Glucose Variables in Type 1 Diabetes Studies With Dapagliflozin: Pooled Analysis of Continuous Glucose Monitoring Data From DEPICT-1 and -2

*Chantal Mathieu,[1] Paresh Dandona,[2] Moshe Phillip,[3,4] Tal Oron,[3,4] Marcus Lind,[5,6] Lars Hansen,[7] Fredrik Thorén,[8] John Xu,[9] and Anna Maria Langkilde,[8] on behalf of the DEPICT-1 and DEPICT-2 Investigators**

Diabetes Care 2019;42:1081–1087 | https://doi.org/10.2337/dc18-1983

OBJECTIVE

This pooled analysis assessed continuous glucose monitoring (CGM) in patients with inadequately controlled type 1 diabetes (HbA_{1c} ≥7.7 to ≤11.0% [≥61 to ≤97 mmol/mol]) who received dapagliflozin as an adjunct to adjustable insulin.

RESEARCH DESIGN AND METHODS

CGM data were pooled from two 24-week, double-blind, randomized, phase 3 studies: Dapagliflozin Evaluation in Patients with Inadequately Controlled Type 1 Diabetes (DEPICT-1 and DEPICT-2). These studies comprised 1,591 patients receiving dapagliflozin 5 mg (*n* = 530), dapagliflozin 10 mg (*n* = 529), or placebo (*n* = 532).

RESULTS

Baseline characteristics were balanced between treatment groups. Patients receiving dapagliflozin 5 mg or 10 mg both spent more time with blood glucose in the range >3.9 to ≤10.0 mmol/L (>70 to ≤180 mg/dL) over 24 h than those receiving the placebo. The adjusted mean (SE) change from baseline at week 24 was 6.48% (0.60) with dapagliflozin 5 mg, 8.08% (0.60) with dapagliflozin 10 mg, and −2.59% (0.61) with placebo. At week 24, the mean amplitude of glucose excursion over 24 h, mean 24-h glucose values, and postprandial glucose values were also improved in patients receiving dapagliflozin over those receiving placebo. No marked differences were found at week 24 between dapagliflozin 5 or 10 mg and placebo in the percentage of glucose values ≤3.9 mmol/L (≤70 mg/dL) or ≤3.0 mmol/L (≤54 mg/dL) over 24 h, or in nocturnal (0000–0559 h) glucose values ≤3.9 mmol/L (≤70 mg/dL).

CONCLUSIONS

In patients with type 1 diabetes, treatment with dapagliflozin over 24 weeks improved time in range, mean glucose, and glycemic variability without increasing the time spent in the range indicating hypoglycemia.

People with type 1 diabetes require lifelong insulin treatment to manage this disease, and they must balance the goal of long-term glycemic control with the day-to-day challenges of insulin therapy. Intensive insulin treatment increases the risk of hypoglycemia in type 1 diabetes (1), and insulin-related hypoglycemia is reported to be the major limiting factor in glycemic management in these patients (2). Severe hypoglycemia has been reported in almost 12% of people with type 1 diabetes (3), and

[1]*Department of Endocrinology, UZ Gasthuisberg, KU Leuven, Leuven, Belgium*
[2]*Department of Medicine, University at Buffalo, The State University of New York, Buffalo, NY*
[3]*Jesse Z and Sara Lea Shafer Institute of Endocrinology and Diabetes, Schneider Children's Medical Center of Israel, Petah Tikva, Israel*
[4]*Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel*
[5]*Institute of Medicine, University of Gothenburg, Gothenburg, Sweden*
[6]*Department of Medicine, NU Hospital Group, Uddevalla, Sweden*
[7]*MedImmune, Gaithersburg, MD*
[8]*AstraZeneca, Mölndal, Sweden*
[9]*AstraZeneca, Gaithersburg, MD*

Corresponding author: Chantal Mathieu, chantal.mathieu@uzleuven.be

Received 19 September 2018 and accepted 8 March 2019

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc18-1983/-/DC1.

**A complete list of the DEPICT-1 and DEPICT-2 principal investigators can be found in the Supplementary Data online.*

between 4% and 10% of deaths of people with type 1 diabetes are believed to be caused by hypoglycemia (4). Glycemic variability, defined as fluctuations in blood glucose that occur throughout the day, comprises both hypoglycemia and postprandial increases (5). Although glycemic variability occurs in healthy individuals, it increases in those with diabetes and has a higher incidence in people with type 1 diabetes than in those with type 2 diabetes (5). Larger glycemic variability, in terms of larger fluctuations, is reported to correlate negatively with microvascular and macrovascular complications (5,6) and with diabetes-related quality of life (7).

Sodium–glucose cotransporter 2 (SGLT2) inhibitors act independently of insulin to block the reabsorption of glucose filtered from the proximal renal tubules (8). The amount of glucose excreted in the urine, and therefore the magnitude of the blood glucose–lowering effect, is dependent on the blood glucose concentration and the reabsorptive capability (8). As such, SGLT2 inhibitors could potentially reduce glycemic variability in people with diabetes and may be useful as adjuncts to insulin therapy in those with type 1 diabetes, although they are not currently approved for use in type 1 diabetes.

Two pivotal phase 3 studies of patients with inadequately controlled type 1 diabetes, Dapagliflozin Evaluation in Patients with Inadequately Controlled Type 1 Diabetes (DEPICT-1 [9] and DEPICT-2 [10]), demonstrated significant improvements in glycemic control, sustained weight loss, and reductions in insulin dose with dapagliflozin 5 mg or 10 mg versus placebo as an adjunct to adjustable insulin over 24 weeks. The number of hypoglycemia events did not increase in those who were treated with dapagliflozin despite a reduction in HbA_{1c}, although the risk of diabetic ketoacidosis (DKA) increased (11). Here we present the results of pooled continuous glucose monitoring (CGM) data from the DEPICT-1 and DEPICT-2 trials. CGM measurements were reported at baseline, 12 weeks, and 24 weeks.

RESEARCH DESIGN AND METHODS

Patient Population

This post hoc analysis pooled 24-week data from 1,591 patients in two double-blind, randomized, parallel-controlled, multicenter, phase 3 studies with essentially identical study designs: DEPICT-1 (NCT02268214) (9) and DEPICT-2 (NCT02460978) (10). The pooled analysis included patients aged ≥18 to ≤75 years who had inadequately controlled type 1 diabetes (HbA_{1c} ≥7.7 to ≤11.0% [≥61 to ≤97 mmol/mol]), had been prescribed insulin for ≥12 months, and had a C-peptide value <0.23 nmol/L and a BMI ≥18.5 kg/m^2. Full details of the patient population and study design have been described previously (9,10).

CGM Methods and Outcomes

Interstitial glucose levels were assessed in all patients in the DEPICT-1 and DEPICT-2 studies by using CGM with electrodes that measured an electrical signal produced by the glucose oxidase reaction. A CGM sensor was inserted subcutaneously at weeks −2, 10, and 22, and CGM data were collected between week −2 and day 1 (providing baseline values), between weeks 10 and 12, and between weeks 22 and 24. During those 2-week periods, CGM data were recorded approximately every 5 min using a Dexcom G4 Platinum system. Sensors were changed 7 days after insertion, in accordance with the manufacturer's instructions; patients were trained how to do this during the week −2 visit. Personnel at the site called patients to remind them to change the sensor 7 days after insertion and called again to confirm that the sensor had been reinserted correctly. An ad hoc visit was available if patients required further assistance. The patients, investigators, and sponsors were masked to the data.

We assessed the following CGM outcomes: time in range (percentage of glucose values within the target range of >3.9 to ≤10.0 mmol/L [>70 to ≤180 mg/dL]) over 24 h; mean amplitude of glucose excursion (MAGE), defined as the arithmetic mean of the differences between consecutive peaks and nadirs over 24 h (provided that the differences are greater than 1 SD of the mean glucose value); mean 24-h glucose value; mean interstitial glucose value, calculated with measurements from 0000 to 2400 h; postprandial glucose (PPG) value (obtained 1.5–2.5 h after the start of breakfast, lunch, and dinner at baseline and for the last 7 days of the CGM collection period); percentage of glucose values within the range indicating hypoglycemia (≤3.9 or ≤3.0 mmol/L [≤70 or ≤54 mg/dL]) over 24 h; percentage of nocturnal (0000–0559 h) glucose values within the range indicating hypoglycemia (≤3.9 mmol/L [≤70 mg/dL]).

Mean interstitial glucose values were measured from 0000 to 2400 h and nocturnal glucose values were measured from 0000 to 0559; otherwise a 24-h period started from the first available time point with a valid glucose reading from the CGM system. All outcomes were secondary or exploratory end points in the original DEPICT-1 and DEPICT-2 studies except mean interstitial glucose values measured from 0000 to 2400 h; percentage of glucose values within the range indicating hypoglycemia (≤3.0 mmol/L [≤54 mg/dL]) over 24 h; and percentage of nocturnal (0000–0559 h) glucose values within the range indicating hypoglycemia (≤3.9 mmol/L [≤70 mg/dL]).

Statistical Analysis

We pooled CGM data from the full analysis sets of both studies; these sets were defined as all randomized patients who received at least one dose of the study drug (the first 55 randomized patients were excluded from the full analysis set in DEPICT-1 because of a randomization error, which has been described previously [9]). Changes and percentage changes from baseline (measured using logarithmic transformation for the end point in the model) were analyzed by using a longitudinal repeated measures analysis. The model included the fixed categorical effects of study, treatment, week, randomization stratification factor (i.e., one term for each combination of all three stratification factors), and treatment-by-week interaction, as well as the continuous fixed covariates of baseline measurement and baseline measurement-by-week interaction. Because this is a post hoc analysis, we did not statistically compare the treatment groups and do not provide *P* values. All analyses were conducted in SAS software version 9.4.

RESULTS

Patients

In total, 1,591 patients were included in the analysis (dapagliflozin 5 mg, *n* = 530;

dapagliflozin 10 mg, *n* = 529; placebo, *n* = 532). Baseline characteristics were balanced between the treatment groups (Table 1).

Results for HbA_{1c} for both 24-week studies have been published previously; dapagliflozin led to larger reductions in HbA_{1c} from baseline than did placebo (mean difference [95% CI] in HbA_{1c} from baseline vs. placebo: DEPICT-1—dapagliflozin 5 mg, −0.42% [−0.56, −0.28] [$P < 0.0001$], and dapagliflozin 10 mg, −0.45% [−0.58, −0.31] [$P < 0.0001$] [9]; DEPICT-2—dapagliflozin 5 mg, −0.37% [−0.49, −0.26] [$P < 0.0001$], and dapagliflozin 10 mg, −0.42% [−0.53, −0.30] [$P < 0.0001$] [10]).

CGM Outcomes

Both doses of dapagliflozin increased the time in range (percentage of glucose values within the target range of >3.9 to ≤10.0 mmol/L [>70 to ≤180 mg/dL]) at 12 weeks, and this was maintained at 24 weeks, whereas time in range was reduced only slightly in the placebo group (Fig. 1*A* and Supplementary Table 1). The adjusted mean (SE) change from baseline in time in target range at week 12 was 8.22% (0.55) with dapagliflozin 5 mg, 8.94% (0.55) with dapagliflozin 10 mg, and −2.30% (0.56) with placebo; at week 24 it was 6.48% (0.60) with dapagliflozin 5 mg, 8.08% (0.60) with dapagliflozin 10 mg, and −2.59% (0.61) with placebo. The difference versus placebo (95% CI) was 10.53% (9.14, 11.91) with dapagliflozin 5 mg and 11.24% (9.86, 12.62) with dapagliflozin 10 mg at week 12, and 9.07% (7.55, 10.59) with dapagliflozin 5 mg and 10.67% (9.15, 12.20) with dapagliflozin 10 mg at week 24.

Dapagliflozin 5 and 10 mg reduced MAGE at 12 weeks, and those reductions were maintained at 24 weeks (Fig. 1*B*). The adjusted mean (SE) change in MAGE from baseline at week 12 was −0.86 (0.07) mmol/L (−15.57 [1.28] mg/dL) with dapagliflozin 5 mg, −0.82 (0.07) mmol/L (−14.83 [1.28] mg/dL) with dapagliflozin 10 mg, and −0.04 (0.07) mmol/L (−0.64 [1.29] mg/dL) with placebo. At week 24 these values were −0.69 (0.08) mmol/L (−12.48 [1.37] mg/dL) with dapagliflozin 5 mg, −0.72 (0.08) mmol/L (−13.06 [1.39] mg/dL) with dapagliflozin 10 mg, and 0.05 (0.08) mmol/L (0.88 [1.40] mg/dL) with placebo. The difference versus placebo (95% CI) was −0.83 mmol/L (−1.01, −0.65) (−14.93 mg/dL [−18.15, −11.71]) with dapagliflozin 5 mg and −0.79 mmol/L (−0.97, −0.61) (−14.19 mg/dL [−17.40, −10.98]) with dapagliflozin 10 mg at week 12; at week 24 these values were −0.74 mmol/L (−0.94, −0.55) (−13.36 mg/dL [−16.89, −9.83]) with dapagliflozin 5 mg and −0.77 mmol/L (−0.97, −0.58) (−13.94 mg/dL [−17.48, −10.40]) with dapagliflozin 10 mg.

Mean 24-h glucose values at 12 weeks were lower than those at baseline with dapagliflozin 5 and 10 mg but were higher with placebo (Table 2). Treatment with dapagliflozin 5 and 10 mg also led to reductions in mean interstitial glucose values over 24 h (0000–2400 h) at week 24, but these reductions were not observed with the placebo. In addition, dapagliflozin reduced mean PPG values at 12 and 24 weeks (Table 2).

We found no notable differences at either 12 or 24 weeks between dapagliflozin and placebo with regard to the percentage of glucose values within the range indicating hypoglycemia (≤3.9 mmol/L [≤70 mg/dL] or ≤3.0 mmol/L [≤54 mg/dL]) over 24 h (Table 2 and Supplementary Table 1). Also, we found no notable differences with

Table 1—Patient demographics and baseline characteristics

	Dapagliflozin 5 mg + insulin (*n* = 530)	Dapagliflozin 10 mg + insulin (*n* = 529)	Placebo + insulin (*n* = 532)
Age, years, mean (SD)	42.3 (13.7)	42.6 (13.4)	42.9 (13.6)
Male sex, *n* (%)	229 (43.2)	251 (47.4)	251 (47.2)
Race, *n* (%)			
Caucasian	458 (86.4)	466 (88.1)	457 (85.9)
Black/African American	9 (1.7)	14 (2.6)	4 (0.8)
Asian	57 (10.8)	44 (8.3)	60 (11.3)
Other	6 (1.1)	5 (0.9)	11 (2.1)
Body weight, kg, mean (SD)	79.83 (17.89)	81.05 (17.89)	81.56 (18.79)
Duration of type 1 diabetes, years, mean (SD)*	19.52 (11.90)	19.66 (11.48)	20.10 (11.97)
Total baseline insulin dose, mean (SD)†			
Dose, IU	60.12 (36.78)	59.05 (28.21)	59.79 (27.46)
Dose by weight, IU/kg	0.74 (0.41)	0.72 (0.27)	0.73 (0.24)
Method of insulin administration, *n* (%)			
MDI	341 (64.3)	343 (64.8)	345 (64.8)
CSII	189 (35.7)	186 (35.2)	187 (35.2)
Uses CGM, *n* (%)‡	173 (32.6)	171 (32.3)	171 (32.1)
HbA_{1c}, mean (SD)			
%	8.49 (0.70)	8.47 (0.67)	8.48 (0.66)
mmol/mol	69 (7.7)	69 (7.3)	69 (7.2)
HbA_{1c} at randomization, *n* (%)			
≥7.5 to <9.0% (≥58 to <75 mmol/mol)	405 (76.4)	408 (77.1)	405 (76.1)
≥9.0 to ≤10.5% (≥75 to <91 mmol/mol)	125 (23.6)	121 (22.9)	127 (23.9)

CSII, continuous subcutaneous insulin infusion; MDI, multiple daily injections. *Number of patients with no missing data at baseline: dapagliflozin 5 mg, *n* = 521; dapagliflozin 10 mg, *n* = 524; placebo, *n* = 521. †Number of patients with no missing data at baseline: dapagliflozin 5 mg, *n* = 530; dapagliflozin 10 mg, *n* = 528; placebo, *n* = 531. ‡Used an unmasked/personal device before enrollment in addition to the CGM device being introduced as part of the study.

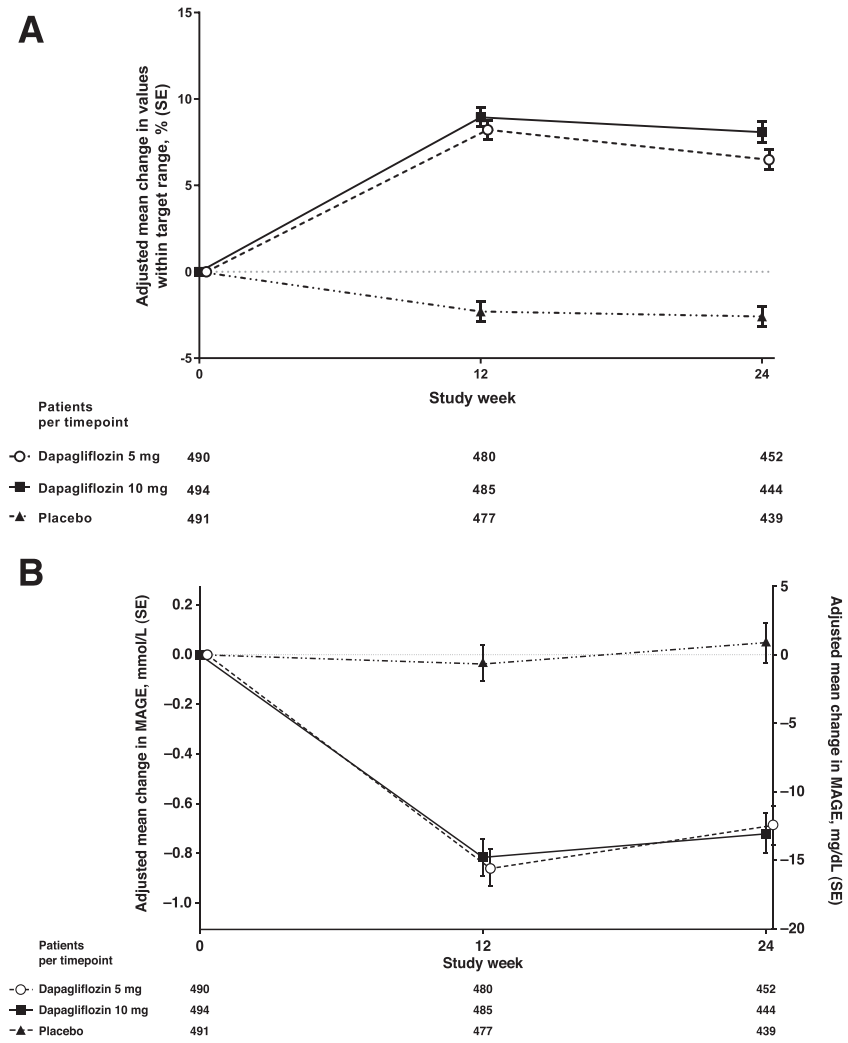

Figure 1—Change from baseline in percentage of glucose values within target range (>3.9 to ≤10.0 mmol/L [>70 to ≤180 mg/dL]) (*A*) and MAGE at weeks 12 and 24 (*B*). *A*: At baseline, the mean (SD) time spent in the target range was 43.38% (12.22%) with dapagliflozin 5 mg, 43.98% (12.32%) with dapagliflozin 10 mg, and 43.66% (12.64%) with placebo. At week 12, the mean (SD) time in target range was 53.54% (12.99%) with dapagliflozin 5 mg, 54.67% (12.75%) with dapagliflozin 10 mg, and 43.11% (13.08%) with placebo. At week 24, the mean (SD) time in target range was 51.69% (14.49%) with dapagliflozin 5 mg, 53.89% (13.26%) with dapagliflozin 10 mg, and 43.10% (13.97%) with placebo. *B*: At baseline, mean (SD) MAGE was 9.46 (1.70) mmol/L (171 [31] mg/dL) with dapagliflozin 5 mg, 9.49 (1.75) mmol/L (171 [32] mg/dL) with dapagliflozin 10 mg, and 9.38 (1.75) mmol/L (169 [31] mg/dL) with placebo. At week 12, the mean (SD) MAGE was 8.42 (1.84) mmol/L (152 [33] mg/dL) with dapagliflozin 5 mg, 8.45 (1.74) mmol/L (152 [31] mg/dL) with dapagliflozin 10 mg, and 9.20 (1.71) mmol/L (166 [31] mg/dL) with placebo. At week 24, the mean (SD) MAGE was 8.58 (1.90) mmol/L (155 [34] mg/dL) with dapagliflozin 5 mg, 8.58 (1.92) mmol/L (155 [35] mg/dL) with dapagliflozin 10 mg, and 9.26 (1.76) mmol/L (167 [32] mg/dL) with placebo.

dapagliflozin relative to placebo in the percentage of nocturnal (0000–0559 h) glucose values within the range indicating hypoglycemia (≤3.9 mmol/L [≤70 mg/dL]) at 12 or 24 weeks (Table 2).

CONCLUSIONS

Although HbA_{1c} is a valuable measure of glycemic control in diabetes—reflecting overall glucose exposure over time—it does not assess glycemic variability (12). In contrast, CGM enables detection throughout the day of important glycemic variables that contribute to clinical outcomes. The Advanced Technologies & Treatments for Diabetes consensus recommends that CGM be used to assess glycemic variability via a range of measurements such as MAGE, SD of the mean glucose value, coefficient of variation (defined as the SD divided by the mean), and time spent in range (12).

This analysis of pooled data from the DEPICT-1 and DEPICT-2 studies uses masked CGM data from 1,591 patients with inadequately controlled type 1 diabetes to explore the effects of dapagliflozin 5 and 10 mg, as an adjunct to adjustable insulin over 24 weeks, on parameters of glycemic control. Dapagliflozin improved glycemic variability and metabolic control, including time spent in range (interstitial glucose >3.9 to ≤10.0 mmol/L [>70 to ≤180 mg/dL]), MAGE, PPG, and mean interstitial glucose values over 24 h; these improvements are consistent with significant reductions in HbA_{1c} that have been observed previously (9,10). Reductions in 24-h glucose values with dapagliflozin seemed to be particularly prominent during the nocturnal hours (~0000–0800 h), potentially because of the glucose-dependent effect of dapagliflozin in stabilizing the glucose level overnight (8), and because of reductions in PPG with dapagliflozin after the evening meal (13).

Improvements in glycemic variability and metabolic control occurred at 12 and 24 weeks but not at the expense of increasing the time spent in the range indicating hypoglycemia compared with placebo, as measured by the percentage of glucose values ≤3.9 or ≤3.0 mmol/L (≤70 or ≤54 mg/dL) over 24 h and the percentage of nocturnal glucose values ≤3.9 mmol/L (≤70 mg/dL). The baseline percentage of readings in the range indicating hypoglycemia were low, however, leaving limited scope for measurable potential improvement. These findings are in line with those of previous dapagliflozin studies that reported no increase in the number of clinical hypoglycemia events (14). That glycemic control was improved in participants in the DEPICT-1 and DEPICT-2 studies without an increase in the number of hypoglycemia or severe hypoglycemia events (9,10) is in contrast with effects of conventional insulin treatment and is likely of great importance to patients with type 1 diabetes in terms of quality of life and psychosocial function (15). Furthermore, reducing glycemic variability could improve treatment satisfaction in people with type 1 diabetes (7), which in turn is associated with better treatment adherence (16) and may improve diabetes self-management and clinical outcomes (17). In addition to improving glycemic control and treatment satisfaction, less glycemic variability may be able to reduce the occurrence of microvascular and macrovascular

Table 2—Change from baseline in CGM parameters at weeks 12 and 24

CGM variables per treatment arm (*n*)	Baseline value, mean (SD)	Week 12		Week 24	
		Adjusted change from baseline, mean (SE)	Difference vs. placebo (95% CI)	Adjusted change from baseline, mean (SE)	Difference vs. placebo (95% CI)
24-h glucose, mmol/L					
Dapagliflozin 5 mg (*n* = 490)	10.71 (1.60)	−0.76 (0.06)	−1.12 (−1.27, −0.96)	−0.47 (0.07)	−0.86 (−1.04, −0.67)
Dapagliflozin 10 mg (*n* = 494)	10.60 (1.56)	−0.80 (0.06)	−1.16 (−1.32, −1.01)	−0.66 (0.07)	−1.05 (−1.23, −0.86)
Placebo (*n* = 491)	10.64 (1.61)	0.36 (0.06)	—	0.39 (0.07)	—
24-h glucose, mg/dL					
Dapagliflozin 5 mg (*n* = 490)	193.00 (28.78)	−13.63 (1.15)	−20.12 (−22.96, −17.27)	−8.40 (1.30)	−15.48 (−18.82, −12.13)
Dapagliflozin 10 mg (*n* = 494)	191.00 (28.11)	−14.46 (1.15)	−20.95 (−23.79, −18.11)	−11.82 (1.32)	−18.90 (−22.25, −15.54)
Placebo (*n* = 491)	191.64 (29.04)	6.49 (1.16)	—	7.07 (1.33)	—
PPG, mmol/L*					
Dapagliflozin 5 mg (*n* = 449)	11.07 (2.25)	−0.42 (0.10)	−0.90 (−1.15, −0.65)	−0.05 (0.11)	−0.47 (−0.76, −0.19)
Dapagliflozin 10 mg (*n* = 452)	10.91 (2.14)	−0.37 (0.10)	−0.85 (−1.10, −0.60)	−0.28 (0.11)	−0.71 (−1.00, −0.42)
Placebo (*n* = 442)	10.95 (2.35)	0.48 (0.10)	—	0.43 (0.11)	—
PPG, mg/dL*					
Dapagliflozin 5 mg (*n* = 449)	199.42 (40.51)	−7.54 (1.79)	−16.17 (−20.67, −11.67)	−0.85 (1.99)	−8.55 (−13.70, −3.41)
Dapagliflozin 10 mg (*n* = 452)	196.61 (38.57)	−6.62 (1.79)	−15.25 (−19.74, −10.77)	−5.05 (2.02)	−12.76 (−17.93, −7.58)
Placebo (*n* = 442)	197.35 (42.32)	8.63 (1.81)	—	7.70 (2.03)	—
Glucose ≤3.9 mmol/L (≤70 mg/dL) over 24 h, %					
Dapagliflozin 5 mg (*n* = 490)	4.96 (4.64)	0.00 (0.21)	0.70 (0.17, 1.24)	−0.43 (0.21)	0.06 (−0.47, 0.59)
Dapagliflozin 10 mg (*n* = 494)	5.30 (4.90)	−0.02 (0.21)	0.68 (0.14, 1.21)	−0.33 (0.21)	0.16 (−0.38, 0.69)
Placebo (*n* = 491)	5.14 (5.56)	−0.70 (0.21)	—	−0.49 (0.21)	—
Glucose ≤3.0 mmol/L (≤54 mg/dL) over 24 h, %					
Dapagliflozin 5 mg (*n* = 490)	2.22 (2.87)	−0.05 (0.14)	0.22 (−0.12, 0.56)	−0.32 (0.13)	−0.14 (−0.47, 0.19)
Dapagliflozin 10 mg (*n* = 494)	2.34 (3.13)	−0.13 (0.14)	0.14 (−0.20, 0.49)	−0.34 (0.13)	−0.16 (−0.48, 0.17)
Placebo (*n* = 491)	2.28 (3.82)	−0.27 (0.14)	—	−0.19 (0.13)	—
Nocturnal glucose ≤3.9 mmol/L (≤70 mg/dL), %†					
Dapagliflozin 5 mg (*n* = 490)	5.94 (7.64)	0.16 (0.36)	1.12 (0.22, 2.02)	−0.38 (0.36)	−0.15 (−1.07, 0.78)
Dapagliflozin 10 mg (*n* = 495)	5.52 (7.22)	0.10 (0.36)	1.06 (0.16, 1.96)	−0.18 (0.37)	0.06 (−0.87, 0.99)
Placebo (*n* = 491)	5.83 (7.74)	−0.96 (0.36)	—	−0.24 (0.37)	—

The *n* values for each treatment arm represent the numbers of patients with no missing values at baseline and at least one value after baseline. *Values obtained 1.5–2.5 h after the start of breakfast, lunch, and dinner for the last 7 days of CGM collection. †0000–0559 h.

complications of type 1 diabetes (5,6). Evidence suggests that measures of glycemic variability might be associated with the risk for complications of type 1 or type 2 diabetes (18–23). A recent analysis of data from the Diabetes Control and Complications Trial (DCCT) showed that time spent in range (3.9–10.0 mmol/L [70–180 mg/dL]) was strongly associated with the risk of developing retinopathy and microalbuminuria; this parallels the HbA_{1c} findings reported in the DEPICT-1 and DEPICT-2 studies and indicates that time spent in range may have clinical application as an outcome measure in clinical trials (24).

Because of its glucose-dependent, insulin-independent mechanism of action (8), dapagliflozin acts to increase urinary glucose excretion without conferring a risk of hypoglycemia, thereby reducing the extent of fluctuations in blood glucose level. As such, the differences in CGM assessments we observed between dapagliflozin and placebo may be partly related to lower insulin doses. Indeed, whereas dapagliflozin has a low intrinsic risk of hypoglycemia because its efficacy varies with glycemic load, insulin is similarly effective across a wide range of glucose values and has an intrinsic risk of inducing hypoglycemia. As seen in the DCCT, improved glycemic control using insulin alone, as assessed on the basis of HbA_{1c}, was directly correlated with an increased risk of hypoglycemia (25). Therefore, lower insulin doses through the use of dapagliflozin as an adjuvant treatment allow for improved glycemic control without increasing the risk of hypoglycemia, as demonstrated in the DEPICT-1 and DEPICT-2 studies (9,10). Insulin dose reductions do, however, seem to attenuate the glucose-lowering effect of dapagliflozin and could potentially increase the risk of DKA. Indeed, an imbalance was observed between the number of DKA cases in the dapagliflozin groups and the placebo group of the DEPICT-1 and DEPICT-2 studies (9–11). The DKA events that occurred during these studies were resolved with conventional treatment. This higher risk of DKA may be at least partially mitigated by avoiding excessive insulin dose reductions (>20%) (26). This potential higher risk of DKA will require careful monitoring when using dapagliflozin to treat type 1 diabetes in future studies and in real-world use. This has been previously discussed in detail (9–11).

The improvements in glycemic variability observed with dapagliflozin in our analysis were comparable with those seen in previous studies of SGLT2 and SGLT1/SGLT2 inhibitors in patients with type 1 diabetes (27–31). However, such

studies have used shorter treatment periods (4–18 weeks), have used smaller samples (33–391 patients), and have collected far less CGM data. As such, to our knowledge, the analysis reported here, which was conducted with data from 1,591 patients, represents the largest cohort of patients with type 1 diabetes treated with an SGLT2 inhibitor as an adjunct to adjustable insulin in whom CGM outcomes have been assessed. Our CGM data are also comparable to glucose outcomes achieved with a hybrid closed-loop system, which uses automated insulin delivery technology in response to CGM (32).

The analysis reported here is post hoc and, as such, we did not calculate *P* values. Furthermore, a period of 24 weeks was not long enough to assess the long-term effects of dapagliflozin on glycemic variability. Pooled CGM data (33) from two studies of the SGLT1 and SGLT2 inhibitor sotagliflozin (34,35) showed broadly similar results. While the sotagliflozin CGM data were obtained from fewer patients and lacked power for some analyses, the studies have a key difference: in DEPICT-1 and DEPICT-2, except for a suggested limit on insulin dose reductions of up to 20%, doses were adjusted at the discretion of the investigator and patient, whereas in the sotagliflozin studies, insulin doses were adjusted under guidance up to week 24, although the exact details about insulin dose adjustments are unclear.

Finally, although a pooled analysis is presented here, it is striking how consistent the CGM data seem to be between the DEPICT-1 (9) and DEPICT-2 (10) studies. This highlights the consistency of the effect of dapagliflozin on CGM variables.

In conclusion, treatment with dapagliflozin over 24 weeks reduced mean glucose and glycemic variability, improving time in range without increasing the proportion of readings within the range indicating hypoglycemia. The reduced variability reported here suggests that treatment with dapagliflozin along with adjustable insulin may improve treatment adherence and reduce the risk of complications in people with type 1 diabetes.

Acknowledgments. The authors thank the patients, their families, and all investigators involved in the DEPICT-1 and DEPICT-2 24-week studies. Medical writing support was provided by Helen Brereton, inScience Communications, Springer Healthcare, and was funded by AstraZeneca.

Duality of Interest. This analysis was supported by AstraZeneca. C.M. serves or has served on advisory panels for Novo Nordisk, Sanofi, Merck Sharp & Dohme Ltd., Eli Lilly and Company, Novartis, Bristol-Myers Squibb, AstraZeneca, Pfizer, Janssen Pharmaceuticals, Boehringer Ingelheim, Hanmi Pharmaceuticals, Roche Diagnostics, Medtronic, MannKind, Intrexon, and UCB; has received research support (to Katholieke Universiteit Leuven) from Novo Nordisk, Sanofi, Merck Sharp & Dohme Ltd., Eli Lilly and Company, Roche Diagnostics, Abbott, Intrexon and Novartis; and serves or has served on speakers bureaus for Novo Nordisk, Sanofi, Merck Sharp & Dohme Ltd., Eli Lilly and Company, Boehringer Ingelheim, AstraZeneca, and Novartis. P.D. serves on the advisory boards of and has received research grants from AstraZeneca, Novo Nordisk, Sanofi, Boehringer Ingelheim, and AbbVie Inc. and serves on the advisory board of Merck Intarcia. M.P.'s institute has received grants/research support from Medtronic, Novo Nordisk, Roche, Eli Lilly and Company, Merck, Sanofi, Bristol-Myers Squibb, Kamada, AstraZeneca, and Lexicon. M.P. has received honoraria or consultation fees from Sanofi, Medtronic, Novo Nordisk, and Eli Lilly and Company; has participated in advisory boards for Sanofi, Medtronic, AstraZeneca, and Eli Lilly and Company; and is a shareholder in DreaMed Diabetes Ltd. M.L. has received research grants from AstraZeneca, Dexcom, Novo Nordisk, and Pfizer; has been a consultant for or received honoraria from AstraZeneca, Eli Lilly and Company, Medtronic, Novo Nordisk, and Rubin Medical; and has participated in advisory boards for Merck Sharp & Dohme and Novo Nordisk. L.H. is an employee of MedImmune. F.T. is an employee of AstraZeneca. J.X. and A.M.L. are employees and shareholders of AstraZeneca. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. C.M., P.D., M.P., T.O., M.L., L.H., F.T., J.X., and A.M.L. conceived and designed the study; analyzed and interpreted the study data; and wrote the manuscript and critical revised it for intellectual content. C.M. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. Parts of this study were presented in poster form at the 78th Scientific Sessions of the American Diabetes Association, Orlando, FL, 22–26 June 2018.

References

1. The Diabetes Control and Complications Trial Research Group. Hypoglycemia in the Diabetes Control and Complications Trial. Diabetes 1997;46:271–286
2. Cryer PE. Hypoglycaemia: the limiting factor in the glycaemic management of type I and type II diabetes. Diabetologia 2002;45:937–948
3. Weinstock RS, Xing D, Maahs DM, et al.; T1D Exchange Clinic Network. Severe hypoglycemia and diabetic ketoacidosis in adults with type 1 diabetes: results from the T1D Exchange clinic registry. J Clin Endocrinol Metab 2013;98:3411–3419
4. Cryer PE. Severe hypoglycemia predicts mortality in diabetes. Diabetes Care 2012;35:1814–1816
5. Suh S, Kim JH. Glycemic variability: how do we measure it and why is it important? Diabetes Metab J 2015;39:273–282
6. Ceriello A, Kilpatrick ES. Glycemic variability: both sides of the story. Diabetes Care 2013;36(Suppl. 2):S272–S275
7. Ayano-Takahara S, Ikeda K, Fujimoto S, et al. Glycemic variability is associated with quality of life and treatment satisfaction in patients with type 1 diabetes. Diabetes Care 2015;38:e1–e2
8. Chao EC. SGLT-2 inhibitors: a new mechanism for glycemic control. Clin Diabetes 2014;32:4–11
9. Dandona P, Mathieu C, Phillip M, et al.; DEPICT-1 Investigators. Efficacy and Safety of Dapagliflozin in Patients With Inadequately Controlled Type 1 Diabetes (DEPICT-1): 24 week results from a multicentre, double-blind, phase 3, randomised controlled trial. Lancet Diabetes Endocrinol 2017;5:864–876
10. Mathieu C, Dandona P, Gillard P, et al.; DEPICT-2 Investigators. Efficacy and Safety of Dapagliflozin in Patients With Inadequately Controlled Type 1 Diabetes (the DEPICT-2 study): 24-week results from a randomized controlled trial. Diabetes Care 2018;41:1938–1946
11. Dandona P, Mathieu C, Phillip M, et al.; DEPICT-1 Investigators. Efficacy and Safety of Dapagliflozin in Patients With Inadequately Controlled Type 1 Diabetes: the DEPICT-1 52-week study. Diabetes Care 2018;41:2552–2559
12. Danne T, Nimri R, Battelino T, et al. International consensus on use of continuous glucose monitoring. Diabetes Care 2017;40:1631–1640
13. 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
14. Anderson SL. Dapagliflozin efficacy and safety: a perspective review. Ther Adv Drug Saf 2014;5:242–254
15. Gonder-Frederick LA, Clarke WL, Cox DJ. The emotional, social, and behavioral implications of insulin-induced hypoglycemia. Semin Clin Neuropsychiatry 1997;2:57–65
16. Barbosa CD, Balp MM, Kulich K, Germain N, Rofail D. A literature review to explore the link between treatment satisfaction and adherence, compliance, and persistence. Patient Prefer Adherence 2012;6:39–48
17. Nam S, Chesla C, Stotts NA, Kroon L, Janson SL. Barriers to diabetes management: patient and provider factors. Diabetes Res Clin Pract 2011;93:1–9
18. Lu J, Ma X, Zhou J, et al. Association of time in range, as assessed by continuous glucose monitoring, with diabetic retinopathy in type 2 diabetes. Diabetes Care 2018;41:2370–2376
19. Brownlee M, Hirsch IB. Glycemic variability: a hemoglobin A1c-independent risk factor for diabetic complications. JAMA 2006;295:1707–1708
20. Sartore G, Chilelli NC, Burlina S, Lapolla A. Association between glucose variability as assessed by continuous glucose monitoring (CGM) and diabetic retinopathy in type 1 and type 2 diabetes. Acta Diabetol 2013;50:437–442
21. Su G, Mi S, Tao H, et al. Association of glycemic variability and the presence and severity of

coronary artery disease in patients with type 2 diabetes. Cardiovasc Diabetol 2011;10:19
22. Matsutani D, Sakamoto M, Iuchi H, et al. Glycemic variability in continuous glucose monitoring is inversely associated with baroreflex sensitivity in type 2 diabetes: a preliminary report. Cardiovasc Diabetol 2018;17:36
23. Gorst C, Kwok CS, Aslam S, et al. Long-term glycemic variability and risk of adverse outcomes: a systematic review and meta-analysis. Diabetes Care 2015;38:2354–2369
24. Beck RW, Bergenstal RM, Riddlesworth TD, et al. Validation of time in range as an outcome measure for diabetes clinical trials. Diabetes Care 2019;42:400–405
25. Nathan DM, Genuth S, Lachin J, et al.; Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977–986
26. Henry RR, Dandona P, Pettus J, Mudaliar S, Xu J, Hansen L. Dapagliflozin in patients with type 1 diabetes: a post hoc analysis of the effect of insulin dose adjustments on 24-hour continuously monitored mean glucose and fasting β-hydroxybutyrate levels in a phase IIa pilot study. Diabetes Obes Metab 2017;19:814–821
27. Henry RR, Rosenstock J, Edelman S, et al. Exploring the potential of the SGLT2 inhibitor dapagliflozin in type 1 diabetes: a randomized, double-blind, placebo-controlled pilot study. Diabetes Care 2015;38:412–419
28. Rodbard HW, Peters AL, Slee A, Cao A, Traina SB, Alba M. The effect of canagliflozin, a sodium glucose cotransporter 2 inhibitor, on glycemic end points assessed by continuous glucose monitoring and patient-reported outcomes among people with type 1 diabetes. Diabetes Care 2017;40:171–180
29. Famulla S, Pieber TR, Eilbracht J, et al. Glucose exposure and variability with empagliflozin as adjunct to insulin in patients with type 1 diabetes: continuous glucose monitoring data from a 4-week, randomized, placebo-controlled trial (EASE-1). Diabetes Technol Ther 2017;19:49–60
30. Perkins BA, Cherney DZ, Soleymanlou N, et al. Diurnal glycemic patterns during an 8-week open-label proof-of-concept trial of empagliflozin in type 1 diabetes. PLoS One 2015;10:e0141085
31. Sands AT, Zambrowicz BP, Rosenstock J, et al. Sotagliflozin, a dual SGLT1 and SGLT2 inhibitor, as adjunct therapy to insulin in type 1 diabetes. Diabetes Care 2015;38:1181–1188
32. Trevitt S, Simpson S, Wood A. Artificial pancreas device systems for the closed-loop control of type 1 diabetes: what systems are in development? J Diabetes Sci Technol 2016;10:714–723
33. Danne T, Cariou B, Buse JB, et al. Increased time-in-range with sotagliflozin as adjunct therapy to insulin in adults with type 1 diabetes as demonstrated by 24-week continuous glucose monitoring (inTandem1, inTandem2). Diabetes 2018;67(Suppl. 1):1170-P
34. Buse JB, Garg SK, Rosenstock J, et al. Sotagliflozin in combination with optimized insulin therapy in adults with type 1 diabetes: the North American inTandem1 study. Diabetes Care 2018;41:1970–1980
35. Danne T, Cariou B, Banks P, et al. HbA_{1c} and hypoglycemia reductions at 24 and 52 weeks with sotagliflozin in combination with insulin in adults with type 1 diabetes: the European inTandem2 study. Diabetes Care 2018;41:1981–1990