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Exposure–response relationships for the sodium-glucose co-transporter-2 inhibitor dapagliflozin with regard to renal risk markers

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Abstract

Aims: To quantitate the consistency of an individual's plasma exposure to dapagliflozin upon re-exposure, and to investigate whether the individual's systemic exposure to dapagliflozin explains inter-individual variation in response to dapagliflozin with regard to multiple renal risk markers.

Methods: Data were used from a crossover randomized clinical trial that assessed the albuminuria-lowering effect of dapagliflozin in 33 people with type 2 diabetes and elevated albuminuria. Fifteen participants were exposed twice to dapagliflozin. Trough plasma concentrations of dapagliflozin were measured for each participant at steady state. Dapagliflozin plasma concentrations were measured by liquid chromatography tandem mass spectrometry, and pharmacokinetic characteristics were simulated based on a population pharmacokinetic model. Linear mixed-effects models were used to quantify the exposure–response relationships.

Results: The median plasma concentration after first and second exposure to dapagliflozin was 5.3 ng/mL vs 4.6 ng/mL, respectively ($P = 0.78$). Lin's concordance correlation coefficient between occasions was 0.73 ($P < 0.0021$). Every 100 ng.h/mL increment in area under the dapagliflozin plasma concentration curve was associated with a decrease in log-transformed urinary albumin:creatinine ratio ($\beta = -5.9$, $P < 0.01$), body weight ($\beta = -0.3$, $P < 0.01$) and estimated glomerular filtration rate ($\beta = -0.7$, $P = 0.01$) and an increase in urinary glucose excretion ($\beta = 17.0$, $P < 0.001$).

Conclusion: An individual's exposure to dapagliflozin is consistent upon re-exposure and correlates with pharmacodynamic response in renal risk markers.

KEYWORDS

dapagliflozin, diabetic nephropathy, pharmacodynamics, pharmacokinetics, SGLT2

1 | INTRODUCTION

Sodium-glucose co-transporter-2 (SGLT2) inhibitors are a relatively new class of oral glucose-lowering drug that have been approved for the treatment of type 2 diabetes mellitus. Dapagliflozin is an SGLT2 inhibitor which has been shown to lower glycated haemoglobin (HbA1c) by promoting urinary glucose excretion.[1] In addition, dapagliflozin also decreases body weight, systolic blood pressure and

albuminuria. A large cardiovascular outcome trial demonstrated that dapagliflozin also significantly reduced the risks of heart failure and progression of chronic kidney disease in people with type 2 diabetes.[2,3]

Despite the observed beneficial effects on a population level, individual patients show a large inter-individual variation in response to SGLT2 inhibitors, as assessed by varying degrees of changes in renal risk markers.[4,5] This inter-individual response variation is reproducible upon re-exposure, suggesting that the individual variation in drug response is not a random variation in the surrogate marker but a real pharmacological response variation.[4] Previous studies have not identified clinical variables that could explain all inter-individual response variability, neither baseline characteristics nor genetic polymorphisms in the SGLT2 gene.[4,6]

In addition to inter-individual variation in pharmacodynamic variables, a study pooling pharmacokinetic data from 20 studies in both healthy volunteers and people with type 2 diabetes mellitus also showed inter-individual variation in pharmacokinetic responses to SGLT2 inhibitors.[7] In addition, previous studies have associated the systemic exposure of SGLT2 inhibitors with changes in urinary glucose excretion, as these responses directly reflect the mechanism of action.[7-9] However, there is limited information on the exposure–response relationship between systemic exposure of SGLT2 inhibitors and changes in other renal risk markers such as systolic blood pressure and albuminuria. To investigate this relationship, it is important firstly to demonstrate the consistency in dapagliflozin exposure after re-exposing the same individual in order to ensure that the exposure is a true pharmacological response and not random.

The aim of the present study, therefore, was to quantitate consistency in plasma exposure to dapagliflozin upon re-exposure. Subsequently, we investigated whether individual systemic exposure to dapagliflozin explained the inter-individual variation in response to dapagliflozin with regard to multiple renal risk markers.

2 | METHODS

2.1 | Clinical trial design and patient population

Data were used from the IMPROVE trial, a prospective, randomized, double-blind, placebo-controlled, crossover clinical trial that evaluated the albuminuria-lowering effect of dapagliflozin and the reproducibility of this effect within patients. The study design, patient population and main results have been published previously.[10] In short, 33 people with type 2 diabetes, a urine albumin to creatinine ratio (UACR) between 11.3 and 395.5 mg/mmol (100 and 3500 mg/g), an estimated glomerular filtration rate (eGFR) ≥45 mL/min/1.73m^2 and aged between 18 and 75 years were enrolled. Participants were required to be treated with a maximum tolerated dose of an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker for at least 4 weeks. Participants were randomized to three 6-week treatment periods: dapagliflozin 10 mg/d, placebo, and dapagliflozin 10 mg/d, or placebo, dapagliflozin 10 mg/d, placebo, with a wash-out period of 6 weeks between treatment periods. The study was registered with the Dutch Trial Register (NTR 4439) and was performed in accordance with the Declaration of Helsinki.

2.2 | Measurements

Participants collected three consecutive first morning void urine samples on day −2, day −1 and day 0 for measurement of urinary albumin and creatinine at baseline and at every first and last visit per treatment period. UACR data were calculated as the geometric mean from the three first morning void urine collections. Body weight and systolic blood pressure were recorded at every visit. eGFR was calculated using the Modification of Diet in Renal Disease equation.[11] Urinary glucose excretion was measured in 24-hour urine samples. Samples for dapagliflozin plasma concentration were taken per protocol at 24 hours after first dosing but before the second dose (C_{trough}). Plasma concentrations of dapagliflozin were measured for all patients (n = 33) by a previously validated liquid chromatography mass spectroscopy technique at Covance Laboratories (Indianapolis, Indiana). Of these, two samples were excluded based on concentration below the lower limit of quantification (n = 2). Participants with a measured C_{trough} plasma concentration that exceeded the 90% confidence interval (CI) of simulated C_{trough} were excluded from analysis because they had most likely taken their study medication prior to sample collection.

2.3 | Consistency upon re-exposure

For the consistency upon re-exposure, a Lins correlation coefficient was calculated in R version 3.6.1 package epi.ccc.[12,13]

2.4 | Demographics

A *t*-test or chi-squared test was performed, as applicable, to compare the demographic variables and baseline characteristics of the included population and those exposed twice to dapagliflozin.

2.5 | Factors associated with plasma concentration

Multiple linear regression models were used to explore the relationships between the exposure (plasma concentrations) and the response variable (clinical demographics and clinical chemistry) associated with plasma concentrations. For the first model, each variable was tested in univariate analysis and included in the multivariate model when the *P* value was ≤0.10. The best model was selected using forward inclusion and backwards elimination.

2.6 | Estimation of inter-individual exposure to dapagliflozin

A previously published population pharmacokinetic model was used to estimate individual exposure for each enrolled participant.[14] This model uses dapagliflozin dose, Child–Pugh score, ideal body weight,

baseline creatinine clearance (calculated with ideal body weight in the Cockcroft–Gault formula) and age, to obtain an individual pharmacokinetic profile. For each participant, the individual pharmacokinetic profile was simulated 1000 times, 10 days after receiving the first dose to ensure steady state, in time steps of 0.01 hours. Simulations were conducted using NONMEM 7.3 (ICON Development Solutions, Ellicott City, Maryland), using the original model structure, model parameters and individual characteristics, and including inter-individual variability. Subsequently, for each participant, the individual median predicted pharmacokinetic profile was used to obtain an estimate of the individual area under the curve at steady state (AUC_{0-24}).

2.7 | Exposure–response analysis

The relationship between dapagliflozin AUC_{0-24} and response was investigated using linear mixed-effects models using only data from the first two treatment periods. Response variables of interest were urinary glucose excretion, systolic blood pressure, body weight, UACR and eGFR. For each response variable, change from baseline was estimated in both the placebo and the treatment period. For analysis, the exposure to dapagliflozin was assumed to be zero in the placebo period. A random intercept model was fitted to the data to correct for the placebo response of each individual participant. The random intercept model was compared to a random intercept model including AUC_{0-24} as a fixed effect. Both models were compared using a chi-squared likelihood ratio test. Furthermore, significance was tested for the fixed regression coefficient of $AUC_{0-24,}$ assuming a t-distribution. The linear mixed-effects models were fitted using full maximum-likelihood estimation in R version 3.2.3 package lme.

3 | RESULTS

3.1 | Baseline characteristics and reproducibility of systemic dapagliflozin exposure

The baseline characteristics of participants receiving dapagliflozin treatment with a dapagliflozin concentration included in the exposure–response analysis (n = 31) are reported in Table 1.

Dapagliflozin plasma concentration at first and re-exposure was available for 12 participants. The median (25th to 75th percentile) C_{trough} was 5.3 (3.7 to 9.3) ng/mL on the first exposure and 4.6 (3.9 to 6.4) ng/mL (P = 0.78 vs. first exposure; Figure 1). Lin's concordance correlation coefficient was 0.73 (P = 0.001; Figure 1).

Table 2 shows the variables associated with dapagliflozin plasma concentration. In univariable analysis, sex, eGFR, aspartate aminotransferase, alanine aminotransferase and UACR were associated with dapagliflozin plasma concentration (all $P \leq 0.10$; Table 2). In multivariable analysis, eGFR (β = −0.01, P = 0.050) and alanine aminotransferase (β = −0.01, P = 0.039) were independently associated with higher dapagliflozin plasma concentration (Table 2).

TABLE 1 Demographics and baseline characteristics of the included population

Characteristic	Total population, N = 31	Re-exposed populaton, N = 12	P
Age, years	61.6 (9.3)	62.5 (8.2)	0.76
Sex, % men	24 (77.4)	11 (91.7)	0.23
White, n (%)	29 (93.5)	12 (100)	0.16
Smoking status, n (%)	8 (25.8)	2 (16.7)	0.91
HbA1c, mmol/mol	57.3 (9.7)	59.7 (11.8)	0.55
Urinary glucose excretion, mmol/24 h	21 (43)	25 (54)	0.81
Diabetes duration, years	10 (7.1)	9 (5.6)	0.80
Systolic blood pressure, mmHg	142.3 (15.1)	138.1 (11.6)	0.33
Diastolic blood pressure, mmHg	77.3 (5.9)	76 (6.3)	0.53
Body mass index, kg/m^2	31.3 (5.7)	31.6 (3.8)	0.81
Body weight, kg	96.7 (22.5)	102.4 (20.9)	0.44
eGFR, mL/min/1.73 m^2	72.1 (21.7)	68.4 (15.4)	0.54
Cardiovascular disease history, n (%)	10 (32.3)	5 (41.7)	0.59
UACR, mg/g	29.9 (14.2–59.9)	21.3 (10.6–35.1)	0.45

Abbreviations: eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; UACR, urinary albumin:creatinine ratio.
Note: Data are presented as mean (SD) or median (interquartile range). P values compare all participants with those exposed twice to dapagliflozin. Bold values are statistically significant.

3.2 | Relationship between systemic dapagliflozin exposure and responses in renal risk markers

For the 31 participants in whom dapagliflozin was measured at least once, mean placebo-adjusted dapagliflozin changes in body weight, systolic blood pressure, urinary glucose excretion, UACR and eGFR after 6 weeks of dapagliflozin are reported in Table 3. Reductions were observed when comparing baseline-corrected values after dapagliflozin treatment versus placebo treatment for all variables. Changes in these values during dapagliflozin treatment periods varied among participants, as reflected by the large CI (Table 3).

The mean AUC_{0-24} after a dose of 10 mg dapagliflozin was 584.4 ng.h/mL (95% CI 391.6–1001.3). Individually predicted dapagliflozin AUC_{0-24} was related to urinary glucose excretion, body weight, UACR and eGFR responses to dapagliflozin. Every 100-ng.hr/mL increment in area under the dapagliflozin plasma concentration curve was associated with a decrease in log-transformed UACR (β = −5.9, P < 0.01), body weight (β = −0.3, P < 0.01), eGFR (β = −0.7, P = 0.01) and urinary glucose excretion (β = 17.0, P < 0.001). No significant association between exposure and systolic blood pressure was identified (Table 4).

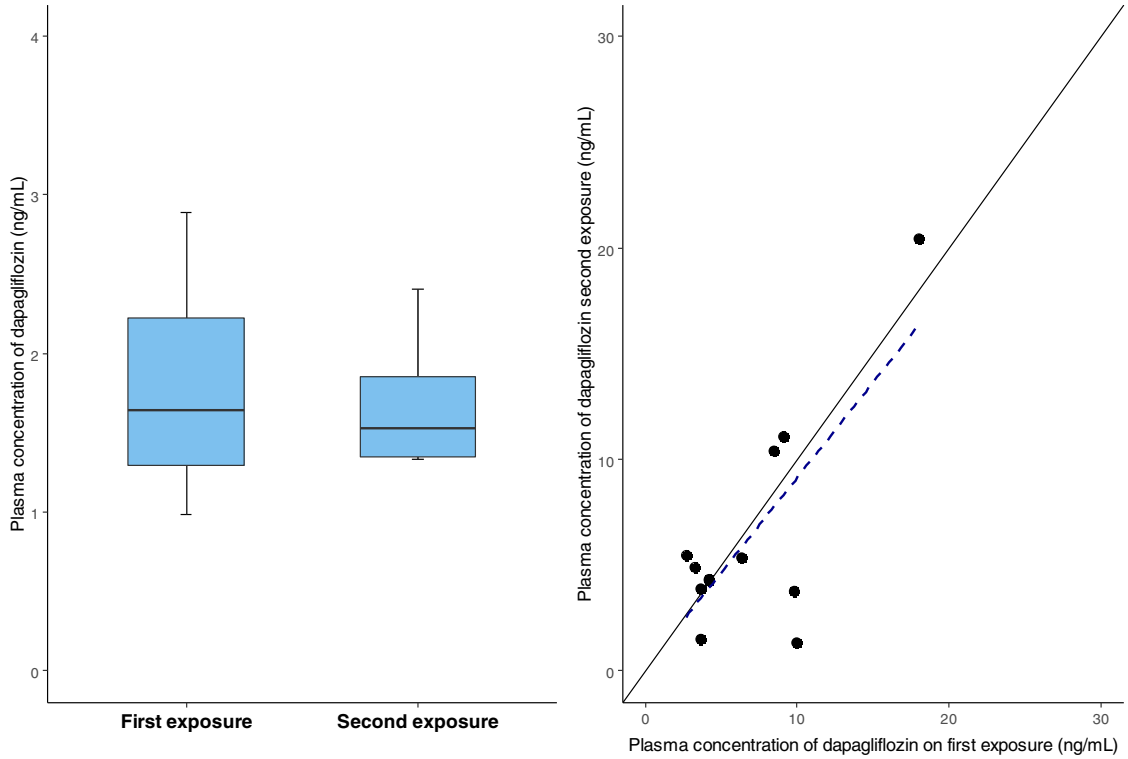

FIGURE 1 Consistency in exposure to dapagliflozin between occasions (left) and between occasions per individual (right)

TABLE 2 Patient characteristics associated with plasma concentration of dapagliflozin

	Dapagliflozin 10 mg/d			
	Univariate		Multivariate	
	β	P	β	P
Age (years)	0.01	0.27		
Gender (female)	**−0.52**	**0.06**		
Body mass index (kg/m^2)	−0.03	0.19		
eGFR (mL/min/1.73m^2)	**−0.02**	**0.01**	**−0.01**	**0.05**
Aspartate aminotransferase **(U/l)**	**−0.02**	**0.02**		
Alanine aminotransferase **(U/l)**	**−0.01**	**0.01**	**−0.01**	**0.04**
Serum albumin (g/L)	0.00	0.96		
Systolic blood pressure (mm/Hg)	0.00	0.77		
Diastolic blood pressure (mm/Hg)	−0.02	0.37		
UACR (mg/g)	**0.00**	**0.09**		
Total protein (g/L)	−0.01	0.81		
C-reactive protein (mg/L)	−0.02	0.65		

Abbreviations: eGFR, estimated glomerular filtration rate; UACR, urinary albumin to creatinine ratio.*The R^2 of the multivariate model is 0.65, geometric mean for UACR was log transformed.
Bold values are statistically significant.

4 | DISCUSSION

In the present study we evaluated the consistency in exposure to dapagliflozin by measuring the plasma concentration of dapagliflozin during two separate treatment periods and assessed the association between dapagliflozin plasma concentration and its pharmacodynamic response with regard to renal risk markers. We demonstrated that individual exposure was consistent upon re-exposure to dapagliflozin and that individual exposure was associated with pharmacodynamic responses in renal risk markers. These data indicate that the individual variation in drug response is in part explained by the individual variation in systemic exposure to dapagliflozin.

Patients show a large inter-individual variation in changes in renal risk markers during treatment with dapagliflozin. This inter-individual

TABLE 3 Change from baseline in pharmacodynamic markers during dapagliflozin and placebo treatment

	Placebo (95%CI)	Dapagliflozin (95%CI)	Placebo-adjusted dapagliflozin effect (95%CI)
Urinary glucose excretion (mmol/24 h)	7.3 (−31.9 to 46.5)	224.2 (183.4 to 265.1)	216.9 (155.0 to 278.8)
Body weight (kg)	0.3 (−0.2 to 0.7)	−1.6 (−2.0 to −1.1)	−1.8 (−2.5 to −1.2)
Systolic blood pressure (mmHg)	0.4 (−5.4 to 6.1)	−7.0 (−12.8 to 1.2)	−7.4 (−13.9 to −0.9)
UACR (%)	5.3 (−10.9 to 24.4)	−33.0 (−43.3 to −20.8)	−36.4 (−49.6 to −19.6)
eGFR (mL/min/1.73m^2)	−0.6 (−3.5 to 2.3)	−5.0 (−7.9 to −2.1)	−4.4 (−7.5 to −1.3)

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; UACR, urinary albumin to creatinine ratio.
Note: Changes are presented as mean and 95% CI.

TABLE 4 Relationship between dapagliflozin exposure and changes in pharmacodynamic markers

	β /100 AUC (ng.h/mL)	*P*
Urinary glucose excretion (mmol/24 h)	17.0 (12.2 to 21.8)	<0.01
Body weight (kg)	−0.3 (−0.4 to −0.2)	<0.01
Systolic blood pressure (mmHg)	−0.7 (−2.1 to 0.7)	0.3
UACR (%)	−5.9 (−9.4 to −2.5)	<0.01
eGFR (mL/min/1.73 m^2)	−0.7 (−1.2 to −0.2)	0.01

Abbreviations: AUC, area under the curve; eGFR, estimated glomerular filtration rate; UACR, urinary albumin to creatinine ratio.
Note: β values are expressed per 100 ng.h/mL, which is approximately equivalent to a 2.5 mg/d dapagliflozin dose.

variation is in part explained by a pharmacological variation in drug response as well as random day-to-day fluctuations in the renal risk markers. Prior studies failed to identify clinical characteristics or genetic polymorphisms in the SGLT2 gene that could predict an individual's drug response to SGLT2 inhibitors, except that lower renal function was associated with a smaller HbA1c response.[15,16] In the present study we demonstrated that inter-individual variability in systemic exposure to dapagliflozin was associated with changes in renal risk markers, suggesting that the pharmacokinetics of dapagliflozin are involved in an individual's drug response. This is relevant from a clinical perspective as it suggests that the exposure is suboptimal in patients not responding to dapagliflozin. Reviewing therapy adherence and increasing the dose within the guideline-recommended dose range, if not contra-indicated, are potential solutions to increase exposure and overcome therapy resistance.

Decreased renal and liver function were associated with higher dapagliflozin plasma trough concentrations in the present analysis. These findings are in line with previous studies reporting that impaired renal and liver function are associated with a higher systemic dapagliflozin exposure. Dapagliflozin is metabolized by the liver via UDP Glucuronosyltransferase Family 1 Member A9 (UGT1A9) and cleared as its metabolite. Reduced hepatic function, as reflected by increases in alanine aminotransferase and aspartate aminotransferase levels, decreases metabolism of dapagliflozin and consequently increases systemic exposure to dapagliflozin. It is important to note that UGT1A9 is also abundantly present in the kidney at concentrations much higher than those observed in the liver. Reduced renal function may thus reflect reduced renal metabolism, which may in turn explain higher systemic exposure and possibly higher intra-renal concentration of dapagliflozin leading to a larger pharmacodynamics response. Interestingly, Ghezzi et al[17] showed that the effect compartment of dapagliflozin is located in the apical membrane of the early proximal tubule. They demonstrated that, after glomerular filtration, dapagliflozin is reabsorbed in the tubuli and metabolized in the liver. The tubular reabsorption of dapagliflozin may explain why higher systemic exposure correlates with larger pharmacodynamic responses.

A previous pharmacokinetic study also reported that age, sex and body weight were associated with individual dapagliflozin exposure.[17] We could not confirm these findings, which is probably attributable to the relatively small sample size and the relatively narrow age range of the included population. Both factors decrease statistical power to detect a potential true correlation.

Exposure–response analyses for SGLT2 inhibitors have generally focused on the relationship between the exposure and urinary glucose excretion, the primary pharmacodynamic effect of SGLT2 inhibitors. These studies showed that a higher exposure resulted in higher urinary glucose excretion[7,9]; however, it is well established that SGLT2 inhibitors exert effects on multiple cardiovascular risk markers which may all contribute to the observed long-term reductions in risks of heart failure and adverse renal outcomes. We extended these prior studies and evaluated the relationship between dapagliflozin exposure with a range of risk markers and demonstrated associations for multiple renal risk markers.

To obtain individual exposures for dapagliflozin we used the pharmacokinetic model developed for dapagliflozin by van der Walt et al.[14] Our individual simulated AUCs (Supplemental Figure S1) were comparable to the AUCs reported for 10 mg dapagliflozin by Kasichayanula et al,[7] supporting the use of the pharmacokinetic model to estimate individual exposure.

The present study has some limitations, the most important of which is the lack of multiple plasma concentrations after dapagliflozin administration. We therefore used a previously validated population pharmacokinetic model to estimate individual dapagliflozin exposure and calculated exposures in line with previous reports from dedicated pharmacokinetic studies. In addition, the relatively small sample size may have impacted statistical power and our ability to identify patient characteristics associated with dapagliflozin exposure. Because of the small number of adverse events we were also unable to assess the relationship between exposure and effects on safety parameters.

Another limitation is that only one dose level was studied. Information on more dose levels would have increased the range of exposures, increased statistical power and probably the precision of the exposure–response relationship. Nevertheless, the large variation in measured plasma concentration and exposure in the present study provided sufficient power for robust conclusions. Finally, the short follow-up precludes any inferences about the relationship between individual dapagliflozin exposure and long-term renal outcomes.

In conclusion, individual exposure to dapagliflozin is consistent within individuals upon re-exposure. The individual exposure to dapagliflozin is associated with inter-individual variability in response in multiple renal risk markers. These data support the importance of understanding the variability in exposure to explain individual pharmacodynamics responses to dapagliflozin.

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CONFLICTS OF INTEREST

M.Y.A.M.K., J.S., S.P. and J.V.K. have no conflict of interest to declare. H.J.L.H. is consultant to Abbvie, AstraZeneca, Boehringer Ingelheim, Fresenius, Gilead, Janssen, Merck, Mundipharma, Mitsubishi Tanabe. He has received research support from AstraZeneca, Abbvie, Boehringer Ingelheim and Janssen. G.D.L. has received lecture fees from Sanofi, Astra Zeneca and Jansen, and has served as a consultant for Abbvie, Sanofi, Novo Nordisk, Astra Zeneca, Boehringer Ingelheim and MSD.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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