 (0.4)	0
Treated	12 (5.3)	1 (0.4)
Culture obtained	1 (0.4)	0
Positive culture	0	0
Female	38/180 (21.1)	10/185 (5.4)
1 event	19 (10.5)	8 (4.3)
2 or 3 events	17 (9.4)	2 (1.1)
>3 events	2 (1.1)	0
Treated	37 (20.6)	8 (4.3)
Culture obtained	5 (2.8)	0
Positive culture	4 (2.2)	0
Assessed as severe in intensity		
Vulvovaginal candidiasis	1 (0.2)	0
Leading to study discontinuation		0
Balanitis	2 (0.5)	0
Vulvovaginal candidiasis	1 (0.2)	0

Table 1—*Continued*

	Dapagliflozin + metformin *n* = 406	Glipizide + metformin *n* = 408
Classified as a SAE	0	0
Signs and symptoms suggestive of UTI‖		
Total	44/406 (10.8)¶	26/408 (6.4)
Male	18/226 (8.0)¶	9/223 (4.0)
1 event	14 (6.2)	7 (3.1)
2 or 3 events	3 (1.3)	2 (0.9)
>3 events	1 (0.4)	0
Treated	10 (4.4)	6 (2.7)
Culture obtained	11 (4.9)	4 (1.8)
Positive culture	6 (2.7)	2 (0.9)
Female	26/180 (14.4)¶	17/185 (9.2)
1 event	20 (11.1)	14 (7.6)
2 or 3 events	6 (3.3)	3 (1.6)
>3 events	0	0
Treated	22 (12.2)	13 (7.0)
Culture obtained	16 (8.9)	7 (3.8)
Positive culture	14 (7.8)	4 (2.2)
Pyelonephritis/pyelocystitis	0	2 (0.5)
Assessed as severe in intensity		
Lower UTI	1 (0.2)	0
Pyelonephritis	0	1 (0.2)
Leading to study discontinuation		
Lower UTI	1 (0.2)	0
Pyelocystitis	0	1 (0.2)
Classified as a SAE		
Pyelonephritis	0	1 (0.2)
Renal impairment/failure#		
Total	24 (5.9)	14 (3.4)
Calculated creatinine renal clearance decreased*	17 (4.2)	7 (1.7)
Renal impairment	4 (1.0)	2 (0.5)
Blood creatinine increased	3 (0.7)	2 (0.5)
Estimated glomerular filtration rate decreased**	1 (0.2)	3 (0.7)
Acute renal failure	1 (0.2)	0
Hypotension/dehydration/hypovolemia	6 (1.5)	3 (0.7)

Data are presented as *n* (%). *Thirteen patients in the dapagliflozin group and six patients in the glipizide group were discontinued due to an AE of "calculated creatinine renal clearance decreased." Calculated creatinine renal clearance (eCC) was estimated using the Cockcroft-Gault equation (14), eCC = ([140 − age] × weight in kg × [1.23 if male, 1.04 if female])/serum creatinine in μmol/L. eCC was calculated using current body weight values at each study visit. All patients discontinued due to an AE of this kind showed calculated creatinine clearance values <60 mL/min at the visit the AE was documented or at a previous visit. Ten patients in the dapagliflozin group and one in the glipizide group showed a decrease in TBW of ≥3% at the time they were discontinued due to this AE. In three patients, an AE of "calculated creatinine renal clearance decreased" was assessed as severe. The two patients in the dapagliflozin group who discontinued due to an AE of "calculated creatinine renal clearance decreased" assessed as severe both showed a decrease in body weight of ≥5%. A post hoc calculation showed no overall mean change in eCC if baseline weight was entered at all study visits (Supplementary Table A5). †Based on definitive MedDRA terms. ‡Major hypoglycemia was defined as a symptomatic episode requiring external assistance due to severely impaired consciousness or behavior, with capillary or plasma glucose levels <3.0 mmol/L and recovery after glucose or glucagon administration. Minor hypoglycemia was defined as either symptomatic episode with capillary or plasma glucose levels <3.5 mmol/L, irrespective of the need for external assistance; or an asymptomatic episode with capillary or plasma glucose levels <3.5 mmol/L that does not qualify as a major episode. Other hypoglycemia was defined as an episode with symptoms suggestive of hypoglycemia but without measurement confirmation. §These values are slightly different from those presented in Fig. 2*A* because these are descriptive statistics using the safety analysis set and the latter are adjusted proportions derived from logistic regression using the full analysis set. ‖These events represented a predefined group of MedDRA terms used to report AEs via protocol-mandated active questioning that could potentially suggest a genital infection or UTI. ¶Nominal $P < 0.05$ for difference vs. glipizide + metformin based on a post hoc analysis (Fisher exact test); no prespecified statistical test was planned. #These events were also identified in the database using prespecified lists of preferred terms, but which also included, for example, laboratory values such as serum creatinine. **Calculation of estimated glomerular filtration rate based on the Modification of Diet in Renal Disease formula: estimated glomerular filtration rate (mL/min/1.73 m^2) = $186 \times (\text{serum creatinine [mg/dL]})^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ if female}) \times (1.21 \text{ if black})$.

Two analysis sets were defined: the safety analysis set, consisting of all patients who received one or more doses of the investigational product, and the full analysis set, consisting of all randomized patients who received one or more doses of the investigational product and who had a nonmissing baseline and one or more postbaseline efficacy value for one or more efficacy variable. Primary, key secondary, and exploratory end points were analyzed using the full analysis set. Missing values at week 52 were replaced using the LOCF method.

Prespecified safety analyses, including events suggestive of genital infection and UTI, were performed using descriptive statistics for the safety analysis set. A post hoc exploratory analysis of risk differences for the proportions of patients reporting events suggestive of genital infections and of UTIs were performed using Fisher exact tests. Sample size calculations are available in the Supplementary Data.

RESULTS

Patients

The full analysis set comprised 801 patients (dapagliflozin: *n* = 400; glipizide: *n* = 401) and the safety analysis set, 814 patients (dapagliflozin: *n* = 406; glipizide: *n* = 408). Overall, 77.9% of randomized patients completed the study. The commonest reasons for discontinuation were withdrawal of consent, AEs, and no longer meeting study criteria (Supplementary Fig. A1). Efficacy analyses used LOCF and the full analysis set, which included 98.2% of randomized patients; therefore, almost all of the discontinued patients were included in these analyses. Demographic and baseline characteristics were balanced across treatment groups (Supplementary Table A2).

At the end of the titration period, 353 patients (86.9%) randomized to receive dapagliflozin were receiving the maximum dose of 10 mg, whereas 296 patients (72.5%) randomized to receive glipizide were receiving the maximum dose of 20 mg, resulting in mean doses of 9.2 mg for dapagliflozin and 16.4 mg for glipizide (Supplementary Table A3). During the titration period, seven patients receiving glipizide versus none receiving dapagliflozin were down-titrated to receive no study treatment. Overall, 2.7% of patients receiving dapagliflozin versus 15.9% of those receiving glipizide were down-titrated during the titration or maintenance periods.

Primary end point

The HbA_{1c} adjusted mean change from baseline at week 52 for dapagliflozin was −0.52 (95% CI −0.60 to −0.44) vs. −0.52 (−0.60 to −0.44) for glipizide; hence, the dapagliflozin HbA_{1c} mean difference from glipizide at week 52 was 0.00 (−0.11 to 0.11). Thus, HbA_{1c} change with dapagliflozin was statistically noninferior to that with glipizide at week 52.

Although the initial drop in HbA_{1c} during the titration period with glipizide was greater than that observed with dapagliflozin, efficacy for glipizide waned during the maintenance period but remained stable for dapagliflozin. This resulted in equivalent efficacy at week 52 (Fig. 1*A*). During the maintenance period, 5.1% of patients in the glipizide group were down-titrated versus 0.5% in the dapagliflozin group (Supplementary Table A3).

Secondary end points

Dapagliflozin produced weight loss, whereas glipizide led to weight gain, resulting in an absolute mean difference of 4.65 kg ($P < 0.0001$) at week 52 (Fig. 1*B*). Dapagliflozin showed a significantly greater adjusted proportion of patients with a body weight reduction of ≥5% at week 52 (Fig. 2*B*).

The adjusted proportion of patients experiencing at least one hypoglycemic episode by week 52 was more than 10-fold lower with dapagliflozin than with glipizide (Fig. 2*A*).

The proportion of patients discontinuing due to inadequate glycemic control by week 52 was 0.2% in the dapagliflozin group versus 3.6% in glipizide group (difference −3.6%; 95% CI −5.3 to −1.5). Time to discontinuation was also prolonged with dapagliflozin versus glipizide (Fig. 2*C*).

Exploratory end points

Dapagliflozin reduced seated systolic and diastolic blood pressure, and increased HDL cholesterol (Supplementary Fig. A2). Dapagliflozin reduced body weight in patients with BMI of >27 or >30 kg/m^2 and produced glycemic changes equivalent to glipizide, as expected from the noninferior HbA_{1c} result, with the exception of the proportion of patients with HbA_{1c} ≤6.5% at week 52, which favored glipizide (Supplementary Table A4).

Safety and tolerability

Overall AEs. AEs and serious AEs (SAEs) leading to study discontinuation were balanced across treatment groups (Table 1). SAEs considered related to study treatments were reported in six patients in the dapagliflozin group (complex ventricular arrhythmia, decreased calculated creatinine clearance, epigastric pain, prostate cancer, pulmonary embolism, and worsening of coronary artery disease) and in four patients in the glipizide group (hypoglycemia in three and pyelonephritis in one). No deaths were reported in patients receiving dapagliflozin. Three deaths were reported in the group receiving glipizide, comprising mesenteric infarction, sudden death at home without autopsy, and acute myocardial infarction.

AEs led to study discontinuation in 37 patients receiving dapagliflozin (9.1%) versus 24 receiving glipizide (5.9%), which was mainly accounted for by an excess of patients who were withdrawn because of decreased calculated creatinine clearance with dapagliflozin (n = 13) versus glipizide (n = 6; Table 1). Creatinine clearance was calculated using the Cockcroft-Gault equation (14), with current body weight values at all visits. A post hoc estimation using baseline weight at each study visit showed no change in mean calculated creatinine clearance (Supplementary Table A5). One patient receiving dapagliflozin developed acute hepatitis and was later diagnosed with drug-induced acute hepatitis as well as probable autoimmune hepatitis. This patient's liver function test values decreased 10 days after suspension of dapagliflozin and normalized 6 months later in response to immunosuppressive treatment.

Prespecified safety analyses of special interest. Fewer hypoglycemic events were reported in patients treated with dapagliflozin compared with glipizide (Table 1), and results were comparable with the efficacy analysis of adjusted proportions of patients experiencing hypoglycemia (Fig. 2*A*). No patients discontinued dapagliflozin treatment as a result of a hypoglycemic event compared with six patients receiving glipizide. Three patients taking glipizide, but none taking dapagliflozin, reported major hypoglycemic episodes (symptomatic patients requiring external assistance and with a plasma glucose <3.0 mmol/L).

Higher proportions of patients receiving dapagliflozin reported events suggestive of genital infections or lower UTIs compared with glipizide. About half of the genital events were recurrent, whereas most of the lower UTIs were single episodes. Except for three patients, all events were reported as mild or moderate in intensity. Not all of these events could be confirmed by microbiologic culture, but they nevertheless responded to routine management and rarely led to study discontinuation (Table 1). Two cases of pyelonephritis were reported in the glipizide group, whereas none were reported in the dapagliflozin group (Table 1).

One report of renal failure (creatinine clearance 106, 95, and 52 mL/min on day −22, 1, and 43, respectively) was considered related to dapagliflozin and resulted in treatment discontinuation. Although this AE was assessed as mild in intensity, nonserious by the investigators, and no treatment was administered, no end date for the AE was documented.

Six patients receiving dapagliflozin and three receiving glipizide experienced AEs of hypotension, dehydration, or hypovolemia (Table 1). None were assessed as serious by the investigators, and no patient discontinued treatment as a consequence.

Laboratory values and vital signs. Dapagliflozin dramatically increased urinary glucose excretion and the urinary glucose/creatinine ratio (Supplementary Table A5), as expected from its mechanism of action. Dapagliflozin-induced glucose excretion remained elevated and constant from week 12 to 52, showing no sign of diminished activity during this period (Supplementary Fig. A3). Changes from baseline at week 52 with dapagliflozin treatment included increased mean values for hematocrit, blood urea nitrogen, magnesium, and phosphorus, and decreased mean values for aspartate aminotransferase, alanine aminotransferase, and serum uric acid. No changes in bilirubin, heart rate, or in the proportions of patients experiencing orthostatic hypotension were noted (Supplementary Table A5).

CONCLUSIONS

—In the context of a dose-titration scheme designed to optimize efficacy and minimize hypoglycemic episodes with glipizide, this head-to-head comparison study demonstrated that the novel SGLT2 inhibitor dapagliflozin produced a long-term HbA_{1c} mean reduction at 52 weeks that was numerically identical and statistically noninferior to the sulfonylurea glipizide in patients poorly controlled with metformin monotherapy. This comparable long-term efficacy of dapagliflozin with a sulfonylurea, considered potent glucose-lowering agents (2), was achieved with >10-fold fewer hypoglycemic episodes along with sustained weight loss. In contrast, weight increased and hypoglycemic episodes were more frequent with glipizide.

The pattern of HbA_{1c} change over time was substantially different between

dapagliflozin and glipizide treatment (Fig. 1*A*). The pattern with glipizide—rapid initial response, followed by gradual increase—is typical of that observed with sulfonylureas (6,16). In contrast, dapagliflozin response was initially smaller during titration but thereafter was sustained during the maintenance period such that it was identical to glipizide response at 52 weeks. It is interesting to speculate whether the durability of HbA_{1c} control with dapagliflozin will outlast that of glipizide during longer-term follow-up of these patients. In this population with a relatively low baseline mean HbA_{1c} (~7.7%), clinically meaningful reductions of >0.5% were achieved by both agents. A higher baseline HbA_{1c}, as observed in other clinical efficacy studies of antidiabetic agents, generally predicts larger drops in response to treatment, whichever agent is tested (17,18).

Weight loss with dapagliflozin was progressive during the first 6 months and stabilized during the latter half of the study. This may have resulted from glucosuria-induced fat loss, fluid loss associated with osmotic diuresis, or a combination of both. Studies of body composition are underway to assess the relative contributions of fat and fluid loss to the changes in TBW observed with dapagliflozin.

Dapagliflozin reduced blood pressure. The mechanism for this effect is unclear but may involve osmotic diuresis or sodium loss. Although modest rises in hematocrit and blood urea nitrogen occurred, no meaningful changes were noted in electrolytes, serum creatinine, heart rate, or proportions of patients experiencing orthostatic hypotension to indicate dehydration. The estimated glomerular filtration rate and concentrations of cystatin-C did not show meaningful changes. In addition, AEs of renal impairment or failure—excluding those of decrease in creatinine clearance calculated using current body weight values at each study visit—were not over-represented with dapagliflozin. Taken together, these data suggest that dapagliflozin treatment was not associated with clinically relevant dehydration or impairment in kidney function.

Patients with type 2 diabetes are at higher risk of fungal genital infections and UTIs compared with the general population (19). Dapagliflozin-treated patients, especially women, reported an increase in events suggestive of genital infections and lower UTIs compared with glipizide-treated patients. For conservative pharmacovigilance purposes with this first-in-class agent, events suggestive of genital infection and UTI were reported spontaneously and in response to questions proactively posed to patients that were related to the signs and symptoms of these infections. Not all of these suggestive events could be confirmed as infections (Table 1). Variable reports of these events have been noted in previous studies with dapagliflozin (13,18,20,21); hence, further analyses using pooled data are required to better evaluate potential risk factors for genital and UTIs with SGLT2 inhibitors such as dapagliflozin.

In conclusion, this head-to-head comparison of dapagliflozin versus glipizide added to metformin in type 2 diabetic patients inadequately controlled with metformin monotherapy demonstrated similar glycemic efficacy at 52 weeks but markedly divergent effects on weight and hypoglycemia. Whereas glipizide treatment led to weight gain and more hypoglycemic episodes, dapagliflozin produced significant weight loss and significantly fewer hypoglycemic episodes. Dapagliflozin treatment was generally safe and well tolerated, but events suggestive of genital and lower UTIs were observed more frequently in this study. Dapagliflozin is a potential valuable alternative to sulfonylureas as add-on therapy when metformin monotherapy fails to maintain adequate glycemic control.

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References

1. International Diabetes Federation. Global guideline for type 2 diabetes [article online], 2005. Available from http://www.idf.org/webdata/docs/IDF%20GGT2D.pdf. Accessed 30 August 2010
2. Nathan DM, Buse JB, Davidson MB, et al.; American Diabetes Association; European Association for Study of Diabetes. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2009;32:193–203
3. Nathan DM, Buse JB, Davidson MB, et al. Management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2006;29:1963–1972
4. National Institute for Health and Clinical Excellence (NICE). Type 2 diabetes: national clinical guideline for management in primary and secondary care (update) [article online], 2008. London, NICE. Available from http://www.nice.org.uk/nicemedia/live/11983/40803/40803.pdf. Accessed 30 August 2010

5. National Institute for Health and Clinical Excellence (NICE). Type 2 diabetes: newer agents [article online], 2009. London, NICE. Available from http://www.nice.org.uk/nicemedia/live/12165/44318/44318.pdf. Accessed 30 August 2010
6. Kahn SE, Haffner SM, Heise MA, et al.; ADOPT Study Group. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. N Engl J Med 2006;355:2427–2443
7. 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 diabetes (UKPDS 33). Lancet 1998;352:837–853
8. Yki-Järvinen H. Combination therapies with insulin in type 2 diabetes. Diabetes Care 2001;24:758–767
9. Meng W, Ellsworth BA, Nirschl AA, et al. Discovery of dapagliflozin: a potent, selective renal sodium-dependent glucose cotransporter 2 (SGLT2) inhibitor for the treatment of type 2 diabetes. J Med Chem 2008;51:1145–1149
10. Bakris GL, Fonseca VA, Sharma K, Wright EM. Renal sodium-glucose transport: role in diabetes mellitus and potential clinical implications. Kidney Int 2009;75:1272–1277
11. Komoroski B, Vachharajani N, Feng Y, Li L, Kornhauser D, Pfister M. Dapagliflozin, a novel, selective SGLT2 inhibitor, improved glycemic control over 2 weeks in patients with type 2 diabetes mellitus. Clin Pharmacol Ther 2009;85:513–519
12. Ferrannini E, Ramos SJ, Salsali A, Tang W, List JF. Dapagliflozin monotherapy in type 2 diabetic patients with inadequate glycemic control by diet and exercise: a randomized, double-blind, placebo-controlled, phase 3 trial. Diabetes Care 2010;33:2217–2224
13. Bailey CJ, Gross JL, Pieters A, Bastien A, List JF. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with metformin: a randomised, double-blind, placebo-controlled trial. Lancet 2010;375:2223–2233
14. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31–41
15. Zhang M, Tsiatis AA, Davidian M. Improving efficiency of inferences in randomized clinical trials using auxiliary covariates. Biometrics 2008;64:707–715
16. Nauck MA, Meininger G, Sheng D, Terranella L, Stein PP; Sitagliptin Study 024 Group. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, compared with the sulfonylurea, glipizide, in patients with type 2 diabetes inadequately controlled on metformin alone: a randomized, double-blind, non-inferiority trial. Diabetes Obes Metab 2007;9:194–205
17. Bloomgarden ZT, Dodis R, Viscoli CM, Holmboe ES, Inzucchi SE. Lower baseline glycemia reduces apparent oral agent glucose-lowering efficacy: a meta-regression analysis. Diabetes Care 2006;29:2137–2139
18. Ferrannini E, Jimenez Ramos S, Salsali A, Tang W, List JF. Dapagliflozin monotherapy in type 2 diabetic patients with inadequate glycemic control by diet and exercise: a randomized, double-blind, placebo-controlled, phase III trial. Diabetes Care 2010;33:2217–2224
19. Shah BR, Hux JE. Quantifying the risk of infectious diseases for people with diabetes. Diabetes Care 2003;26:510–513
20. List JF, Woo V, Morales E, Tang W, Fiedorek FT. Sodium-glucose cotransport inhibition with dapagliflozin in type 2 diabetes. Diabetes Care 2009;32:650–657
21. Wilding JP, Norwood P, T'joen C, Bastien A, List JF, Fiedorek FT. 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