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ORIGINAL ARTICLE

Dapagliflozin treatment in patients with different stages of type 2 diabetes mellitus: effects on glycaemic control and body weight

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Aim: Dapagliflozin is a stable, competitive, reversible, and highly selective inhibitor of sodium-glucose co-transporter 2, the major transporter responsible for renal glucose reabsorption. With an insulin-independent mechanism of action, dapagliflozin is currently being developed for the treatment of type 2 diabetes mellitus (T2DM). This work aims to compare the efficacy of dapagliflozin, as measured by the change in hemoglobin A1c concentration (A1c) and body weight, and to determine the pharmacodynamic effects of dapagliflozin, as measured by urinary glucose excretion in early-stage and late-stage T2DM patient populations.

Methods: A total of 151 early-stage patients and 58 late-stage patients with T2DM randomly assigned 10 or 20 mg once daily (QD) dapagliflozin treatment or placebo for 12 weeks from two phase 2 studies were included in the analysis. A1c, body weight, and urinary glucose were compared between the two patient populations.

Results: Compared with the early-stage population, patients in the late-stage population had a longer duration of T2DM and higher baseline levels of A1c, body weight, fasting plasma glucose, and urinary glucose excretion. After 12 weeks of dapagliflozin treatment, A1c reduction, weight loss, and increased urinary glucose excretion from baseline were observed in both populations. Baseline A1c level impacted the A1c reduction after dapagliflozin treatment with a comparable effect in patients with early and late stage disease. Late-stage patients had greater reduction in body weight. There was no statistically significant difference in the amount of urinary glucose excretion between the early-stage and late-stage patients.

Conclusions: Dapagliflozin treatment at 10 and 20 mg QD for 12 weeks resulted in significant improvement in glycaemic control and body weight reduction in both early-stage and late-stage patients with T2DM. The findings suggest that dapagliflozin could be a promising treatment option for a wide range of patients with T2DM.

Keywords: A1c, body weight, dapagliflozin, sodium-glucose co-transporter 2, type 2 diabetes mellitus

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Introduction

Type 2 diabetes mellitus (T2DM), the most common form of diabetes, is a progressive disease caused by insulin resistance and a loss of pancreatic β-cell function [1]. The prevalence of T2DM has increased to epidemic proportions over the last 20 years [2]. Despite the wide selection of available T2DM therapies, a substantial proportion of patients with T2DM do not achieve and maintain goals for glycaemic control and remain at risk for chronic complications [3,4]. The rising prevalence of T2DM and the suboptimal glycaemic control underscores the urgent unmet need for medications that are efficacious in treating T2DM in a wide array of patient types.

Dapagliflozin (BMS-512148) is a member of a class of oral inhibitors of sodium-glucose co-transporter 2 (SGLT2), a protein expressed almost exclusively in the kidney, designed for the treatment of T2DM [5]. By inhibiting the renal reabsorption of glucose through SGLT2 and promoting urinary glucose excretion, dapagliflozin lowers plasma glucose in an insulin-independent manner. Dapagliflozin, at doses up to 100 mg for 2 weeks, was shown to dose-dependently increase urinary glucose excretion and to improve fasting serum glucose in patients with T2DM [6,7]. Because the pharmacologic mechanism of dapagliflozin is insulin-independent, it is reasonable to hypothesize that the efficacy of dapagliflozin is independent of the loss of pancreatic β-cell function or the level of insulin resistance. Therefore, dapagliflozin may be equally effective regardless of the stage of diabetes or concomitant antihyperglycaemic therapy.

This study aims to compare the efficacy and pharmacodynamic effect of dapagliflozin in two T2DM patient populations that represent the progressive nature of diabetes: early-stage and late-stage patients. 'Early-stage' refers to patients with T2DM who are not receiving pharmacotherapy to treat their hyperglycaemia. This population represents the early stages of clinical diabetes, and the treatment effects of dapagliflozin in this population reflect the potential of this drug as monotherapy.

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'Late-stage' refers to patients on high doses of insulin plus oral insulin sensitizers. This population represents treatment resistance after years or decades of disease progression has ensued. The treatment effects of dapagliflozin in this population reflect its potential to combine with multiple insulin-based therapies because of the insulin-independent mechanism of SGLT2 inhibition.

In two separate phase 2 studies, dapagliflozin has been shown to promote urinary glucose excretion and to decrease hyperglycaemia and body weight in early-stage and late-stage patient populations [8,9]. Acknowledging the differences in disease status and background medications between the different T2DM populations, this analysis used data from the two studies, and compared the change from baseline in A1c, body weight, and urinary glucose after 12 weeks of treatment with dapagliflozin 10 and 20 mg QD.

Methods

Patients

The number of patients included in the analysis and their baseline characteristics are summarized in Table 1. Descriptions of the studies from which these patients were enrolled are provided below.

Data for early-stage patients with T2DM were obtained from study MB102008, the safety and efficacy results of which were described by List et al. [8]. This study was a double-blinded, placebo-controlled, randomized clinical trial to evaluate the safety and efficacy of dapagliflozin as monotherapy in patients with T2DM who had inadequate glycaemic control, defined as $A1c \geq 7.0\%$ (9.57 mmol/l) and $\leq 10\%$ (15.51 mmol/l), with diet and exercise alone, and were treatment naive, defined as patients with less than 30 days of prior treatment with antihyperglycaemic medication and less than 3 continuous days and 7 total days of antihyperglycaemic treatment during the prior 30 days. As most of these patients had less than 1 year of T2DM history and minimal previous treatment, their T2DM progression is still in early stage, and the term 'early-stage' was used to describe the group. A total of 266 of early-stage patients were randomly assigned to dapagliflozin 2.5, 5, 10, 20, or 50 mg QD, or to placebo, for 12 weeks. Daily dapagliflozin was generally safe and well tolerated with no major difference in adverse events across treatment groups. The hypoglycaemia experience supports the potential for dapagliflozin to achieve meaningful glycaemic efficacy with relatively low hypoglycaemic risk. For comparisons with the late-stage population, only the 151 patients assigned to dose groups that matched the late stage dose groups—placebo, 10 or 20 mg dapagliflozin—were included in the analysis.

Data for late-stage patients were obtained from study MB102009, the safety and efficacy results of which were described by Wilding et al. [9]. This study was a placebo-controlled, double-blind, randomized clinical trial designed to evaluate the safety and efficacy of dapagliflozin in patients with T2DM who had inadequate glycaemic control, defined as $A1c \geq 7.5\%$ (10.56 mmol/l) and $\leq 10\%$ (15.51 mmol/l), despite aggressive treatment with insulin and insulin-sensitizing, defined as taking stable doses of insulin sensitizer therapy for at least 6 weeks (metformin daily dose >1000 mg, and/or pilglitazone daily dose >30 mg, or rosiglitazone daily dose of 4 mg) in addition to large doses of subcutaneous insulin (daily dose equivalent to ≥50 units of U100 insulin for at least 12 weeks). As most of these patients had more than 10 years of T2DM history and failed to achieve adequate glycaemic control even under multiple treatment intervention, their T2DM progression was in the late stage, hence the term 'late-stage' was used to describe the group. A total of 58 late-stage patients randomly assigned to 10 or 20 mg dapagliflozin QD or to placebo for 12 weeks were included in the analysis. To minimize the possibility of hypoglycaemia in these insulin-treated patients, the total daily dose of insulin was reduced to 50% of the baseline dose on the day of randomization. Generally dapagliflozin in combination with insulin and insulin sensitizer therapy was safe in this study.

Table 1. Baseline characteristics of early-stage and late-stage patients with T2DM.

	Early-stage (MB102008)		Late-stage (MB102009)	
Baseline characteristics	Dapagliflozin-treated	Placebo	Dapagliflozin-treated	Placebo
Number of subjects	102 [10-mg group, n = 45; 20-mg group, n = 57]	49	44 [10-mg group, n = 19; 20-mg group, n = 25]	14
Age (year)	55.0 [41.0, 71.0]	52.0 [34.4, 70.6]	57.0 [38.0, 71.6]	60.0 [49.6, 69.0]
Gender	Male: 54 [53] Female: 48 [47]	Male: 27 [55] Female: 22 [45]	Male: 22 [50] Female: 24 [50]	Male: 13 [71] Female: 4 [29]
eGFR (ml/min)*	79.0 [55.4, 117]	79.8 [55.1, 126]	76.6 [51.6, 122]	80.4 [58.3, 113]
Body weight (kg)	86.6 [60.6, 115]	89.8 [59.2, 122]	104 [82.0, 120]	95.7 [77.3, 113]
Duration of T2DM (year)	0.990 [0.01, 8.44]	0.440 [0.04, 6.97]	11.1† [6.61, 25.3]	19.3† [12.0, 24.0]
Urinary glucose (g/24 h)	0.400 [0, 68.2]	0.300 [0, 70.6]	2.60 [0.100, 16.5]	2.55 [0.165, 18.2]
FPG (mmol/l)	7.72 [6.00, 12.44]	8.00 [5.54, 12.17]	9.00 [5.31, 14.33]	8.67 [6.00, 13.67]
A1c (%)	7.60 [6.80, 9.89]	7.60 [6.70, 9.12]	8.35 [7.50, 9.47]	8.00 [7.57, 9.61]

Summary for continuous variables are presented as median [5th–95th percentile]; for categorical variables are presented as number [percentage]. A1c, hemoglobin A1c; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; T2DM, type 2 diabetes mellitus.
*eGFR was calculated by applying Cockcroft–Gault formula. Ideal body weight was used as body mass descriptor.
†Eight of dapagliflozin-treated subjects and three placebo subjects had information for duration of T2DM available.

Data

In both studies, A1c level and body weight were measured at baseline and at weeks 4, 6, 8, 10, and 12. Urinary glucose was measured at baseline and at weeks 6 and 12. Evaluable A1c, body weight, and urinary glucose measurements were retained in the analysis, with no imputation for missing records.

A1c, weight, and urinary glucose comparison

The comparison of changes in A1c, body weight, and urinary glucose between the early-stage and late-stage populations was carried out in three steps: (i) the change in A1c, body weight, and urinary glucose from baseline to the end of week 12 were compared by treatment assignment using Wilcoxon Rank Sum test; (2) the effect of baseline and treatment group on changes in A1c, body weight, and urinary glucose during the 12-week treatment period was evaluated and graphically presented. The 90% confidence interval (CI) of the relationship was assessed by 500 bootstrap iterations, and the statistical significance of the relationship was assessed by Spearman correlation and ANCOVA test. (iii) The identified significant relationships between patient baseline characteristics and the change in A1c, body weight, and urinary glucose were quantified using linear regression.

S-Plus® (Version 6.2.1 for Windows, Insightful, Seattle, WA, USA) was used for statistical analysis and graphics. Significance was defined as $p < 0.05$.

Results

Patient Characteristics

A total of 151 early-stage patients with T2DM (102 assigned to dapagliflozin; 49 assigned to placebo) from study MB102008 and 58 late-stage patients with T2DM (44 assigned to dapagliflozin; 14 assigned to placebo) from study MB102009 were included in the analysis. The patient baseline characteristics are shown in Table 1. The patient populations were similar with regard to age, estimated glomerular filtration rate, and the relative ratio of males and females. Compared with the early-stage population, patients in the late-stage population had a longer duration of T2DM and higher baseline levels of A1c, body weight, fasting plasma glucose, urinary glucose excretion, and background therapy.

A1c Comparison

At week 12, dapagliflozin-treated patients in the early-stage and the late-stage patient populations achieved reductions in A1c from baseline (Table 2). The change in A1c from baseline was not significantly different in patients assigned to the same treatment across early-stage and late-stage populations (Wilcoxon Rank Sum test). The patients assigned to placebo in the both populations had similar A1c responses.

Next, the A1c reductions during the 12-week treatment period between the early-stage and late-stage patients were also compared. Figure 1 shows that during the first 6 weeks, dapagliflozin-treated patients in the two populations have an almost identical time course in A1c reduction. The trend was slightly different from week 6 to week 12, but the deviation between the two populations was generally within ±0.2%.

Table 2. Change in A1c at week 12 in early-stage and late-stage patients.

Dose (mg)	Early-stage median [5th–95th percentile] (%)	Late-stage median [5th–95th percentile] (%)	p-Value
Placebo	−0.20 [−1.68, 2.48]	0 [−1.21, 1.14]	0.3
10	−0.70 [−3.28, 1.02]	−0.60 [−1.71, 0.51]	0.2
20	−0.50 [−2.18, 0.78]	−0.80 [−2.74, 0.94]	0.08

It has been known that the A1c treatment response in patients with T2DM to any antihyperglycaemic therapy is closely related to the patients' baseline A1c level. The relationship between baseline A1c and the change in A1c at week 12 in the early-stage and late-stage patients was therefore quantified. As shown in Figure 2, within the range of baseline A1c levels, the magnitude

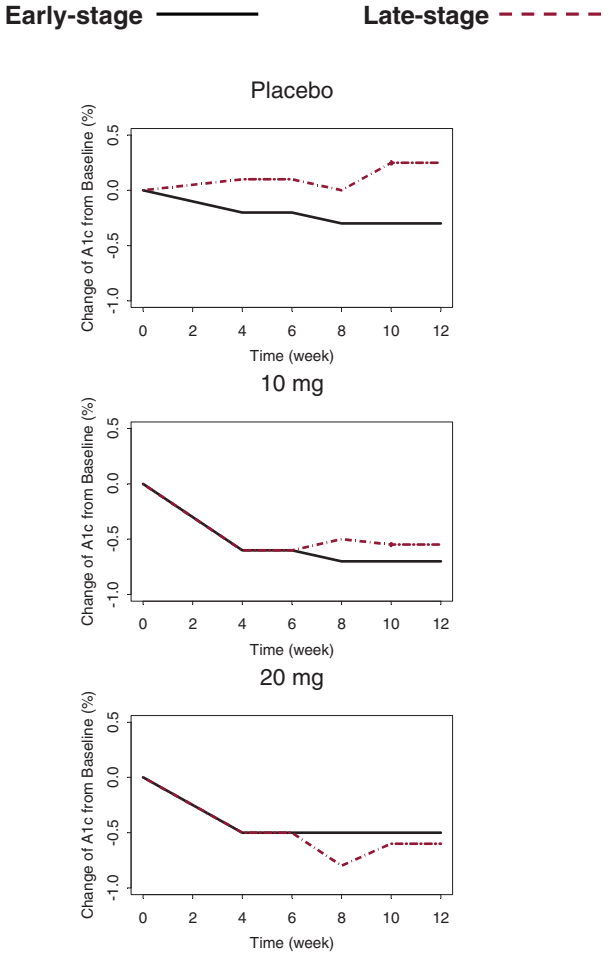

Figure 1. Change in A1c from baseline up to week 12 in early-stage and late-stage patients assigned to placebo, 10 and 20 mg once daily dapagliflozin. Solid and dashed lines are locally smoothed lines depicting the change of A1c over 12 weeks in early-stage and late-stage patients.

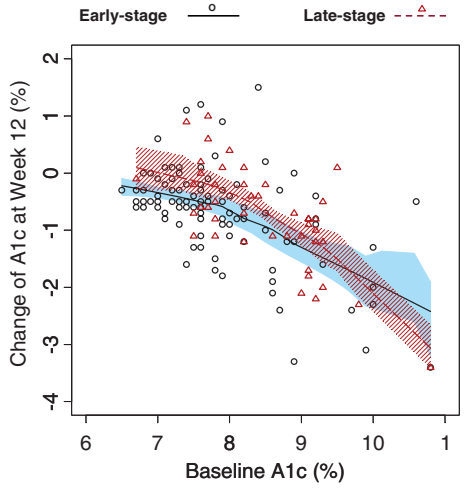

Figure 2. Change in A1c from baseline at week 12 versus baseline A1c in early-stage and late-stage patients assigned to 10 and 20 mg once daily dapagliflozin. Circles and triangles denote the observed change of A1c from baseline at week 12 for early-stage and late-stage patients, respectively. The straight line and dashed line are locally smoothed lines depicting the trend in the observed change of A1c from baseline given baseline A1c in the two populations. Shaded areas are the 90% confidence interval of smoothed lines (the trend) from 500 bootstrap iterations for each corresponding population.

of A1c reduction at week 12 increased as baseline A1c level increased, and that the relationship was similar in both patient populations.

The Spearman correlation test was performed to quantify the relationship between baseline A1c and change in A1c at week 12. The A1c reduction at week 12 was significantly correlated with the baseline A1c in patients assigned to dapagliflozin treatment in early-stage patients (Spearman correlation coefficient = −0.472; $p < 0.001$) and late-stage patients (Spearman correlation coefficient = −0.606; $p < 0.001$). The patients' group (early-stage vs. late-stage) was not a statistically significant factor for A1c reduction at week 12, further suggesting that the A1c reductions are comparable between the two populations for patients with the same baseline A1c level. Hence, A1c data from patients assigned to dapagliflozin in both populations were pooled to quantify the relationship between baseline A1c and ΔA1c at week 12. Using linear regression, ΔA1c can be related to baseline A1c as: ΔA1c = 3.48 − 0.52 × baseline A1c. The linear relationship had a coefficient of variation of −0.57, and a coefficient determination of 0.33, suggesting that the baseline A1c is negatively correlated with the change in A1c from baseline. Approximately 33% of the variance in A1c reduction at week 12 can be explained by the baseline A1c.

Body Weight Comparison

At week 12, all dapagliflozin-treated patients in the early-stage and the late-stage groups achieved a reduction in body weight from baseline (Table 3). In contrast to the A1c response, the change in body weight from baseline at week 12 was significantly different between early-stage and late-stage patients (Wilcoxon Rank Sum test). A greater body weight reduction was observed among late-stage patients, both in the dapagliflozin-treated and the placebo groups. On average, late-stage patients lost 0.6, 2.3, and 2.5 kg more than the early-stage patients, when compared across the placebo, dapagliflozin 10 mg, and dapagliflozin 20 mg treatment groups, respectively.

Table 3. Change in body weight at week 12 in early-stage and late-stage patients.

Dose (mg)	Early-stage median [5th–95th percentile] (kg)	Late-stage median [5th–95th percentile] (kg)	p-Value
Placebo	−0.95 [−5.41, 2.80]	−1.55 [−7.14, −0.163]	0.03
10	−2.00 [−9.27, 1.40]	−4.30 [−8.63, −0.263]	0.0006
20	−2.50 [−7.85, 0.36]	−5.05 [−8.54, 1.26]	0.02

The relationship between the change in body weight at week 12 and baseline body weight is presented in Figure 3. Body weight reduction in early-stage patients appeared to be unrelated to baseline body weight, whereas body weight reduction in late-stage patients was positively correlated with baseline body weight. However, the relationship between baseline body weight and body weight reduction was not

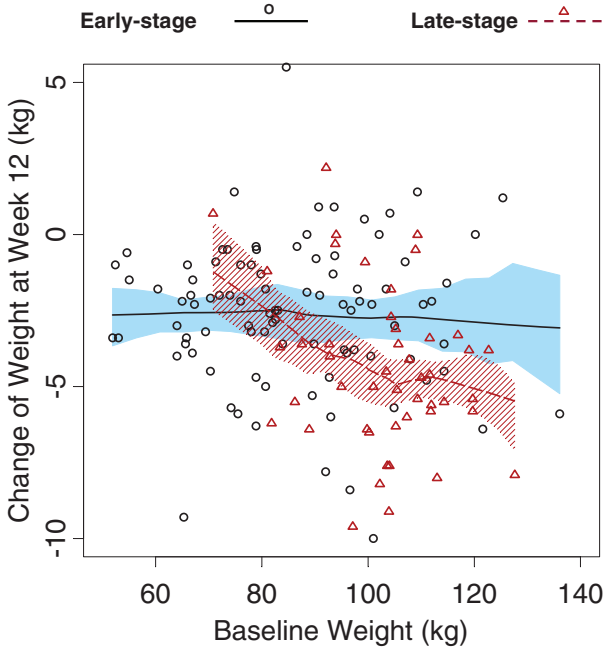

Figure 3. Change in body weight from baseline at week 12 versus baseline weight in early-stage and late-stage patients assigned to 10 and 20 mg once daily dapagliflozin. Circles and triangles denote the observed change of weight from baseline at week 12 for early-stage and late-stage patients, respectively. The straight line and dashed line are locally smoothed lines depicting the trend in the observed change of weight from baseline given baseline weight in the two populations. Shaded areas are the 90% confidence interval of smoothed lines (the trend) from 500 bootstrap iterations for each corresponding population.

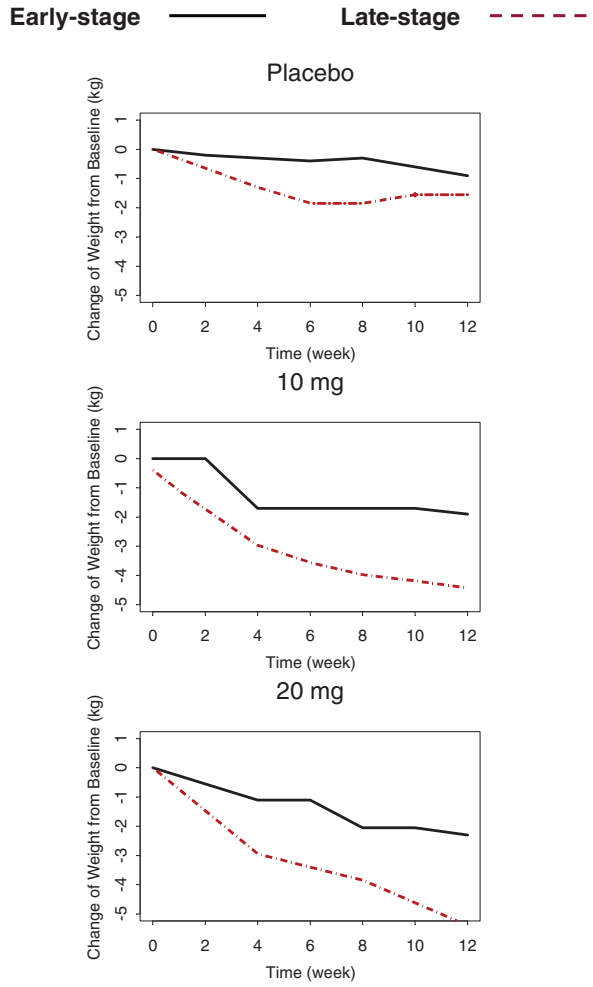

Figure 4. Change in body weight from baseline at week 12 in early-stage and late-stage patients assigned to placebo, 10 and 20 mg once daily dapagliflozin. Solid and dashed lines are locally smoothed lines depicting the change of weight over 12 weeks in early-stage and late-stage patients.

statistically significant within each population (Spearman correlation test, $p = 0.74$ for early-stage patients; $p = 0.14$ for late-stage patients).

The dynamics of body weight reduction during the 12-week treatment period was also compared between the early-stage and late-stage populations. Figure 4 shows that the slope of the body weight reduction relative to time is consistent within each patient population group but is different between the early-stage and late-stage patients. Body weight reduction did not appear to reach steady state in the late-stage group at the end of week 12, whereas the body weight reduction in the early-stage group was approaching a stable level.

Insulin treatment is known to cause weight gain [10,11]. In addition to diet and exercise, late-stage patients took oral antidiabetes drugs and insulin, and had their total daily dose of insulin reduced by 50% at the beginning of the study. To evaluate the impact of insulin reduction on body weight, ANCOVA test was performed to test the significant covariates on weight change in the placebo group of both patient populations. There the body weight reduction was significantly greater among late-stage patients taking placebo compared with early-stage patients taking placebo patients ($p = 0.03$), suggesting that reduced insulin intake may contribute to additional weight loss in late-stage patients.

Table 4. Change in urinary glucose at week 12 in early-stage and late-stage patients.

Dose (mg)	Early-stage median [5th–95th percentile] (g/24 h)	Late-stage median [5th–95th percentile] (g/24 h)	p-Value
Placebo	0.0 [−32.7, 10.6]	−0.8 [−10.1, 5.38]	0.2
10	55.0 [−0.3, 124]	87.2 [21.7, 188]	0.06
20	71.2 [13.7, 160]	87.6 [21.6, 163]	0.77

Urinary Glucose Comparison

At week 12, all dapagliflozin treatment groups had significant increases in urinary glucose excretion from baseline (Table 4). The change in urinary glucose excretion from baseline at week 12 was not significantly different between the two patient populations (Wilcoxon Rank Sum test, $p > 0.05$).

Given the wide range of urinary glucose excretion at baseline, the changes in individual 24-h urinary glucose at week 12 were binned by individual baseline urinary glucose levels (Figure 5). All dapagliflozin-treated individual patients experienced an increase in urinary glucose, with the exception of one patient who had a 24-h urinary glucose of 172 g at baseline. The increase in the amount of urinary glucose was attenuated as the baseline 24-h urinary glucose reached 50 g or more, although the number of patients in this category was small.

Discussion

This is the first report comparing the treatment effect of an SGLT2 inhibitor in patients at different stages of T2DM. We studied two very different patient populations with respect to baseline glycaemic control, body weight, diabetes duration, background antihyperglycaemic therapy, and treatment strategy. Admitting the limitations to generalize the results because of small treatment group size and short study duration, examining the treatment effect of dapagliflozin across the two patient populations is intended to generate insights into the potential efficacy of dapagliflozin treatment across the spectrum of T2DM, from early disease (treatment-naïve) to late-stage patients on insulin-based regimens.

Significant reductions in A1c and body weight, and an increase urinary glucose excretion were seen after 12 weeks of dapagliflozin treatment in both early-stage and late-stage patients. Increased urinary glucose excretion, the direct pharmacodynamic effect of SGLT2 inhibition, was similar between the two populations, and of a magnitude similar to that previously reported in a 2-week study of T2DM patients stable on metformin or diet alone [7]. The increased urinary glucose excretion appears to be attenuated as the baseline

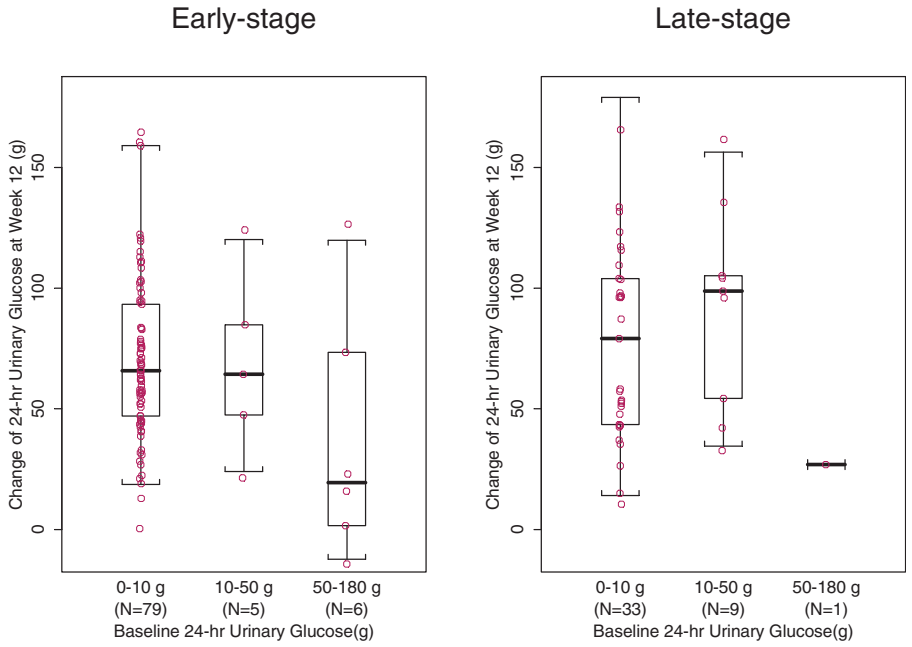

Figure 5. Change in 24-h urinary glucose at week 12 in early-stage and late-stage patients assigned to 10 and 20 mg once daliy dapagliflozin. Circles denote the observed change of urinary glucose from baseline. For each box, the centre bar, bottom, and top whiskers mark the median, 5th, and 95th percentiles of observed change of urinary glucose from baseline of each group.

urinary glucose reaches 50 g or more. Despite this, the glycaemic efficacy clearly increases with higher baseline A1c [7–9].

Dapagliflozin treatment led to similar time course of A1c reduction and its relationship to baseline A1c across the two distinct populations of patients with T2DM. The consistency of dapagliflozin treatment on glycaemic control among early-stage and late-stage patients can be explained by the insulin-independent mechanism of action of dapagliflozin [7]. We posit that dapagliflozin induces a similar increase in urinary glucose excretion, which drives the lowering of plasma glucose concentration in a manner that is independent of the metabolic parameters by which the studied populations differ, namely the β-cell function and the degree of insulin resistance in peripheral tissues. In light of these data, it is reasonable to hypothesize that dapagliflozin could be equally efficacious at improving glycaemic control in a wide range of patients with T2DM, regardless of disease duration or background antihyperglycaemic medications.

Loss of body weight was different between the two patient populations. Baseline body weight was higher in the late-stage patients compared with the early-stage patients. Late-stage patients experienced a greater weight reduction than did early-stage patients. The factors driving this difference are not clear, although treatment strategy, with late-stage patients undergoing a dose-reduction in exogenous insulin (a weight-increasing hormone) is probably to play an important role. The difference in body weight reduction between the two patient populations is of interest, given the similar degree of urinary glucose excretion and glycaemic control. Caloric loss in the form of urinary glucose did not differ between the two patient populations. Thus, other factors that regulate caloric balance, such as food intake or metabolic rate, may explain the difference between the two patient populations. The greater bodyweight reduction in the late-stage patients suggests that SGLT2 inhibition could be of particular clinical benefit to these patients. Late-stage T2DM patients are typically overweight or obese, which leads to further weight gain and insulin resistance. Dapagliflozin has the potential to afford these patients improved glucose control with weight loss, which has beneficial effects on glycaemic control, coincident cardiovascular disease risk factors, and all cause mortality. [12]

Conclusion

Dapagliflozin treatment at 10 and 20 mg QD for 12 weeks resulted in clinically significant improvements in glycaemic control and weight reduction in both early-stage and late-stage patients with T2DM. The beneficial effects of dapagliflozin treatment were observed in both patient populations despite the differences in disease status and background medications. Our results suggest that dapagliflozin's insulin-independent mechanism could be a promising treatment option across the different stages of clinical progression of T2DM. This therapeutic approach may lend itself to reducing the weight gain that otherwise might occur when insulin therapy is intensified.

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