Annals of Internal Medicine | ORIGINAL RESEARCH

Long-Term Efficacy of Dapagliflozin in Patients With Type 2 Diabetes Mellitus Receiving High Doses of Insulin

A Randomized Trial

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Background: Dapagliflozin, a selective inhibitor of sodium–glucose cotransporter 2, may improve glycemic control with a lower dose of insulin and attenuate the associated weight gain in patients with inadequate control despite high doses of insulin.

Objective: To evaluate the efficacy and safety of adding dapagliflozin therapy in patients whose type 2 diabetes mellitus is inadequately controlled with insulin with or without oral antidiabetic drugs.

Design: A 24-week, randomized, placebo-controlled, multicenter trial followed by a 24-week extension period. An additional 56-week extension period is ongoing. (ClinicalTrials.gov registration number: NCT00673231)

Setting: 126 centers in Europe and North America from 30 April 2008 to 19 November 2009.

Patients: 808 patients with inadequately controlled type 2 diabetes mellitus receiving at least 30 U of insulin daily, with or without up to 2 oral antidiabetic drugs.

Intervention: Patients were randomly assigned in a 1:1:1:1 ratio and allocated with a computer-generated scheme to receive placebo or 2.5, 5, or 10 mg of dapagliflozin, once daily, for 48 weeks.

Measurements: The primary outcome was change in hemoglobin A_{1c} from baseline to 24 weeks. Secondary outcomes included changes in body weight, insulin dose, and fasting plasma glucose level at 24 weeks and during the 24-week extension period. Adverse events were evaluated throughout both 24-week periods.

Results: 800 patients were analyzed. After 24 weeks, mean hemoglobin A_{1c} decreased by 0.79% to 0.96% with dapagliflozin compared with 0.39% with placebo (mean difference, −0.40% [95% CI, −0.54% to −0.25%] in the 2.5-mg group, −0.49% [CI, −0.65% to −0.34%] in the 5-mg group, and −0.57% [CI, −0.72% to −0.42%] in the 10-mg group). Daily insulin dose decreased by 0.63 to 1.95 U with dapagliflozin and increased by 5.65 U with placebo (mean difference, −7.60 U [CI, −10.32 to −4.87 U] in the 2.5-mg group, −6.28 U [CI, −8.99 to −3.58 U] in the 5-mg group, and −6.82 U [CI, −9.56 to −4.09 U] in the 10-mg group). Body weight decreased by 0.92 to 1.61 kg with dapagliflozin and increased by 0.43 kg with placebo (mean differences, −1.35 kg [CI, −1.90 to −0.80 kg] in the 2.5-mg group, −1.42 kg [CI, −1.97 to −0.88 kg] in the 5-mg group, and −2.04 kg [CI, −2.59 to −1.48 kg] in the 10-mg group). These effects were maintained at 48 weeks. Compared with the placebo group, patients in the pooled dapagliflozin groups had a higher rate of hypoglycemic episodes (56.6% vs. 51.8%), events suggesting genital infection (9.0% vs. 2.5%), and events suggesting urinary tract infection (9.7% vs. 5.1%).

Limitation: Insulin doses were not titrated to target, and the study was not designed to evaluate long-term safety.

Conclusion: Dapagliflozin improves glycemic control, stabilizes insulin dosing, and reduces weight without increasing major hypoglycemic episodes in patients with inadequately controlled type 2 diabetes mellitus.

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* **Appendix 1** (available at www.annals.org) lists the investigators of the Dapagliflozin 006 Study Group.

Nearly 1 in 4 patients with type 2 diabetes mellitus eventually requires insulin therapy (1) because of progressive deterioration of glycemic control (2). However, patients with inadequately controlled diabetes despite substantial doses of insulin are particularly challenging to treat. Therapeutic options for these patients are limited, because increasing the dosage of insulin also increases the risks for weight gain, hypoglycemia, fluid retention, and congestive heart failure (3–8).

Sodium–glucose cotransporter 2 is a low-affinity, high-capacity transporter that mediates renal glucose reabsorption (9). Dapagliflozin, a competitive and highly selective inhibitor of sodium–glucose cotransporter 2 (10, 11), reduces renal glucose reabsorption, increases renal glucose excretion, and reduces hyperglycemia in a dose-dependent manner (12). Because dapagliflozin acts independently of insulin, it may provide additional glycemic control when used with insulin (3). Moreover, the caloric loss and osmotic diuresis secondary to increased urinary glucose excretion may counter insulin-related weight gain and fluid retention, respectively.

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Context

Persons with type 2 diabetes who receive ongoing insulin therapy may still have inadequate glycemic control, but increasing the insulin dose can result in troubling or dangerous side effects. Dapagliflozin inhibits the renal absorption of glucose and improves glycemic control as monotherapy or when added to metformin in clinical trials.

Contribution

In this 24-week randomized trial, adding dapagliflozin to insulin therapy for type 2 diabetics with inadequate glycemic control resulted in improved hemoglobin A_{1c} values and weight loss compared with placebo.

Caution

Genital infections were more common with dapagliflozin, and the study was not designed to evaluate long-term safety.

Implication

Dapagliflozin may be helpful for hyperglycemia in type 2 diabetes that is poorly controlled despite insulin therapy.

—The Editors

In clinical trials of up to 24 weeks in patients with type 2 diabetes, dapagliflozin improved glycemic control and body weight when administered as monotherapy (13–15) or when added to therapy with metformin (16) or glimepiride (17). In a 12-week pilot study of 71 patients with type 2 diabetes mellitus whose initial insulin dosages were reduced by 50% (18), dapagliflozin reduced hemoglobin A_{1c} (HbA_{1c}), improved fasting and postprandial blood glucose levels, and lowered body weight compared with placebo.

The aim of our large, long-term study was to evaluate glycemic efficacy, weight loss, and safety over 48 weeks of dapagliflozin therapy in patients whose type 2 diabetes was inadequately controlled with insulin therapy.

METHODS

Our double-blind, placebo-controlled, parallel-group trial was conducted at 126 centers worldwide from 30 April 2008 to 19 November 2009. The protocol was approved by institutional review boards and independent ethics committees, and all participants gave written, informed consent. The study was conducted in accordance with the principles of the Declaration of Helsinki (2004 version) and the requirements of good clinical practice.

After a 2-week enrollment, patients were randomly assigned on a 1:1:1:1 basis to receive placebo or 2.5, 5, or 10 mg of dapagliflozin, once daily, in addition to open-label therapy with their usual daily dose of insulin and existing oral antidiabetic drugs (OADs). Treatment continued for 24 weeks, during which patients, investigators, study monitors, and study sponsors were blinded. This period was followed by a 24-week extension period. A further 56-week extension period is in progress. Patients, investigators, and study monitors remained blinded during the extension periods.

A computer-generated, stratified, block-randomization schedule containing stratum, randomization code, and treatment was provided by AstraZeneca. Patients were randomly assigned sequentially in 2 strata (with and without OADs) in balanced block sizes of 4, with the goal of randomly assigning at least 40% of study participants to the insulin-only stratum. A double-dummy technique was used because the 10-mg dapagliflozin tablets were slightly larger than the 2.5- or 5-mg tablets. All placebos were identical in appearance, odor, and taste to their corresponding investigational products.

Patients, investigators, study monitors, and personnel at AstraZeneca and Bristol-Myers Squibb had no access to the randomization scheme, except for cases of medical emergencies. Because primary efficacy analyses were planned at 24 weeks, personnel at AstraZeneca and Bristol-Myers Squibb had access to the data at that time. During the double-blind extension periods, investigators, patients, and study monitors remained blinded, except for cases of medical emergencies.

No dose modifications of study medication or OADs were allowed during the treatment phase, except to decrease doses of OADs when hypoglycemia after cessation of insulin therapy was a concern. Daily insulin doses were held constant (within 10% of the baseline dose) during the study unless changes were needed to ensure patients' well-being. Up-titration of insulin (defined as an increase in daily dose of <5 U and of $<10\%$ from baseline) was permitted if fasting blood glucose level was greater than 13.3 mmol/L (>240 mg/dL) between weeks 0 and 12, greater than 12.2 mmol/L (>220 mg/dL) between weeks 12 and 24, or greater than 9.9 mmol/L (>180 mg/dL) between weeks 25 and 48 on at least 3 self-monitored readings in the 7 days before the study visit or on a site-measured reading at the study visit (confirmed by repeated site and central laboratory measurements). Up-titration was also permitted if HbA_{1c} was greater than 8% between weeks 25 and 48. Insulin was down-titrated if 2 or more self-monitored blood glucose readings were 4.4 mmol/L or less (≤80 mg/dL) in the first 7 days of active randomized treatment or 3.8 mmol/L or less (≤70 mg/dL) after the first 7 days.

Patients

Men and women aged 18 to 80 years were enrolled if they had type 2 diabetes mellitus, a body mass index of 45 kg/m^2 or less, and inadequate glycemic control (HbA_{1c} ≥7.5% and ≤10.5%). Participants had to have received a stable insulin regimen with a mean daily insulin dose of 30 U or more for at least 8 weeks, with daily insulin requirements varying by more than 10% on no more than 1 occasion in the 7 days before randomization. Additional treatment with stable doses of up to 2 OADs was allowed.

Patients had to receive at least 1500 mg daily or their maximum tolerated dose of metformin or at least half of the daily maximum dose of other OADs for at least 8 weeks before enrollment. Patients were instructed to follow a stable diet and exercise regimen after enrollment.

Major exclusion criteria were type 1 diabetes mellitus; symptoms of poorly controlled diabetes; calculated creatinine clearance less than 50 mL/min per 1.73 m^2; or a measured serum creatinine level greater than 177 μmol/L (>2 mg/dL) or, if receiving metformin, greater than 133 μmol/L (>1.5 mg/dL) for men and at least 124 μmol/L (≥1.4 mg/dL) for women.

Trial Outcomes

All primary and key secondary efficacy variables were prespecified. The primary outcome was change in HbA_{1c} from baseline to week 24. The 4 key secondary efficacy variables at 24 weeks were change in total body weight from baseline, change in calculated mean daily insulin dose, proportion of patients with calculated mean daily insulin dose reductions of 10% or more from baseline, and change in fasting plasma glucose (determined by 1 central laboratory measurement at each study visit) from baseline. The aim at 48 weeks was to assess the safety and tolerability of dapagliflozin therapy and to explore whether the effects on HbA_{1c} and the secondary efficacy variables were maintained.

Safety evaluations over 48 weeks included adverse events, laboratory variables, and vital signs. Major hypoglycemia was defined as a symptomatic episode in which the patient required external assistance, had a capillary or plasma glucose level less than 3 mmol/L (<54 mg/dL), and promptly recovered after receiving glucose or glucagon. Minor hypoglycemia was defined as a symptomatic episode in which the patient had a capillary or plasma glucose level less than 3.5 mmol/L (<63 mg/dL), regardless of the need for external assistance, or an asymptomatic capillary or plasma glucose level less than 3.5 mmol/L (<63 mg/dL) that did not qualify as a major episode. Other hypoglycemia was defined as a suggestive episode that did not meet the criteria for a major or minor episode. A prespecified list of preferred terms from the Medical Dictionary for Regulatory Activities, version 12.1, identified signs, symptoms, and other reports in the database that suggested genital infection or urinary tract infection (UTI). This list included terms for nonspecific signs and symptoms that suggested genital infection (such as genital or vulvovaginal pruritus) and terms for clinical infection (such as vaginal infection) but did not include terms for sexually transmitted diseases. Patients reported these events both spontaneously and in response to questions proactively asked by the investigator during study visits. Both spontaneous and solicited responses were coded by using the prespecified list of preferred terms.

Statistical Analysis

Two analysis sets were defined: the safety set, comprising all randomly assigned patients who received at least 1 dose of study medication, and the full set, comprising all randomly assigned patients who received at least 1 dose of study medication and had a nonmissing baseline value and at least 1 postbaseline efficacy value for at least 1 efficacy variable.

Efficacy variables were analyzed with the full analysis set. Planned analyses over 48 weeks are reported with data from after insulin up-titration for all variables. Adjusted point estimates and 95% CIs are shown as originally planned. All reported *P* values are nominal and unadjusted for multiple comparisons.

For continuous variables, a mixed model (using the PROC MIXED procedure in SAS [SAS Institute, Cary, North Carolina]) assessed changes from baseline with fixed effects for treatment group, OAD use, week, baseline value as a covariate, and interactions of week with treatment group and week with the baseline covariate. An unstructured covariance matrix was applied for repeated measures in a patient (19). To probe the validity of the missing-at-random assumption underlying the mixed model and to explore the potential effect of informative missing data, missing not at random, a sensitivity analysis was conducted by using pattern-mixture modeling that assumed control-based pattern imputation (20). **Appendix 2** (available at www.annals.org) provides further details.

Categorical variables were analyzed by using the method of Zhang and colleagues (21), with adjustment for baseline mean daily dose of insulin and OAD use. Patients with missing data were included in these analyses and considered nonresponders.

The Kaplan–Meier method was used to analyze time to onset of up-titration for not achieving prespecified glycemic targets or discontinuation of therapy due to poor glycemic control.

Analysis of differences in proportions of patients experiencing adverse events of interest between the pooled dapagliflozin groups and the placebo group was performed by using Proc-StatXact 4 (Cytel Software, Cambridge, Massachusetts). All other statistical analyses were done with SAS, version 8.2. The frequency of general adverse events and changes in laboratory variables were summarized by using descriptive statistics.

Sample sizes were calculated on the basis of anticipated differences in the primary efficacy variable. To detect a difference of 0.5% at a 2-sided significance level of 0.019 between dapagliflozin versus placebo for changes in HbA_{1c} level from baseline to week 24 (assuming an SD of 1.2%), 153 patients per group were needed to provide 90% power. Assuming that 5% of patients would not be evaluable, the randomization target was 161 patients per group (a total of 644). An initial enrollment target of 1610 patients was calculated to account for screening failures.

Role of the Funding Source

Our study was sponsored by AstraZeneca and Bristol-Myers Squibb. The sponsors were involved in the study

design and the data collection, review, and analysis. The report was prepared by the authors, with editorial assistance funded by the sponsors. All authors had full access to the data, were responsible for interpreting the data, and had final responsibility for the content of the report and the decision to submit the manuscript for publication.

RESULTS

Demographic and Baseline Characteristics

Because screening failure rates were lower than anticipated, 808 of 1240 enrolled patients were randomly assigned before enrollment could be stopped (**Figure 1**). Demographic and baseline characteristics were similar across all groups (**Table 1**). The mean duration of insulin therapy was approximately 6 years, about half of the mean time since diagnosis of type 2 diabetes mellitus (13.6 years). Mean daily insulin dose was 77.1 U, with 17% using only long-acting basal insulin and 83% using a sliding scale (bolus) regimen. Fifty percent of patients were receiving other background OADs (principally metformin) in addition to insulin, mean baseline HbA_{1c} level was 8.53%, and mean baseline fasting plasma glucose level was 9.9 mmol/L (177.6 mg/dL).

Efficacy Outcomes

Primary Efficacy Variable

The most rapid decreases in mean HbA_{1c} level with dapagliflozin occurred over the first 8 weeks; differences were significantly greater in all dapagliflozin groups than in the placebo group at 24 weeks, and these differences were maintained at 48 weeks (**Figure 2**, *top*). Mean HbA_{1c} level in the 10-mg dapagliflozin group was reduced by 0.54% (95% CI, 0.38% to 0.70%; $P < 0.001$) compared with placebo at 48 weeks.

A sensitivity analysis using a pattern-mixture model (under the assumption that patients receiving dapagliflozin who discontinued the study would exhibit the same future evolution of disease as patients receiving placebo who remained in the study) provided results similar to those from the primary mixed-model analysis of HbA_{1c} (**Appendix 2**). Alternative means of handling missing data resulted in similar results for the primary efficacy variable (**Appendix 3**, available at www.annals.org).

An analysis by strata showed an adjusted mean difference in HbA_{1c} at 48 weeks between the 10-mg dapagliflozin and placebo groups of −0.61% (CI, −0.82% to −0.40%) in patients receiving insulin and 1 or 2 OADs, compared with −0.46% (CI, −0.71% to −0.21%) in those receiving insulin alone (**Appendix Table 1**, available at www.annals.org).

Key Secondary Efficacy Variables

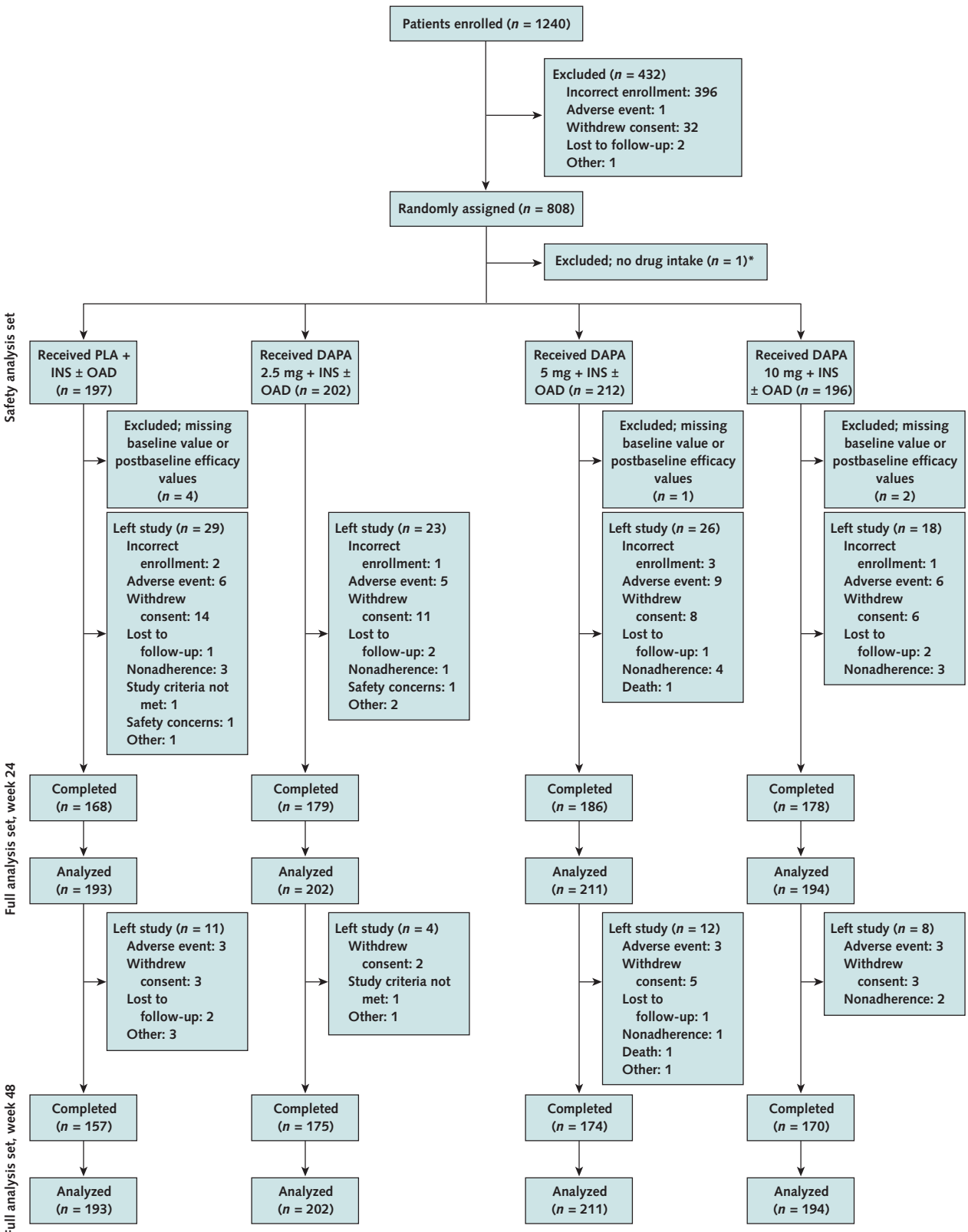
Steady decreases in body weight occurred over time with dapagliflozin. At 24 weeks, significantly greater differences were found in all dapagliflozin groups than in the placebo group, and these differences were maintained at 48 weeks (**Figure 3**, *top*). Mean total body weight decreased by 1.61 kg in the 10-mg dapagliflozin group over 24 weeks, compared with an increase of 0.43 kg in the placebo group (mean difference, −2.04 kg [CI, −2.59 to −1.48 kg]; $P < 0.001$). At 48 weeks, the mean difference was −2.43 kg (CI, −3.18 to −1.68 kg; $P < 0.001$).

Dapagliflozin therapy did not increase mean daily insulin requirements over 48 weeks, but these requirements increased progressively in the placebo group (**Appendix Figure 1**, *top* [available at www.annals.org]), resulting in a total increase of 10.54 U at 48 weeks (**Appendix Figure 1**, *bottom*). At 24 weeks, the adjusted proportion of patients with a mean daily insulin dose reduction of at least 10% from baseline was 10.2% in the placebo group; this proportion differed from the placebo group by 6.3 percentage points (CI, −0.4 to 13.0 percentage points; $P = 0.064$) in the 2.5-mg dapagliflozin group, 6.3 percentage points (CI, −0.3 to 12.9 percentage points; $P = 0.060$) in the 5-mg dapagliflozin group, and 8.9 percentage points (CI, 1.9 to 15.9 percentage points; $P = 0.013$) in the 10-mg dapagliflozin group. At 48 weeks, the adjusted proportion of patients with a mean daily insulin dose reduction of at least 10% from baseline was 10.5% in the placebo group; this proportion differed from the placebo group by 7.6 percentage points (CI, 0.8 to 14.5 percentage points; $P = 0.030$) in the 2.5-mg dapagliflozin group, 7.0 percentage points (CI, 0.3 to 13.7 percentage points; $P = 0.041$) in the 5-mg dapagliflozin group, and 8.1 percentage points (CI, 1.1 to 15.1 percentage points; $P = 0.024$) in the 10-mg dapagliflozin group.

The differences in adjusted mean change in fasting plasma glucose level from baseline at 24 weeks were −0.65 mmol/L (CI, −1.19 to −0.11 mmol/L) in the 2.5-mg dapagliflozin group, −1.12 mmol/L (CI, −1.66 to −0.59 mmol/L) in the 5-mg dapagliflozin group, and −1.10 mmol/L (CI, −1.64 to −0.56 mmol/L) in the 10-mg dapagliflozin group (all $P < 0.001$). At 48 weeks, these values were −0.69 mmol/L (CI, −1.28 to −0.11 mmol/L), −0.90 mmol/L (CI, −1.48 to −0.33 mmol/L), and −0.94 mmol/L (CI, −1.53 to −0.36 mmol/L), respectively (all $P < 0.001$). (To convert fasting plasma glucose values from mmol/L to mg/dL, divide by 0.0555.)

After 24 weeks, 9.7% to 11.2% of patients receiving dapagliflozin required insulin up-titration (an increase in daily dose of >5 U and of >10% from baseline) or discontinued the study because of poor glycemic control, compared with 29.2% of patients receiving placebo. Most of these differences were accounted for by insulin up-titration, with only 2 discontinuations due to poor control by week 24 (1 in the 2.5-mg dapagliflozin group and the other in the placebo group). Over 48 weeks, the differences between the placebo and dapagliflozin groups increased further (**Appendix Figure 2** and **Appendix Table 2**, available at www.annals.org).

Figure 1. **Study flow diagram.**



DAPA = dapagliflozin; INS = insulin; OAD = oral antidiabetic drug; PLA = placebo.
* This patient received no study medication or postbaseline assessments.

Table 1. **Major Demographic and Baseline Characteristics**

Characteristic	Placebo Plus Insulin Group (*n* = 193)	Dapagliflozin Group		
		2.5 mg Plus Insulin (*n* = 202)	5 mg Plus Insulin (*n* = 211)	10 mg Plus Insulin (*n* = 194)
Mean age (SD), *y*	58.8 (8.6)	59.8 (7.6)	59.3 (7.9)	59.3 (8.8)
Sex, *n (%)*				
Male	95 (49.2)	100 (49.5)	100 (47.4)	87 (44.8)
Female	98 (50.8)	102 (50.5)	111 (52.6)	107 (55.2)
Race, *n (%)*				
White	186 (96.4)	190 (94.1)	200 (94.8)	184 (94.8)
Black or African American	6 (3.1)	3 (1.5)	5 (2.4)	5 (2.6)
Asian	0	7 (3.5)	3 (1.4)	3 (1.5)
Other	1 (0.5)	2 (1.0)	3 (1.4)	2 (1.0)
Mean total body weight (SD), *kg*	94.5 (19.8)	93.0 (16.7)	93.3 (17.4)	94.5 (16.8)
Mean BMI (SD), kg/m^2	33.1 (5.9)	33.0 (5.0)	33.0 (5.3)	33.4 (5.1)
Mean waist circumference (SD), *cm*	110.2 (14.5)	109.7 (13.4)	109.3 (13.4)	109.6 (12.5)
Mean duration of type 2 diabetes (SD), *y*	13.5 (7.3)	13.6 (6.6)	13.1 (7.8)	14.2 (7.3)
Mean duration of insulin treatment (SD), *y*	5.9 (5.9)	6.1 (5.2)	5.8 (5.1)	6.3 (5.7)
Insulin regimen, *n (%)*				
Basal	44 (22.8)	29 (14.4)	31 (14.7)	32 (16.5)
Sliding scale (bolus)	149 (77.2)	173 (85.6)	180 (85.3)	162 (83.5)
Sliding scale only	60 (31.1)	81 (40.1)	76 (36.0)	65 (33.5)
Sliding scale plus basal	89 (46.1)	92 (45.5)	104 (49.3)	97 (50.0)
Mean total daily insulin dose, *U*	73.7 (42.4)	79.6 (46.8)	77.0 (44.3)	78.0 (45.0)
Background OAD, *n (%)*				
None	96 (49.7)	104 (51.5)	104 (49.3)	96 (49.5)
Metformin alone	78 (40.4)	80 (39.6)	78 (37.0)	83 (42.8)
Metformin plus a sulfonylurea	13 (6.7)	13 (6.4)	12 (5.7)	8 (4.1)
Metformin plus a thiazolidinedione	1 (0.5)	1 (0.5)	2 (0.9)	0
Metformin plus other OAD	1 (0.5)	1 (0.5)	2 (0.9)	1 (0.5)
Other drugs or drug combinations	4 (2.1)	3 (1.5)	13 (6.2)	6 (3.1)
Mean HbA_{1c} level (SD), %	8.47 (0.77)	8.46 (0.78)	8.62 (0.89)	8.57 (0.82)
Mean fasting plasma glucose level (SD)				
mmol/L	9.5 (3.2)	10.0 (3.3)	10.3 (3.3)	9.6 (3.0)
mg/dL	170.6 (57.2)	180.1 (59.9)	185.4 (58.7)	173.1 (54.9)
History of cardiovascular disease, *n (%)*				
Hypertension only	107 (55.4)	99 (49.0)	110 (52.1)	92 (47.4)
≥1 condition other than hypertension	64 (33.2)	82 (40.6)	67 (31.8)	83 (42.8)
Concomitant medications, *n (%)*				
Antihypertensive agents	154 (78.2)	170 (84.2)	170 (80.2)	163 (83.2)
Lipid-lowering agents	122 (61.9)	141 (69.8)	141 (66.5)	134 (68.4)
Acetylsalicylic acid	90 (45.7)	104 (51.5)	104 (49.1)	108 (55.1)

BMI = body mass index; HbA_{1c} = hemoglobin A_{1c}; OAD = oral antidiabetic drug.

Vital Signs, Safety, and Adverse Events Over 48 Weeks

Greater mean decreases from baseline in seated systolic blood pressure were observed in some dapagliflozin groups compared with the placebo group. Mean change in seated diastolic blood pressure and heart rate from baseline to 24 and 48 weeks did not systematically differ between the dapagliflozin and placebo groups. No increase in the proportion of patients who had orthostatic hypotension was noted in the dapagliflozin groups (**Appendix Table 3**, available at www.annals.org).

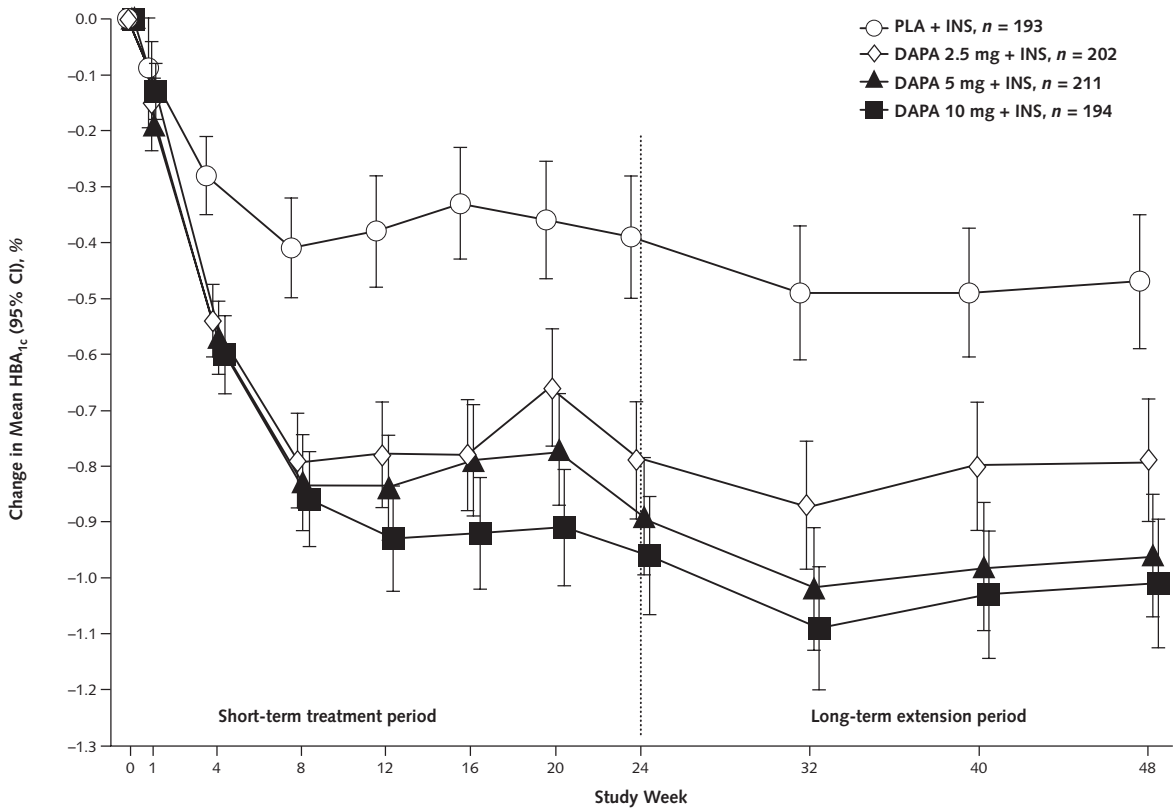
Similar proportions of patients experienced adverse events over 48 weeks across all groups (**Table 2**). Higher proportions of patients in the dapagliflozin groups had adverse events that were considered treatment-related by a blinded investigator (21.3% in the 2.5-mg dapagliflozin group, 29.2% in the 5-mg dapagliflozin group, and 29.1% in the 10-mg dapagliflozin group) than in the placebo group (20.8%). Proportions of patients with serious adverse events were similar across groups (13.2% in the placebo group and ≤13.4% in the dapagliflozin groups). Three serious adverse events were considered treatment-related by the investigator (1 patient with hypoglycemia and 1 with a change of bowel habit, both in the 5-mg dapagliflozin group, and 1 patient with constipation in the 10-mg dapagliflozin group). Two deaths occurred in the 5-mg dapagliflozin group (1 patient died of cardiogenic shock 2 days after receiving aortic valve replacement and coronary artery bypass graft surgery, 13 days after dapagliflozin therapy had been stopped, and 1 patient died of acute myocardial infarction).

Higher proportions of patients had at least 1 hypoglycemic event in the dapagliflozin groups than in the placebo group (60.4%, 55.7%, and 53.6% in the 2.5-mg, 5-mg, and 10-mg dapagliflozin groups, respectively, vs. 51.8%) (**Table 2**). Three patients experienced serious adverse events due to hypoglycemia: 2 patients in the 5-mg dapagliflozin group had events that the study investigator con-

sidered to be serious, and 1 patient in the placebo group had hypoglycemic coma. No patient discontinued the study because of hypoglycemia.

Events suggesting genital infection or UTI were higher in all dapagliflozin groups than in the placebo group (**Table 2**). The difference in proportions of patients between the pooled dapagliflozin groups and the placebo group was significant for genital infection (6.5 percentage points [CI, 1.2 to 12.4 percentage points]) but not for UTI (4.6 percentage points [CI, −1.3 to 11.1 percentage points]). These events were more common in women and mostly occurred during the first 24 weeks of treatment (**Appendix Figure 3**, available at www.annals.org). Most suggestive events were classified as mild or moderate in intensity and responded to routine management. Two patients in the 10-mg dapagliflozin group discontinued treatment because

Figure 2. **Adjusted mean changes in HbA_{1c} level over time (*top*) and at 48 weeks (*bottom*).**

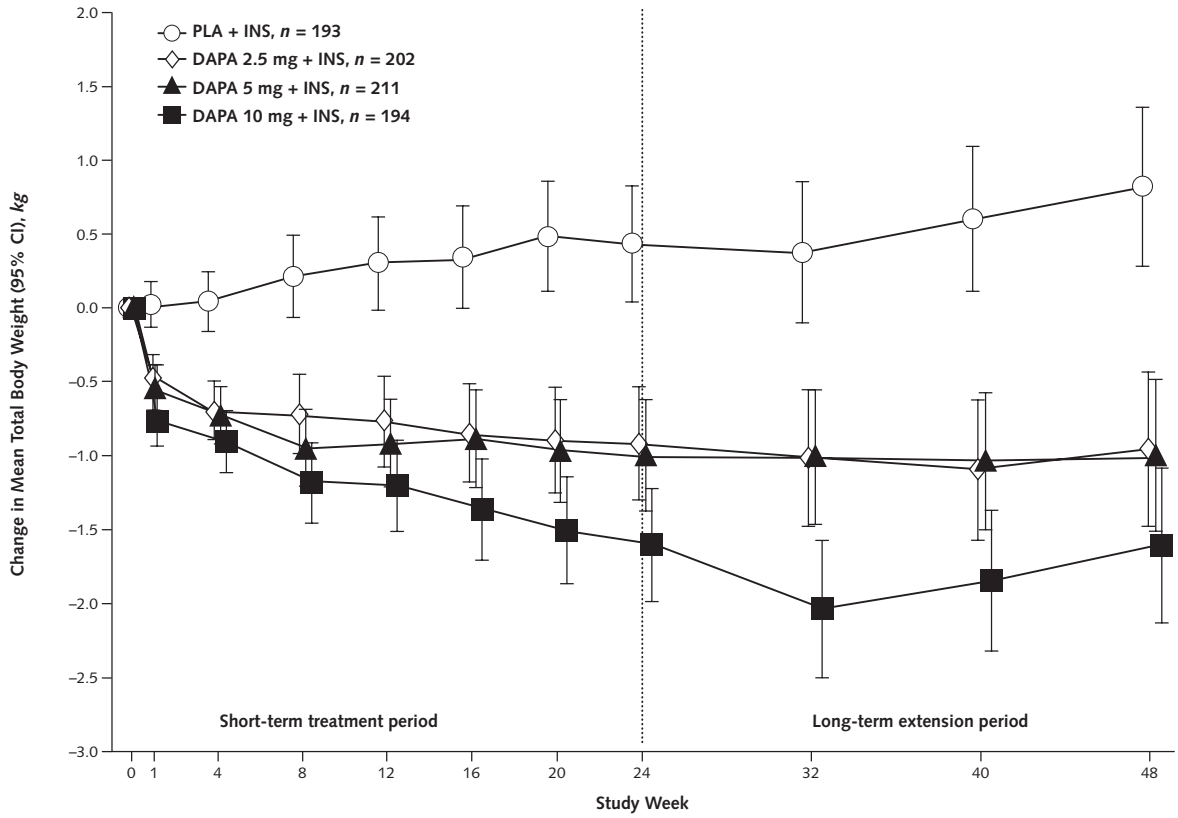


Sample size, *n*										
PLA + INS	189	183	173	169	167	164	166	163	159	157
DAPA 2.5 mg + INS	202	198	190	187	185	181	179	175	176	172
DAPA 5 mg + INS	210	201	195	191	187	187	185	184	180	173
DAPA 10 mg + INS	189	188	184	183	179	176	173	175	173	164

Time and Variable	PLA + INS	DAPA 2.5 mg + INS	DAPA 5 mg + INS	DAPA 10 mg + INS
Baseline HbA_{1c}, %	8.47	8.46	8.62	8.57
Week 24				
Adjusted mean change from baseline, %	−0.39	−0.79	−0.89	−0.96
Difference vs. PLA + INS (95% CI), %	–	−0.40 (−0.54 to −0.25)	−0.49 (−0.65 to −0.34)	−0.57 (−0.72 to −0.42)
P value of difference	–	<0.001	<0.001	<0.001
Week 48				
Adjusted mean change from baseline, %	−0.47	−0.79	−0.96	−1.01
Difference vs. PLA + INS (95% CI), %	–	−0.32 (−0.48 to −0.16)	−0.49 (−0.65 to −0.33)	−0.54 (−0.70 to −0.38)
P value of difference	–	<0.001	<0.001	<0.001

Samples are patients in the full analysis set with nonmissing baseline values and nonmissing values for a given time point. Sample sizes at time 0 are 193, 202, 211, and 193 for the PLA, 2.5-mg DAPA, 5-mg DAPA, and 10-mg DAPA groups, respectively. Treatment group symbols are shifted horizontally to prevent the error bars from overlapping. DAPA = dapagliflozin; HbA_{1c} = hemoglobin A_{1c}; INS = insulin; PLA = placebo.

Figure 3. **Adjusted mean changes in total body weight over time (*top*) and at 48 weeks (*bottom*).**



Sample size, *n*										
PLA + INS	192	185	175	170	170	165	168	164	158	157
DAPA 2.5 mg + INS	202	198	191	188	188	182	180	176	176	174
DAPA 5 mg + INS	211	201	196	193	190	188	187	184	181	174
DAPA 10 mg + INS	192	190	186	183	180	178	177	176	174	166

Time and Variable Baseline total body weight, *kg*	PLA + INS 94.5	DAPA 2.5 mg + INS 93.0	DAPA 5 mg + INS 93.4	DAPA 10 mg + INS 94.5
Week 24				
Adjusted mean change from baseline, *kg*	0.43	−0.92	−1.00	−1.61
Difference vs. PLA + INS (95% CI), *kg*	–	−1.35 (−1.90 to −0.80)	−1.42 (−1.97 to −0.88)	−2.04 (−2.59 to −1.48)
P value of difference	–	<0.001	<0.001	<0.001
Week 48				
Adjusted mean change from baseline, *kg*	0.82	−0.96	−1.00	−1.61
Difference vs. PLA + INS (95% CI), *kg*	–	−1.78 (−2.53 to −1.03)	−1.82 (−2.56 to −1.07)	−2.43 (−3.18 to −1.68)
P value of difference	–	<0.001	<0.001	<0.001

Samples are patients in the full analysis set with nonmissing baseline values and nonmissing values for a given time point. Sample sizes at time 0 are 193, 202, 211, and 193 for the PLA, 2.5-mg DAPA, 5-mg DAPA, and 10-mg DAPA groups, respectively. Treatment group symbols are shifted horizontally to prevent the error bars from overlapping. DAPA = dapagliflozin; INS = insulin; PLA = placebo.

of genital infection before week 24; 2 patients in the 5-mg dapagliflozin group discontinued treatment because of lower UTI, 1 before week 24 and 1 during weeks 24 to 48; and 1 patient in the 2.5-mg dapagliflozin group discontinued treatment because of pyelonephritis before week 24.

Clinically meaningful increases were observed in urinary glucose, hematocrit, serum creatinine, blood urea nitrogen, and cystatin C levels and decreases in serum uric acid levels and calculated creatinine clearance, with greater absolute changes in the dapagliflozin groups (**Appendix Table 4**, available at www.annals.org). However, these changes were not accompanied by increased rates of renal impairment or failure, hypotension, dehydration, or hypovolemia (**Table 2**).

Table 2. **Patients With Adverse Events***

Adverse Events	Placebo Group (*n* = 197)	Dapagliflozin Groups				Difference in Proportions, Total Dapagliflozin vs. Placebo (95% CI)
		2.5 mg Plus Insulin (*n* = 202)	5 mg Plus Insulin (*n* = 212)	10 mg Plus Insulin (*n* = 196)	Total (*n* = 610)	
Overall, *n (%)*						
≥1 event	144 (73.1)	153 (75.7)	153 (72.2)	145 (74.0)	451 (73.9)	
≥1 drug-related event	41 (20.8)	43 (21.3)	62 (29.2)	57 (29.1)	162 (26.6)	
Event leading to discontinuation	9 (4.6)	7 (3.5)	15 (7.1)	10 (5.1)	32 (5.2)	
≥1 serious event	26 (13.2)	27 (13.4)	19 (9.0)	23 (11.7)	69 (11.3)	
≥1 drug-related serious event	0	0	2 (0.9)	1 (0.5)	3 (0.5)	
Serious event leading to discontinuation	3 (1.5)	2 (1.0)	5 (2.4)	5 (2.6)	12 (2.0)	
Death	0	0	2 (0.9)	0	2 (0.3)	
Events with frequency ≥5% in any group, *n (%)*†						
Nasopharyngitis	23 (11.7)	32 (15.8)	35 (16.5)	25 (12.8)	92 (15.1)	
UTI	8 (4.1)	11 (5.4)	16 (7.5)	14 (7.1)	41 (6.7)	
Headache	15 (7.6)	11 (5.4)	14 (6.6)	5 (2.6)	30 (4.9)	
Back pain	11 (5.6)	11 (5.4)	8 (3.8)	11 (5.6)	30 (4.9)	
Hypertension	20 (10.2)	18 (8.9)	16 (7.5)	11 (5.6)	45 (7.4)	
Diarrhea	8 (4.1)	7 (3.5)	11 (5.2)	10 (5.1)	28 (4.6)	
Constipation	3 (1.5)	12 (5.9)	7 (3.3)	6 (3.1)	25 (4.1)	
Peripheral edema	15 (7.6)	8 (4.0)	5 (2.4)	9 (4.6)	22 (3.6)	
Upper respiratory tract infection	12 (6.1)	6 (3.0)	8 (3.8)	9 (4.6)	23 (3.8)	
Arthralgia	11 (5.6)	4 (2.0)	3 (1.4)	7 (3.6)	14 (2.3)	
Events of special interest						
Hypoglycemia (≥1 episode), *n (%)*‡						
Any episode	102 (51.8)	122 (60.4)	118 (55.7)	105 (53.6)	345 (56.6)	4.8 (−3.3 to 12.8)
Major episodes	2 (1)	3 (1.5)	2 (0.9)	3 (1.5)	8 (1.3)	
Minor episodes	99 (50.3)	118 (58.4)	113 (53.3)	99 (50.5)	330 (54.1)	
Other episodes	11 (5.6)	19 (9.4)	24 (11.3)	21 (10.7)	64 (10.5)	
Events suggesting genital infection§						
Total patients, *n/N (%)*	5/197 (2.5)	13/202 (6.4)	21/212 (9.9)	21/196 (10.7)	55/610 (9.0)	6.5 (1.2 to 12.4)
Men, *n/N (%)*	0/98	5/100 (5.0)	2/100 (2.0)	8/88 (9.1)		
1 event, *n (%)*	0	4 (80.0)	1 (50.0)	6 (75.0)		
2–3 events, *n (%)*	0	1 (20.0)	1 (50.0)	2 (25.0)		
>3 events, *n (%)*	0	0	0	0		
Women, *n/N (%)*	5/99 (5.1)	8/102 (7.8)	19/112 (17.0)	13/108 (12.0)		
1 event, *n (%)*	4 (80.0)	6 (75.0)	14 (73.7)	10 (76.9)		
2–3 events, *n (%)*	1 (20.0)	2 (25.0)	2 (10.5)	3 (23.1)		
>3 events, *n (%)*	0		3 (15.8)	0		
Events suggesting UTI§						
Total patients, *n/N (%)*	10/197 (5.1)	16/202 (7.9)	23/212 (10.8)	20/196 (10.2)	59/610 (9.7)	4.6 (−1.3 to 11.1)
Men, *n/N (%)*	3/98 (3.1)	6/100 (6.0)	5/100 (5.0)	5/88 (5.7)		
1 event, *n (%)*	3 (100.0)	3 (50.0)	3 (60.0)	5 (100.0)		
2–3 events, *n (%)*	0	3 (50.0)	2 (40.0)	0		
>3 events, *n (%)*	0	0	0	0		
Women, *n/N (%)*	7/99 (7.1)	10/102 (9.8)	18/112 (16.1)	15/108 (13.9)		
1 event, *n (%)*	7 (100.0)	7 (70.0)	12 (66.7)	10 (66.7)		
2–3 events, *n (%)*	0	3 (30.0)	6 (33.3)	5 (33.3)		
>3 events, *n (%)*	0	0	0	0		
Renal impairment or failure, *n (%)*‖	3 (1.5)	2 (1.0)	6 (2.8)	4 (2.0)	12 (2.0)	0.4 (−4.2 to 5.9)
Hypotension, dehydration, or hypovolemia, *n (%)*‖	2 (1.0)	5 (2.5)	5 (2.4)	3 (1.5)	13 (2.1)	1.1 (−3.4 to 6.4)

UTI = urinary tract infection.
* From patients in the safety analysis set. Includes data from after insulin up-titration.
† Based on definitive preferred terms from Medical Dictionary for Regulatory Activities, version 12.1.
‡ A major episode was defined as a symptomatic episode in which the patient required external assistance due to severe impairment in consciousness or behavior, had a capillary or plasma glucose level <3 mmol/L (<54 mg/dL), and promptly recovered after receiving glucose or glucagon. A minor episode was defined as a symptomatic episode in which the patient had a capillary or plasma glucose level <3.5 mmol/L (<63 mg/dL), regardless of the need for external assistance, or an asymptomatic capillary or plasma glucose level <3.5 mmol/L (<63 mg/dL) that did not qualify as a major episode. Other episodes were defined as reported suggestive episodes that did not meet the criteria for a major or minor episode. No episodes of hypoglycemia led to study discontinuation.
§ Identified in the database by using prespecified lists of preferred terms. These events included signs, symptoms, and other reports suggesting genital infection or UTI as well as definitive terms for genital infection obtained from spontaneous reporting and active questioning at each study visit.
‖ Identified in the database by using prespecified lists of preferred terms but also by other indicators, such as serum creatinine level.

DISCUSSION

Many patients with type 2 diabetes treated with OADs eventually require insulin to manage progressive deterioration in glycemic control (3). However, weight gain and peripheral edema commonly occur with escalating insulin therapy, reducing patient satisfaction and treatment adherence (22). In our 48-week study, dapagliflozin improved glycemic control, prevented insulin dose escalation, and produced significant and sustained weight loss.

To better comprehend the effects of adding dapagliflozin therapy to preexisting background insulin therapy, we did not reduce insulin doses before starting trial therapy, in contrast to the previous dapagliflozin pilot study (18) that reported lower rates of hypoglycemia and greater weight loss. In our study, more minor hypoglycemic episodes were noted in the dapagliflozin groups than in the placebo group, and a higher proportion of patients who received dapagliflozin required insulin down-titration of more than 10%. An increase in hypoglycemia is commonly observed when agents with a low intrinsic hypoglycemic propensity are added to insulin (23) or sulfonylurea (24) therapy.

Diabetes is associated with increased genital infection and UTI in women (25, 26), possibly due to poor glycemic control, which includes hyperglycemia as well as glucosuria (27). Because the mechanism of action of dapagliflozin involves increased urinary glucose excretion, monitoring rates of genital infection and UTI in clinical trials is important. Treatment with dapagliflozin was associated with increased signs, symptoms, and reports suggesting genital infection and UTI, predominantly during the first 24 weeks of the study, although many reported instances of UTI were not confirmed with urine cultures. This aspect of dapagliflozin use requires further investigation, but it is reassuring to note that these events responded to conventional management and rarely led to study withdrawals.

Diabetes also increases risk for cancer of the liver, pancreas, endometrium, colon, rectum, breast, and bladder (28, 29). Dapagliflozin has not demonstrated genotoxicity in animal studies, and no increase in tumors has been observed over 2 years in carcinogenicity studies in rodents (30) when mice and rats were exposed to doses 105 and 186 times higher, respectively, than the 10-mg daily dose used in humans. Consistent with these preclinical safety data, no overall imbalance in cases of cancer has been observed between the 4459 patients who received dapagliflozin and the 2239 control patients from the dapagliflozin clinical development program. Although some types of cancer were overrepresented in control patients, numerical imbalances were noted in occurrences of breast and bladder cancer in patients who received dapagliflozin (30), including 3 cases of each of these types of cancer in the dapagliflozin groups from our study after 2 years of follow-up. Dapagliflozin is highly selective for sodium–glucose cotransporter 2, which is not known to be expressed in either bladder or breast tissue. The mechanism of action of dapagliflozin has no known link to tumor risk; however, long-term surveillance will be required to exclude any potential association.

Our study has limitations. First, insulin doses were not titrated to target. However, our study was designed to demonstrate whether adding dapagliflozin to insulin therapy can improve glycemic control, requiring baseline therapy to remain unchanged, unless deteriorating glycemic control dictates the need for insulin up- or down-titration according to predefined study criteria. Second, because more appropriate analytic methods than those that were initially planned were used, our *P* values are considered post hoc, nominal, and unadjusted for multiple comparisons. Third, approximately 95% of recruited patients were white, although racial origin is unlikely to affect the mechanism of action of dapagliflozin. Finally, we could not fully evaluate potential concerns about risk for breast or bladder cancer with dapagliflozin because of the lack of statistical power in a study of this sample size and duration.

In conclusion, in patients whose type 2 diabetes mellitus was inadequately controlled with insulin therapy, adding dapagliflozin reduced HbA_{1c} levels and weight over 48 weeks without increasing overall insulin dose; however, increased rates of minor hypoglycemia were noted. Conversely, patients for whom placebo was added to insulin therapy had a progressive increase in insulin dose and weight. These data suggest that dapagliflozin may offer a new treatment option for patients receiving insulin therapy whose type 2 diabetes remains inadequately controlled.

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Appendix 2: Sensitivity Analysis of the Primary Efficacy Variable Using Pattern-Mixture Modeling

To probe the validity of the missing-at-random (MAR) assumption underlying the mixed model and to explore the potential effect of informative missing data, missing not at random (MNAR), we used pattern-mixture modeling to conduct a sensitivity analysis that assumed control-based pattern imputation—the assumption that after study discontinuation, patients who discontinue therapy in the experimental treatment groups will exhibit the same future evolution of the disease as patients receiving placebo therapy who continue in the study. Patients who discontinue therapy in the placebo group are assumed to evolve in the same way as patients receiving placebo therapy who continue in the study. The analysis was conducted with the safety analysis set by using HbA_{1c}. Most missing data in longitudinal clinical trials result from patients discontinuing therapy at a particular time point and subsequent data being unavailable; this is known as *monotone missing data*. A small amount of missing data may result from patients who skip a visit but return for subsequent visits, known as *nonmonotone missing data*. The pattern-mixture modeling method assumes monotone missing data. Thus, Markov-chain Monte Carlo multiple imputation was used as a preliminary step to generate 100 data sets that contained imputed values for nonmonotone missing data. Each of the resulting data sets, now containing exclusively monotone missing data, was subjected to further stepwise imputation resulting in 100 fully imputed data sets. At each step, monotone missing values at time t were imputed by fitting a regression model that estimated the relationship between the values at week t and week $t - 1$ on the basis of the available cases in a selected treatment group. Mean imputed HbA_{1c} was compared graphically among patients who completed versus those who dropped out of the study (**Appendix Figure 4**), and an analysis of covariance (ANCOVA) model of imputed mean change in HbA_{1c} from baseline was conducted by using the MIANALYZE procedure in SAS and compared with the results obtained from the primary mixed-model analysis (**Appendix Table 5**).

The difference in the adjusted mean change in imputed HbA_{1c} between the 10-mg dapagliflozin group and the placebo group according to the ANCOVA model (−0.50% [CI, −0.68% to −0.32%]) was similar to that obtained from the mixed-model analysis (−0.54% [CI, −0.70% to −0.38%]), indicating that missing data are unlikely to have substantially affected our assessment of dapagliflozin efficacy for the primary variable (**Appendix Table 6**).

Appendix 3: Alternative Means of Handling Missing Data

The primary efficacy variable was tested by using the Dunnett method with an α of 0.019 for each pairwise group comparison of dapagliflozin versus placebo (overall α level = 0.05) by using ANCOVA with treatment group and OAD use as fixed effects and baseline value as a covariate in the full analysis set. Data after insulin up-titration were excluded, and these and other missing values were replaced by using the last-observation-carried-forward (LOCF) method (**Appendix Table** 7).

Although our analysis was prespecified, it is important to note that recent U.S. Committee on National Statistics recommendations (31) for the prevention and treatment of missing data in clinical trials have stated that LOCF analyses are problematic for the following reasons (32).

First, a necessary but insufficient assumption required by the LOCF method is that data are missing completely at random (for example, a specimen is accidentally dropped in the laboratory). In practice, this assumption is rarely valid and data are more commonly either MAR (for example, a patient withdraws from a study because he or she does not achieve a predefined threshold for treatment efficacy) or MNAR (for example, a patient drops out of the study because of an unforeseen adverse change in his or her health status). Second, the LOCF method further assumes that patients' responses remain unchanged from the last observed value to the end point of the trial and is regarded by some as a conservative estimate of treatment effect. However, these conditions are seldom valid because patients could have either improved or deteriorated had they remained in the trial. This may lead to under- or overestimation of treatment effects when using the LOCF method (32). Alternative models that are valid under the MAR assumption, such as repeated measures mixed-effects analyses, can reduce bias due to dropout by using data before dropout to project individual-patient regression lines to the end of the study, rather than by simply projecting the last observed value to the end of the study (as with the LOCF method) (33). Finally, carrying values forward from an early point in the trial can lead to underestimation of the associated SEs, artificially increasing the amount of information in the data by treating imputed and actually observed values on equal footing, which may result in an erroneous declaration of statistical significance (32).

In addition, analyses that exclude data on the basis of post-randomization events are subject to bias. We therefore used more appropriate means of analysis in our report: Mixed-effects models valid under MAR data with an exploration of the potential effect of MNAR data probed by using pattern-mixture model sensitivity analyses (31).

31. **National Research Council.** The Prevention and Treatment of Missing Data in Clinical Trials. Washington, DC: National Academies Pr; 2010.

32. **Beunckens C, Molenberghs G, Kenward MG.** Direct likelihood analysis versus simple forms of imputation for missing data in randomized clinical trials. Clin Trials. 2005;2:379-86. [PMID: 16315646]

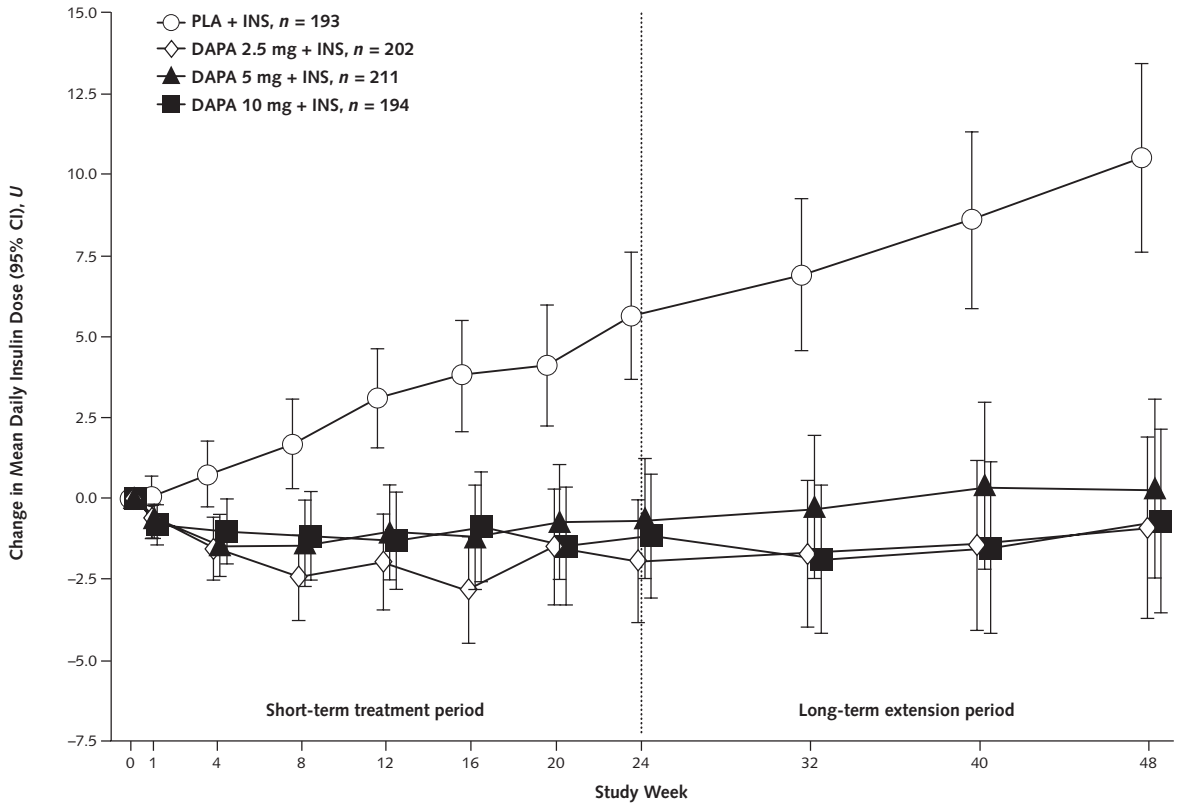
33. **Hamer RM, Simpson PM.** Last observation carried forward versus mixed models in the analysis of psychiatric clinical trials [Editorial]. Am J Psychiatry. 2009;166:639-41. [PMID: 19487398]

Appendix Table 1. **Analysis by Strata: Adjusted Mean Changes in HbA_{1c} Level at Week 48 in Patients Receiving Insulin Alone or With Other OADs**

Group and Value	Placebo Plus Insulin Group	Dapagliflozin Groups		
		2.5 mg Plus Insulin	5 mg Plus Insulin	10 mg Plus Insulin
Patients receiving insulin alone				
Patients, *n*	96	104	104	96
Mean HbA_{1c} level at baseline (SD), %	8.46 (0.78)	8.50 (0.76)	8.60 (0.97)	8.63 (0.85)
Adjusted mean change from baseline at week 48 (95% CI), %*	−0.50 (−0.68 to 0.33)	−0.80 (−0.96 to −0.63)	−0.89 (−1.06 to −0.73)	−0.96 (−1.13 to −0.79)
Difference vs. placebo plus insulin group (95% CI), %		−0.29 (−0.54 to −0.05)	−0.39 (−0.63 to −0.15)	−0.46 (−0.71 to −0.21)
Patients receiving insulin plus other OADs				
Patients, *n*	97	98	173	166
Mean HbA_{1c} level at baseline (SD), %	8.48 (0.76)	8.41 (0.80)	8.63 (0.82)	8.52 (0.78)
Adjusted mean change from baseline at week 48 (95% CI), %*	−0.44 (−0.59 to −0.28)	−0.79 (−0.94 to −0.64)	−1.02 (−1.16 to −0.87)	−1.04 (−1.19 to −0.90)
Difference vs. placebo plus insulin group (95% CI), %		−0.35 (−0.57 to −0.14)	−0.58 (−0.79 to −0.37)	−0.61 (−0.82 to −0.40)

HbA_{1c} = hemoglobin A_{1c}; OAD = oral antidiabetic drug.
* Estimated from a mixed model with terms for baseline value, treatment, OAD use, week, week-by-treatment interaction, and week-by-baseline value interaction by using the full analysis set.

Appendix Figure 1. **Adjusted mean changes in daily insulin dose over time (*top*) and at 48 weeks (*bottom*).**

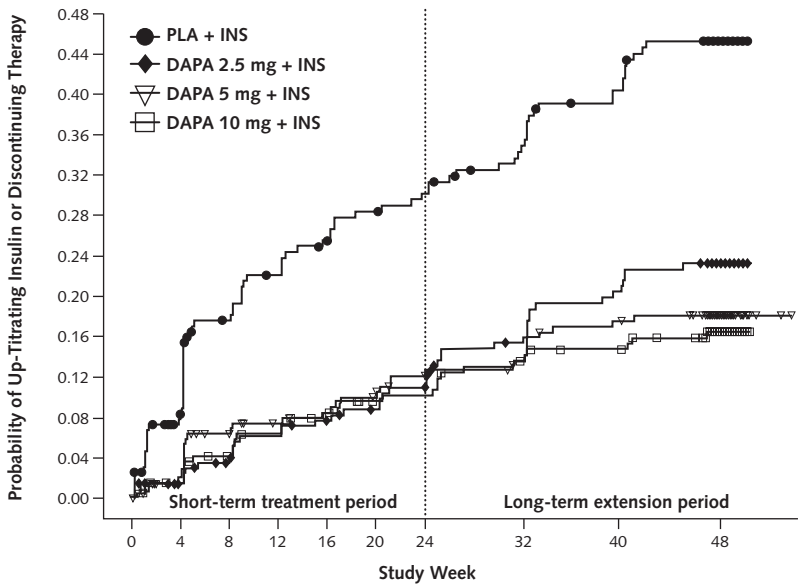


Sample size, *n*										
PLA + INS	190	185	176	171	170	165	168	164	158	157
DAPA 2.5 mg + INS	200	197	189	187	186	181	180	174	176	173
DAPA 5 mg + INS	209	202	194	194	190	188	187	183	181	171
DAPA 10 mg + INS	194	189	185	183	180	178	177	175	173	166

Time and Variable	PLA + INS	DAPA 2.5 mg + INS	DAPA 5 mg + INS	DAPA 10 mg + INS
Baseline mean daily insulin dose, *U*	73.7	79.8	77.0	78.0
Week 24				
Adjusted mean change from baseline, *U*	5.65	−1.95	−0.63	−1.18
Difference vs. PLA + INS (95% CI), *U*	–	−7.60 (−10.32 to −4.87)	−6.28 (−8.99 to −3.58)	−6.82 (−9.56 to −4.09)
P value of difference	–	<0.001	<0.001	<0.001
Week 48				
Adjusted mean change from baseline, *U*	10.54	−0.92	0.30	−0.70
Difference vs. PLA + INS (95% CI), *U*	–	−11.46 (−15.51 to −7.41)	−10.24 (−14.27 to −6.22)	−11.25 (−15.32 to −7.18)
P value of difference	–	<0.001	<0.001	<0.001

Samples are patients in the full analysis set with nonmissing baseline values and nonmissing values for a given time point. Sample sizes at time 0 are 191, 200, 209, and 194 for the PLA, 2.5-mg DAPA, 5-mg DAPA, and 10-mg DAPA groups, respectively. Treatment group symbols are shifted horizontally to prevent the error bars from overlapping. DAPA = dapagliflozin; INS = insulin; PLA = placebo.

Appendix Figure 2. **Probability of insulin up-titration due to not achieving prespecified glycemic targets or of discontinuation due to poor glycemic control over time.**



Patients at risk, *n*										
PLA + INS	193	172	148	138	131	125	121	109	98	67
DAPA 2.5 mg + INS	202	194	185	179	174	169	165	152	143	101
DAPA 5 mg + INS	211	198	186	180	178	173	167	162	153	107
DAPA 10 mg + INS	194	186	179	174	168	162	161	153	149	106

Symbols represent censored observations. "Week" is the actual number of days from the first dose of double-blind study medication divided by 7, not the scheduled visit week. Values for patients at risk are for the beginning of the period. DAPA = dapagliflozin; INS = insulin; PLA = placebo.

Appendix Table 2. **Patients Receiving Insulin Up-Titration or Discontinuing Therapy for Not Achieving Prespecified Glycemic Targets***

Time Point and Variable	Placebo Plus Insulin Group	Dapagliflozin Groups		
		2.5 mg Plus Insulin	5 mg Plus Insulin	10 mg Plus Insulin
At 24 wk				
Patients, *n/N*	54/193	22/202	24/211	19/194
Adjusted proportion†	29.2	11.2	10.6	9.7
Difference vs. placebo plus insulin group (95% CI), *percentage points*		−18 (−25.5 to −10.5)	−18.6 (−26.1 to −11.0)	−19.5 (−26.9 to −12.0)
At 48 wk				
Patients, *n/N*	80/193	43/303	35/211	30/194
Adjusted proportion†	42.8	21.7	15.6	15.3
Difference vs. placebo plus insulin group (95% CI), *percentage points*		−21.1 (−29.9 to −12.4)	−27.2 (−35.6 to −18.8)	−27.5 (−35.9 to −19.1)

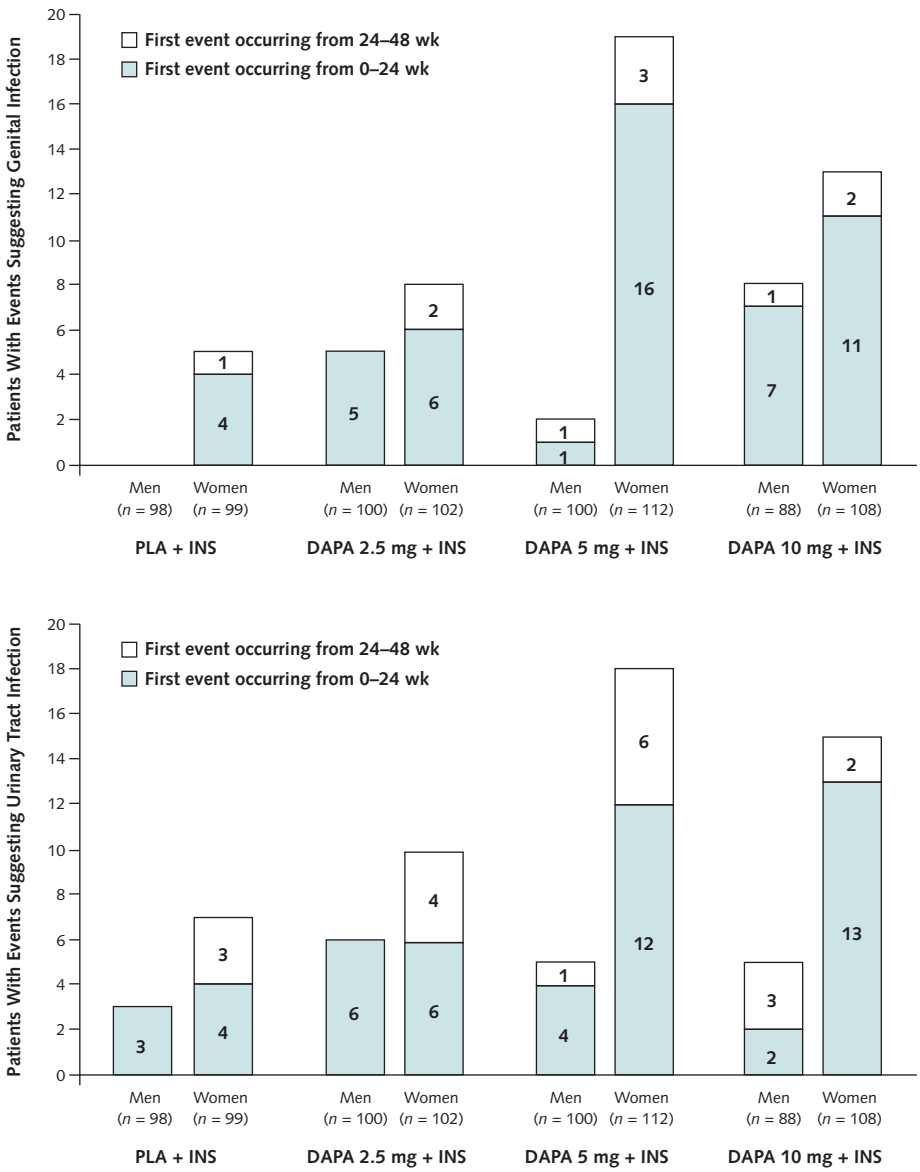
* Patients who received up-titration or discontinued therapy out of those in the full analysis set with nonmissing values for hemoglobin A_{1c} at baseline.
† Logistic regression is based on the methods of Zhang and colleagues (21), with adjustment for baseline hemoglobin A_{1c} level and stratum.

Appendix Table 3. Adjusted Mean Changes in Vital Signs at Weeks 24 and 48*

Vital Sign	Placebo Plus Insulin Group	Dapagliflozin Groups		
		2.5 mg Plus Insulin	5 mg Plus Insulin	10 mg Plus Insulin
Seated systolic blood pressure				
Mean (SD) at baseline, *mm Hg*	136.1 (17.2)	139.6 (17.7)	137.8 (16.2)	140.6 (16.7)
Week 24				
Patients, *n/N*†	166/193	180/202	187/211	176/194
Adjusted mean change from baseline (95% CI), *mm Hg*	−3.56 (−5.47 to −1.64)	−4.21 (−6.05 to −2.38)	−5.93 (−7.74 to −4.12)	−6.66 (−8.53 to −4.80)
Difference vs. placebo plus insulin group (95% CI), *mm Hg*		−0.66 (−3.32 to 2.00)	−2.37 (−5.01 to 0.26)	−3.11 (−5.79 to −0.43)
Week 48				
Patients, *n/N*†	156/193	174/202	173/211	166/194
Adjusted mean change from baseline (95% CI), *mm Hg*	−1.49 (−3.55 to 0.57)	−5.30 (−7.25 to −3.34)	−4.33 (−6.28 to −2.38)	−4.09 (−6.09 to −2.09)
Difference vs. placebo plus insulin group (95% CI), *mm Hg*		−3.81 (−6.65 to −0.97)	−2.84 (−5.67 to −0.01)	−2.61 (−5.48 to 0.27)
Seated diastolic blood pressure				
Mean at baseline (SD), *mm Hg*	80.0 (9.6)	79.5 (10.1)	81.1 (8.9)	79.9 (9.3)
Week 24				
Patients, *n/N*†	166/193	180/202	187/211	176/194
Adjusted mean change from baseline (95% CI), *mm Hg*	−1.86 (−2.95 to −0.77)	−2.11 (−3.17 to −1.06)	−3.04 (−4.08 to −2.01)	−2.70 (−3.76 to −1.64)
Difference vs. placebo plus insulin group (95% CI), *mm Hg*		−0.25 (−1.77 to 1.26)	−1.18 (−2.68 to 0.32)	−0.84 (−2.36 to 0.69)
Week 48				
Patients, *n/N*†	156/193	174/202	173/211	166/194
Adjusted mean change from baseline (95% CI), *mm Hg*	−1.31 (−2.50 to −0.11)	−2.96 (−4.10 to −1.82)	−2.64 (−3.78 to −1.51)	−2.85 (−4.01 to −1.69)
Difference vs placebo plus insulin group (95% CI), *mm Hg*		−1.65 (−3.30 to −0.00)	−1.33 (−2.98 to 0.31)	−1.54 (−3.20 to 0.12)
Seated heart rate				
Mean at baseline (SD), *beats/min*	74.9 (11.5)	75.4 (11.9)	73.9 (11.1)	74.8 (11.2)
Week 24				
Patients, *n/N*†	168/193	180/202	187/211	176/194
Adjusted mean change from baseline (95% CI), *beats/min*	−0.23 (−1.45 to 1.00)	−1.44 (−2.63 to −0.26)	−1.25 (−2.41 to −0.08)	−0.84 (−2.04 to 0.37)
Difference vs. placebo plus insulin group (95% CI), *beats/min*		−1.22 (−2.92 to 0.48)	−1.02 (−2.71 to 0.67)	−0.61 (−2.33 to 1.11)
Week 48				
Patients, *n/N*†	157/193	174/202	173/211	165/194
Adjusted mean change from baseline (95% CI), *beats/min*	−0.69 (−1.98 to 0.60)	−2.32 (−3.55 to −1.08)	−1.61 (−2.84 to −0.38)	−2.68 (−3.94 to −1.42)
Difference vs. placebo plus insulin group (95% CI), *beats/min*		−1.63 (−3.41 to 0.16)	−0.92 (−2.71 to 0.86)	−1.99 (−3.80 to −0.18)
Patients with orthostatic hypotension, *n/N (%)*‡				
Baseline	9/197 (4.6)	13/201 (6.5)	10/212 (4.7)	12/196 (6.1)
Week 24	11/167 (6.6)	11/180 (6.1)	10/186 (5.4)	8/176 (4.6)
Week 48	10/157 (6.4)	7/173 (4.1)	7/173 (4.1)	8/166 (4.8)

* The adjusted mean changes from baseline (95% CIs) are estimated from a mixed model with terms for baseline value, treatment, oral antidiabetic drug use, week, week-by-treatment interaction, and week-by-baseline value interaction using the full analysis set.
† Patients with nonmissing values for baseline and week 24 or 48, out of the full analysis set.
‡ Patients with orthostatic hypotension from among those in the safety analysis set with nonmissing values for baseline and week 24 or 48. Orthostatic hypotension was defined as a decrease of >20 mm Hg in systolic blood pressure or >10 mm Hg in diastolic blood pressure from supine to standing.

Appendix Figure 3. **Patients with events suggesting genital infection (*top*) or urinary tract infection (*bottom*) at 24 and 48 weeks.**



DAPA = dapagliflozin; INS = insulin; PLA = placebo.

Appendix Table 4. Change in Laboratory Values of Interest From Baseline to Week 48*

Laboratory Value	Placebo Plus Insulin Group (*n* = 197)	Dapagliflozin Groups		
		2.5 mg Plus Insulin (*n* = 202)	5 mg Plus Insulin (*n* = 212)	10 mg Plus Insulin (*n* = 196)
Serum creatinine				
Patients, *n*	153	171	171	163
Mean at baseline (SD)				
μmol/L	79.5 (19.9)	79.5 (16.7)	82.2 (20.7)	79.0 (21.3)
mg/dL	0.90 (0.23)	0.90 (0.19)	0.93 (0.23)	0.89 (0.24)
Mean change at week 1 (SD)				
μmol/L	−1.50 (9.31)	2.39 (7.92)	2.30 (10.45)	3.89 (9.37)
mg/dL	−0.02 (0.11)	0.03 (0.09)	0.03 (0.12)	0.04 (0.11)
Mean change at week 48 (SD)				
μmol/L	0.97 (9.84)	1.77 (11.06)	1.86 (12.48)	1.50 (10.60)
mg/dL	0.01 (0.11)	0.02 (0.13)	0.02 (0.14)	0.02 (0.12)
Calculated creatinine clearance				
Patients, *n*	153	171	171	163
Mean at baseline (SD), *mL/min per 1.73 m²*	115.9 (39.7)	111.3 (36.0)	109.7 (36.7)	114.3 (34.9)
Mean change at week 48 (SD), *mL/min per 1.73 m²*	−0.8 (14.4)	−4.8 (14.5)	−4.7 (16.4)	−4.4 (13.2)
Estimated glomerular filtration rate				
Patients, *n*	153	171	171	163
Mean at baseline (SD), *mL/min per 1.73 m²*	79.9 (18.5)	78.5 (18.32)	76.2 (19.6)	79.3 (19.0)
Mean change at week 48 (SD), *mL/min per 1.73 m²*	−0.7 (11.1)	−2.0 (11.0)	−2.0 (13.5)	−1.1 (10.1)
Cystatin C				
Patients, *n*	152	163	164	151
Mean at baseline (SD), *nmol/L*	58.3 (14.1)	59.1 (13.2)	58.5 (14.4)	57.3 (13.7)
Mean change at week 48 (SD), *nmol/L*	4.94 (6.86)	6.66 (8.99)	6.74 (9.01)	7.93 (7.65)
Serum uric acid				
Patients, *n*	153	172	172	163
Mean at baseline (SD), *μmol/L*	333.7 (98.3)	326.0 (89.2)	323.6 (95.2)	324.8 (93.9)
Mean change at week 48 (SD), *μmol/L*	4.16 (59.08)	−11.30 (61.39)	−12.49 (61.78)	−14.28 (62.95)
Blood urea nitrogen				
Patients, *n*	153	172	172	163
Mean at baseline (SD)				
mmol/L	5.93 (1.87)	6.00 (1.62)	6.10 (1.95)	6.00 (1.85)
mg/dL	16.61 (5.24)	16.81 (4.54)	17.09 (5.46)	16.81 (5.18)
Mean change at week 1 (SD)				
mmol/L	0.04 (1.38)	0.57 (1.29)	0.57 (1.32)	0.86 (1.62)
mg/dL	0.11 (3.87)	1.60 (3.61)	1.60 (3.70)	2.41 (4.54)
Mean change at week 48 (SD)				
mmol/L	0.18 (1.52)	0.64 (1.71)	0.54 (1.69)	0.82 (1.53)
mg/dL	0.50 (4.26)	1.79 (4.79)	1.51 (4.73)	2.30 (4.29)
Urinary glucose†				
Patients, *n*	113	122	112	112
Mean at baseline (SD)				
mmol/L	18.9 (47.2)	11.6 (36.0)	16.8 (45.6)	17.2 (48.8)
mg/dL	340.54 (850.45)	209.01 (648.65)	302.70 (821.62)	309.91 (879.28)
Mean change at week 48 (SD)				
mmol/L	−9.3 (54.4)	64.6 (80.2)	86.6 (83.4)	129.3 (120.1)
mg/dL	−167.57 (980.18)	1163.96 (1445.05)	1560.36 (1502.70)	2329.73 (2163.96)
Urinary albumin				
Patients, *n*	155	173	170	162
Mean at baseline (SD), *mg/L*	62.1 (182.5)	66.6 (181.6)	117.0 (428.0)	55.4 (140.9)
Mean change at week 48 (SD), *mg/L*	4.7 (10.1)	−17.8 (9.1)	−34.3 (22.2)	−27.1 (8.1)
Urinary albumin–creatinine ratio				
Patients, *n*	154	172	170	162
Mean at baseline (SD), *mg/g*	69.6 (220.8)	68.4 (192.5)	108.4 (369.2)	52.8 (129.2)
Mean change at week 48 (SD), *mg/g*	−1.6 (192.6)	−22.1 (164.3)	−24.8 (163.6)	−17.3 (85.9)

Continued on following page

Appendix Table 4—**Continued**

Laboratory Value	Placebo Plus Insulin Group (*n* = 197)	Dapagliflozin Groups		
		2.5 mg Plus Insulin (*n* = 202)	5 mg Plus Insulin (*n* = 212)	10 mg Plus Insulin (*n* = 196)
Urinary total protein				
Patients, *n*	156	173	171	164
Mean at baseline (SD), *g/L*	0.16 (0.26)	0.18 (0.27)	0.24 (0.56)	0.16 (0.20)
Mean change at week 48 (SD), *g/L*	0.0 (0.18)	−0.04 (0.19)	−0.07 (0.40)	−0.06 (0.15)
Sodium				
Patients, *n*	154	172	172	163
Mean at baseline (SD), *mmol/L*	142.1 (3.29)	141.2 (2.89)	141.5 (2.90)	141.7 (3.29)
Mean change at week 48 (SD), *mmol/L*	0.9 (4.0)	0.7 (3.0)]	1.2 (3.3)	1.1 (3.9)
Potassium				
Patients, *n*	154	171	171	163
Mean at baseline (SD), *mmol/L*	4.54 (0.56)	4.60 (0.50)	4.60 (0.53)	4.58 (0.56)
Mean change at week 48 (SD), *mmol/L*	0.02 (0.52)	−0.08 (0.56)	−0.09 (0.55)	−0.09 (0.51)
Calcium				
Patients, *n*	153	172	172	163
Mean at baseline (SD)				
mmol/L	2.42 (0.10)	2.39 (0.17)	2.40 (0.12)	2.41 (0.13)
mg/dL	9.68 (0.40)	9.56 (0.68)	9.60 (0.48)	9.64 (0.52)
Mean change at week 48 (SD)				
mmol/L	−0.03 (0.13)	−0.02 (0.21)	−0.02 (0.14)	−0.04 (0.16)
mg/dL	−0.12 (0.52)	−0.08 (0.84)	−0.08 (0.56)	−0.16 (0.64)
Magnesium				
Patients, *n*	154	171	171	163
Mean at baseline (SD)				
mmol/L	1.69 (0.24)	1.62 (0.16)	1.63 (0.20)	1.64 (0.21)
mEq/L	3.38 (0.48)	3.24 (0.32)	3.26 (0.40)	3.28 (0.42)
Mean change at week 48 (SD)				
mmol/L	−0.06 (0.19)	0.08 (0.15)	0.06 (0.17)	0.09 (0.17)
mEq/L	−0.12 (0.38)	0.16 (0.30)	0.12 (0.34)	0.18 (0.34)
Inorganic phosphorus				
Patients, *n*	153	171	171	163
Mean at baseline (SD)				
mmol/L	1.16 (0.18)	1.14 (0.18)	1.16 (0.18)	1.17 (0.15)
mg/dL	3.59 (0.56)	3.53 (0.56)	3.59 (0.56)	3.62 (0.46)
Mean change at week 48 (SD)				
mmol/L	0.01 (0.16)	0.02 (0.18)	0.05 (0.16)	0.04 (0.17)
mg/dL	0.03 (0.50)	0.06 (0.56)	0.15 (0.50)	0.12 (0.53)
Hematocrit				
Patients, *n*	155	169	170	163
Mean at baseline (SD)	0.4175 (0.0358)	0.4083 (0.0378)	0.4125 (0.0380)	0.4134 (0.0390)
Mean change at week 1 (SD)	−0.0029 (0.0175)	0.0041 (0.0150)	0.0040 (0.0154)	0.0064 (0.0213)
Mean change at week 12 (SD)	−0.0014 (0.0188)	0.0157 (0.0246)	0.0201 (0.0217)	0.0213 (0.0243)
Mean change at week 48 (SD)	0.0012 (0.0207)	0.0192 (0.0263)	0.0239 (0.0231)	0.0263 (0.0270)
Aspartate aminotransferase				
Patients, *n*	153	172	172	163
Mean at baseline (SD), *U/L*	24.6 (14.1)	26.6 (17.5)	25.1 (13.4)	23.0 (9.7)
Mean change at week 48 (SD), *U/L*	1.0 (11.4)	−2.1 (13.7)	−1.1 (9.7)	0.0 (7.2)
Alanine aminotransferase				
Patients, *n*	153	172	172	163
Mean at baseline (SD), *U/L*	28.1 (15.7)	28.6 (18.2)	27.0 (16.0)	26.7 (12.7)
Mean change at week 48 (SD), *U/L*	0.2 (12.0)	−2.2 (13.2)	−1.6 (10.7)	−1.5 (10.7)
Alkaline phosphatase				
Patients, *n*	153	172	172	163
Mean at baseline (SD), *μkat/L*	1.34 (0.44)	1.31 (0.39)	1.32 (0.44)	1.33 (0.45)
Mean change at week 48 (SD), *μkat/L*	−0.05 (0.21)	−0.06 (0.22)	−0.03 (0.26)	−0.06 (0.24)

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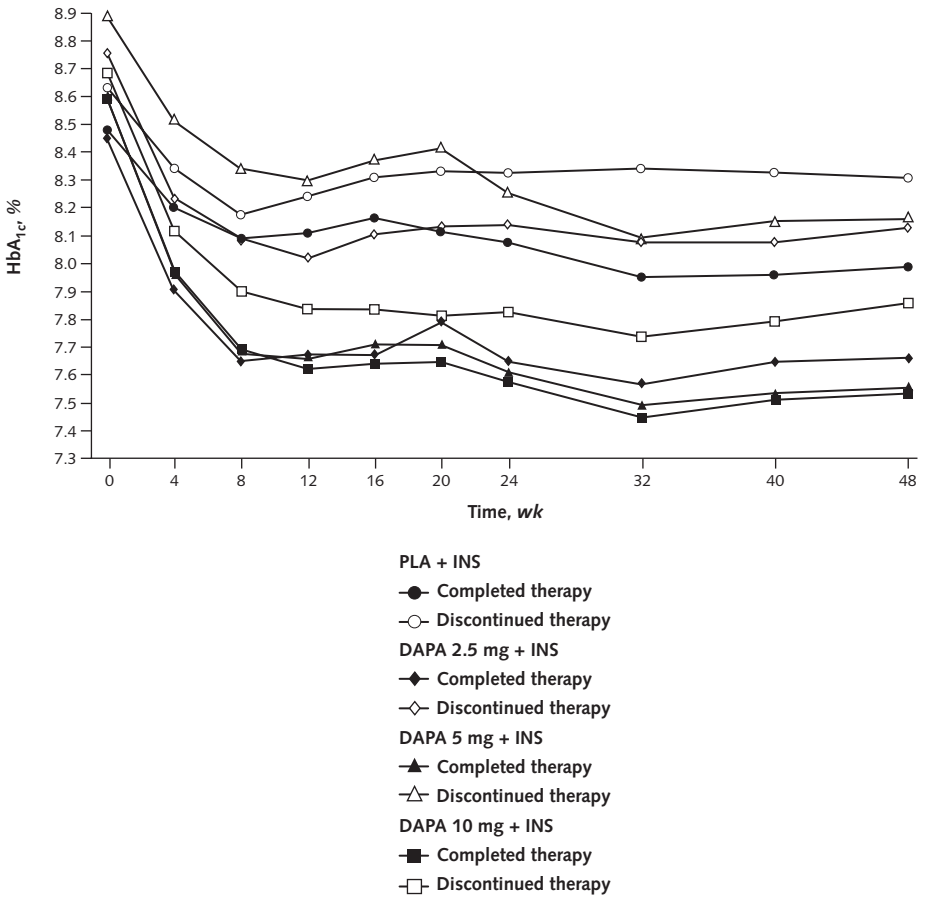
Appendix Table 4—Continued

Laboratory Value	Placebo Plus Insulin Group (*n* = 197)	Dapagliflozin Groups		
		2.5 mg Plus Insulin (*n* = 202)	5 mg Plus Insulin (*n* = 212)	10 mg Plus Insulin (*n* = 196)
Total bilirubin				
Patients, *n*	153	171	172	163
Mean at baseline (SD)				
μmol/L	7.70 (3.61)	7.87 (3.83)	8.72 (4.87)	7.70 (3.86)
mg/dL	0.45 (0.21)	0.42 (0.22)	0.51 (0.28)	0.45 (0.23)
Mean change at week 48 (SD)				
μmol/L	0.34 (3.05)	0.68 (2.91)	0.17 (3.50)	0.34 (3.01)
mg/dL	0.02 (0.18)	0.04 (0.17)	0.01 (0.20)	0.02 (0.18)
Parathyroid hormone				
Patients, *n*	146	154	160	145
Mean at baseline (SD), *ng/L*	36.3 (25.8)	35.9 (18.2)	36.0 (20.9)	37.3 (21.4)
Mean change at week 48 (SD), *ng/L*	1.8 (18.5)	2.7 (14.3)	3.2 (17.9)	4.3 (15.2)
25-hydroxyvitamin D				
Patients, *n*	154	169	168	158
Mean at baseline (SD), *nmol/L*	51.9 (19.3)	52.9 (18.0)	51.7 (20.6)	52.4 (21.4)
Mean change at week 48 (SD), *nmol/L*	−2.00 (13.69)	−0.75 (13.92)	−0.75 (14.17)	−2.75 (16.06)

* Values are numbers of patients with nonmissing baseline and week-48 values in the safety analysis set.
† Derived from a urinary spot-check performed in the morning fasting state.

Appendix Figure 4. **Change in mean HbA_{1c} level over time calculated by using the placebo group to impute missing data in the safety analysis set and analyzed by treatment group and discontinuation status.**



DAPA = dapagliflozin; HbA_{1c} = hemoglobin A_{1c}; INS = insulin; PLA = placebo.

Appendix Table 5. **Patients in the Safety Analysis Set With Total, Monotone, and Nonmonotone Missing Data***

Variable	Placebo Plus Insulin Group			Dapagliflozin Groups								
				2.5 mg Plus Insulin			5 mg Plus Insulin			10 mg Plus Insulin		
Patients at baseline, *n (%)*	197 (100.0)			202 (100.0)			212 (100.0)			196 (100.0)		
Patients with evaluable data at 48 wk, *n (%)*	157 (79.7)			172 (85.1)			173 (81.6)			164 (83.7)		
	Total†	Monotone†	Nonmonotone	Total†	Monotone†	Nonmonotone	Total†	Monotone†	Nonmonotone	Total†	Monotone†	Nonmonotone
Patients with missing data, *n (%)*												
0–4 wk	14 (7.1)	12 (6.1)	2 (1)	4 (2)	4 (2)	0	11 (5.6)	10 (5.1)	1 (0.5)	8 (4.1)	6 (3)	2 (1)
4–8 wk	24 (12.2)	18 (9.1)	6 (3)	12 (6.1)	9 (4.6)	3 (1.5)	17 (8.6)	14 (7.1)	3 (1.5)	12 (6.1)	7 (3.6)	5 (2.5)
8–12 wk	28 (14.2)	24 (12.2)	4 (2)	15 (7.6)	12 (6.1)	3 (1.5)	21 (10.7)	18 (9.1)	3 (1.5)	13 (6.6)	11 (5.6)	2 (1)
12–16 wk	30 (15.2)	26 (13.2)	4 (2)	17 (8.6)	13 (6.6)	4 (2)	25 (12.7)	20 (10.2)	5 (2.5)	17 (8.6)	14 (7.1)	3 (1.5)
16–20 wk	33 (16.8)	29 (14.7)	4 (2)	21 (10.7)	18 (9.1)	3 (1.5)	25 (12.7)	22 (11.2)	3 (1.5)	20 (10.2)	18 (9.1)	2 (1)
20–24 wk	31 (15.7)	30 (15.2)	1 (0.5)	23 (11.7)	21 (10.7)	2 (1)	27 (13.7)	25 (12.7)	2 (1)	23 (11.7)	19 (9.6)	4 (2)
24–32 wk	34 (17.3)	33 (16.8)	1 (0.5)	27 (13.7)	25 (12.7)	2 (1)	28 (14.2)	28 (14.2)	0	21 (10.7)	20 (10.2)	1 (0.5)
32–40 wk	38 (19.3)	36 (18.3)	2 (1)	26 (13.2)	26 (13.2)	0	32 (16.2)	31 (15.7)	1 (0.5)	23 (11.7)	22 (11.2)	1 (0.5)
40–48 wk	40 (20.3)	40 (20.3)	0	30 (15.2)	30 (15.2)	0	39 (19.8)	39 (19.8)	0	32 (16.2)	32 (16.2)	0

* Between 80% and 85% of patients were still available to provide data at 48 wk.
† Values for total and monotone missing data are cumulative.

Appendix Table 6. Adjusted Mean Differences in Change in Hemoglobin A_{1c} Level at Week 48*

Group	Pattern-Mixture Model Estimate (95% CI)†	Mixed-Model Estimate (95% CI)
Placebo, plus insulin	Reference	Reference
Dapagliflozin, 2.5 mg, plus insulin	−0.31 (−0.49 to −0.13)	−0.32 (−0.48 to −0.16)
Dapagliflozin, 5 mg, plus insulin	−0.44 (−0.62 to −0.26)	−0.49 (−0.65 to −0.33)
Dapagliflozin, 10 mg, plus insulin	−0.50 (−0.68 to −0.32)	−0.54 (−0.70 to −0.38)

* Derived from an analysis-of-covariance model with terms for baseline value, stratum, and treatment using the safety analysis set.
† The placebo group was used to impute missing values for the groups that received dapagliflozin.

Appendix Table 7. Protocol-Prespecified Analysis of the Primary Efficacy Variable at 24 Weeks*

Variable	Placebo Plus Insulin Group (n = 193)	Dapagliflozin Groups		
		2.5 mg Plus Insulin (n = 202)	5 mg Plus Insulin (n = 211)	10 mg Plus Insulin (n = 194)
Patients analyzed, n†	188	198	210	192
Mean HbA_{1c} level at baseline (SD), %	8.46 (0.76)	8.47 (0.78)	8.61 (0.89)	8.58 (0.82)
Adjusted mean change from baseline (95% CI), %	−0.30 (−0.40 to −0.20)	−0.75 (−0.85 to −0.65)	−0.82 (−0.92 to −0.73)	−0.90 (−1.00 to −0.80)
Difference from placebo plus insulin group (95% CI), %		−0.45 (−0.59 to −0.31)	−0.52 (−0.66 to −0.38)	−0.60 (−0.74 to −0.45)
P value of difference‡		<0.001	<0.001	<0.001

HbA_{1c} = hemoglobin A_{1c}.
* Excluding data after insulin up-titration.
† Patients in the full analysis set with nonmissing baseline and week-24 values (using the last-observation-carried-forward method).
‡ Significant P value for primary efficacy variable, tested at $\alpha = 0.019$ with the Dunnett adjustment applied.