Renal Glucose Handling

Impact of chronic kidney disease and sodium-glucose cotransporter 2 inhibition in patients with type 2 diabetes

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OBJECTIVE—Ipragliflozin, a sodium-glucose cotransporter 2 inhibitor, stimulates glycosuria and lowers glycemia in patients with type 2 diabetes (T2DM). The objective of this study was to assess the pharmacodynamics of ipragliflozin in T2DM patients with impaired renal function.

RESEARCH DESIGN AND METHODS—Glycosuria was measured before and after a single ipragliflozin dose in 8 nondiabetic subjects and 57 T2DM patients (age 62 ± 9 years, fasting glucose 133 ± 39 mg/dL, mean ± SD) with normal renal function (assessed as the estimated glomerular filtration rate [eGFR]) ($eGFR_1$ ≥90 mL · min^{-1} · 1.73 m^{-2}), mild ($eGFR_2$ ≥60 to <90), moderate ($eGFR_3$ ≥30 to <60), or severe reduction in eGFR ($eGFR_4$ ≤15 to <30).

RESULTS—Ipragliflozin significantly increased urinary glucose excretion in each eGFR class ($P < 0.0001$). However, ipragliflozin-induced glycosuria declined (median [IQR]) across eGFR class (from 46 mg/min [33] in $eGFR_1$ to 8 mg/min [7] in $eGFR_4$, $P < 0.001$). Ipragliflozin-induced fractional glucose excretion (excretion/filtration) was 39% [27] in the T2DM patients (pooled data), similar to that of the nondiabetic subjects (37% [17], P = ns). In bivariate analysis of the pooled data, ipragliflozin-induced glycosuria was directly related to eGFR and fasting glucose ($P < 0.0001$ for both, $r^2 = 0.55$), predicting a decrement in 24-h glycosuria of 15 g for each 20 mL/min decline in eGFR and an increase of 7 g for each 10 mg/dL increase in glucose above fasting normoglycemia.

CONCLUSIONS—In T2DM patients, ipragliflozin increases glycosuria in direct, linear proportion to GFR and degree of hyperglycemia, such that its amount can be reliably predicted in the individual patient. Although absolute glycosuria decreases with declining GFR, the efficiency of ipragliflozin action (fractional glucose excretion) is maintained in patients with severe renal impairment.

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Patients with type 2 diabetes mellitus (T2DM) often experience worsening of their quality-of-life because of the long-term complications of the disease and the lifelong use of polypharmacy. Despite the use of pharmacotherapy, many T2DM patients do not attain or maintain adequate control of blood glucose levels (1). Therefore, there is still a need for novel glucose-lowering drugs that may extend the armamentarium for the treatment of T2DM.

Sodium-glucose cotransporter 2 (SGLT2) inhibitors are a new class of glucose-lowering agents (2). SGLT2 is a low-affinity, high-capacity glucose transporter located in the proximal tubules of the kidneys that accounts for ~90% of glucose reabsorption (3–5). Inhibition of SGLT2 results in an increase of urinary glucose excretion, thereby improving glycemic control in T2DM patients (6). Ipragliflozin (ASP1941) is an oral, potent, and selective SGLT2 inhibitor in phase 3 development for the treatment of T2DM. It dose-dependently increased urinary glucose excretion in healthy subjects (7,8) and in T2DM patients and reduced body weight, fasting plasma glucose (FPG), and HbA_{1c} in T2DM patients (9,10).

Because SGLT2 inhibitors act on the kidney, and the amount of glucose excreted is closely dependent on the glomerular filtration rate (GFR), it can be anticipated that SGLT2 inhibitors will have a reduced efficacy in T2DM patients with renal impairment. This has recently been reported for dapagliflozin, which showed a reduction in urinary glucose excretion of ~85% in T2DM patients with moderate to severe renal impairment compared with T2DM patients with normal renal function (11). It is unclear, however, whether this reduced efficacy is simply the result of a decrease in the filtered glucose load (consequent upon the fall in GFR) or whether impairment in the absorptive capacity of the SGLT2 system inherently restrains the strength of SGLT2 inhibition.

In the studies analyzed here, we quantitatively investigated the effect of ipragliflozin on renal glucose handling in T2DM patients with normal renal function or various degrees of renal impairment.

RESEARCH DESIGN AND METHODS

Two parallel studies—one in European subjects and the other in Japanese subjects—were carried out in T2DM patients with normal and impaired renal function and in healthy subjects. Both studies were conducted in accordance with ethical principles based on the Declaration of Helsinki, good clinical practice, and International Conference on Harmonization guidelines, and were approved by a local institutional review board. All subjects provided written informed consent.

European study

This trial (NCT01302028) was an open-label, phase 1, multicenter study. Ipragliflozin was administered as a single oral dose of 100 mg to healthy subjects (estimated GFR [eGFR] ≥90 mL · min^{-1} · 1.73 m^{-2}) and T2DM patients with normal renal function ($eGFR_1$ ≥90 mL · min^{-1} · 1.73 m^{-2}), mild renal impairment ($eGFR_2$ ≤60 to <90 mL · min^{-1} · 1.73 m^{-2}), moderate renal impairment ($eGFR_3$ ≤30 to < 60 mL · min^{-1} · 1.73 m^{-2}), and severe

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renal impairment ($eGFR_4$ ≤15 to <30 mL · min^{-1} · 1.73 m^{-2}). The eGFR was estimated based on the Modification of Diet in Renal Disease formula: eGFR (mL · min^{-1} · 1.73 m^{-2}) = 186 · [serum creatinine (mg/dL)]$^{-1.154}$ · [age (years)]$^{-0.203}$ · 1.212 [if black] · 0.742 [if female] (12). The Modification of Diet in Renal Disease calculated from the serum creatinine value measured at screening and on day −1 gave essentially superimposable results (data not shown).

The study included healthy subjects or patients with stable T2DM, aged 45–80 years, with a BMI of 25–40 kg/m^2 and a FPG <100 mg/dL for healthy subjects or ≤200 mg/dL for T2DM patients. The study excluded patients with type 1 diabetes, subjects who underwent kidney transplantation or required hemodialysis, T2DM patients on a diet-only treatment or not on a stable treatment regimen, and patients with renal impairment due to renal disease secondary to malignancy or a fluctuating or rapidly deteriorating renal function. Other exclusion criteria were hypertension and any clinically significant abnormality, illness, or medical condition.

Subjects were screened before admission (day −21 to −2). The eGFR was determined at screening and on day −1. Eligible subjects were then admitted to the clinical research center, where they received one oral dose of ipragliflozin (100 mg) on day 1 in the morning after an overnight fast. Urine was collected on day −1 and day 1 for the measurement of urinary output and urinary concentrations of ipragliflozin and glucose (for 20 h on day −1 and for 24 h on day 1). On both occasions, plasma glucose was measured after an overnight fast (before dosing on day 1) and at 4-h intervals for 24 h. All subjects were followed up for 1 to 2 weeks after dosing.

Japanese study

This trial (NCT1097681) was an open-label, phase-1, multicenter study. Ipragliflozin was administered as a single oral dose of 50 mg to T2DM patients with an eGFR in the categories $eGFR_1$, $eGFR_2$ or $eGFR_3$, as defined above. GFR was calculated based on the Japanese GFR estimation equation: eGFR (mL · min^{-1} · 1.73 m^{-2}) = 194 · [serum creatinine (mg/dL)]$^{-1.094}$ · [age (years)]$^{-0.287}$ · [0.739 if female] 13. The study included patients with a diabetes duration of >3 months, on a stable treatment regimen, aged 20–79 years, with BMI of 20–35 kg/m^2, FPG <240 mg/dL, and eGFR ≥30 mL · min^{-1} · 1.73 m^{-2}. Subjects were excluded if they had type 1 diabetes, diabetic ketoacidosis, dysuria, symptomatic urinary tract or genital infection, current or historical significant renal, hepatic, cardiovascular or severe gastrointestinal diseases, or had received insulin within 12 weeks of screening. HbA_{1c} was 8.3 ± 2.4% (mean ± SD) in category $eGFR_1$, 6.6 ± 0.5% in $eGFR_2$, and 6.7 ± 1.4% in $eGFR_3$. Subjects were screened before admission (day −14 to −7). The eGFR was determined at screening. Eligible subjects were then admitted to the clinical research center, where they received one

Table 1—*Glucose parameters before and after a single dose of ipragliflozin in European subjects and Japanese subjects*

	European study (single-dose 100 mg ipragliflozin)					Japanese study (single-dose 50 mg ipragliflozin)		
		T2DM				T2DM		
	Healthy subjects	$eGFR_1$	$eGFR_2$	$EGFR_3$	$eGFR_4$	$eGFR_1$	$eGFR_2$	$eGFR_3$
Sex, *n*								
Males	5	5	3	5	5	5	7	6
Females	3	3	5	3	3	3	2	2
Age (years)	55 ± 8	57 ± 8	65 ± 2	69 ± 7	66 ± 5	55 ± 12	61 ± 11	64 ± 10
BMI (kg/m^2)	27.3 ± 1.8	33.3 ± 4.0	28.8 ± 3.3	33.2 ± 2.5	31.1 ± 5.6	27.3 ± 2.1	25.1 ± 3.8	24.0 ± 2.9
eGFR*	97 ± 5	107 ± 14	74 ± 9	46 ± 11	25 ± 4	111 ± 19	72 ± 10	47 ± 10
eGFR (mL/min)	106 ± 14	128 ± 18	80 ± 10	53 ± 14	28 ± 8	117 ± 30	72 ± 15	45 ± 10
FPG (mg/dL)								
Baseline	92 ± 11	129 ± 23	141 ± 36	130 ± 47	119 ± 38	160 ± 58	133 ± 30	122 ± 29
Postdose	88 ± 6	129 ± 22	136 ± 25	147 ± 42	119 ± 31	135 ± 36	121 ± 23	117 ± 37
Urine output (L)								
Baseline	1.4 ± 0.5	2.1 ± 0.7	2.2 ± 0.8	1.5 ± 0.7	2.4 ± 1.2	2.7 ± 1.3	1.9 ± 0.8	2.2 ± 0.9
Postdose	2.8 ± 1.0	3.5 ± 0.9	4.2 ± 1.0	3.4 ± 0.9	3.3 ± 1.5	3.2 ± 1.0	2.5 ± 0.8	2.6 ± 0.8
Filtered G (mg/min)								
Baseline	99 [32]	168 [43]	107 [58]	56 [39]	38 [27]	146 [181]	89 [56]	55 [23]
Postdose	94 [25]	165 [31]	105 [43]	62 [34]	36 [26]	133 [125]	83 [48]	55 [27]
Absorbed G (mg/min)								
Baseline	101 [55]	165 [43]	107 [55]	62 [25]	37 [27]	141 [115]	84[49]	54 [16]
Postdose	60 [13]	122 [46]	61 [27]	46 [35]	26 [17]	71 [54]	32 [19]	27 [21]
Excreted G (mg/min)								
Baseline	0.1 [0.1]	0.1 [0.2]	0.1 [2.3]	0.1 [1.6]	0.1 [2.1]	4.7 [64.8]	4.3 [8.0]	0.5 [1.3]
Postdose	35 [21]	45 [26]	54 [45]	13 [15]	8 [7]	77 [74]	44 [22]	28 [18]
FGE (%)								
Baseline	0.1 [0.1]	0.1 [0.1]	0.1 [1.5]	0.1 [2.3]	0.2 [4.7]	4.0 [20.6]	2.7 [8.1]	0.7 [2.6]
Postdose	37.0 [16.8]	25.9 [19.3]	45.9 [22.8]	16.7 [21.9]	30.2 [17.6]	52.6 [16.6]	53.1 [17.8]	57.2 [15.6]

Data are mean ± SD or median [interquartile range]. Absorbed G, glucose absorption rate; Excreted G, glucose excretion rate; Filtered G, glucose filtration rate; FGE, fractional glucose excretion. *Measured as mL · min^{-1} · 1.73 m^{-2}.

oral dose of ipragliflozin (50 mg) on day 1 in the morning after an overnight fast. On day −1 and day 1, urine was collected for the following 24 h for the measurement of urinary output and urinary concentrations of ipragliflozin and glucose.

All T2DM subjects were taking antidiabetic agents (mainly metformin or sulfonylureas). Insulin was used in 25–50% of T2DM patients with moderate or severe renal impairment compared with none of the T2DM patients with normal renal function or mild impairment.

Assessments

Safety assessment included recording of adverse events, physical examination, vital signs (pulse and blood pressure), laboratory tests (urine analysis, hematology, and biochemistry), and 12-lead electrocardiogram. Plasma and urine concentrations of ipragliflozin and its metabolites were measured using validated liquid chromatography–mass spectrometry/mass spectrometry methods with lower limit of quantification values for ipragliflozin of 1.00 ng/mL for plasma and 2.0 ng/mL for urine. Glucose was assayed by a glucose oxidase method. Detailed pharmacokinetic analysis is reported separately.

Data analysis

The eGFR ($mL \cdot min^{-1} \cdot 1.73\ m^{-2}$) was recalculated as mL/min with the use of individual body surface area (BSA; m^2), using the Dubois and Dubois formula [$BSA = 0.007184 \cdot height\ (cm)^{0.725} \cdot weight\ (kg)^{0.425}$]. For each of the two examination days, filtered glucose (in mg/min) was calculated as the product of eGFR and the respective FPG concentration. Urinary glucose excretion was obtained as the product of urine output and urinary glucose concentration, absorbed glucose was the difference between filtered and excreted glucose, and fractional glucose excretion was calculated as the ratio of excreted to filtered glucose.

Statistical analysis

Data are given as mean ± SD. Because of their skewed distribution, glucose fluxes are given as median (interquartile range [IQR]). Group comparisons were carried out by Mann-Whitney or Kruskal-Wallis test, as appropriate, and paired comparisons by Wilcoxon signed rank test. General linear models were used to test the simultaneous dependence of outcome variables on multiple explanatory variables. All statistical analyses were performed using SAS 9.1 software (SAS Institute Inc., Cary, NC). A P value ≤0.05 was considered statistically significant.

RESULTS—In the European study, T2DM patients were older and heavier than the nondiabetic subjects; in the Japanese study, the patients' age was similar to that of the European patients, but their BMI was lower. The eGFR was progressively lower across eGFR classes, by definition, and similar between European and Japanese patients; none of the latter, however, were in the lowest eGFR class (Table 1). After ipragliflozin dosing, urine output increased above baseline values by an average of 1.1 L in European subjects and 0.5 L in Japanese subjects.

Pharmacokinetics

Preclinical studies indicated that ipragliflozin is metabolized to multiple, pharmacologically inactive metabolites predominantly via glucuronidation by the uridine diphosphate-glucuronosyltransferase (UGT) enzymes, UGT2B7, UGT2B4, UGT1A9, and UGT1A8.

Only ~1.44% of the administered dose of ipragliflozin was excreted unchanged in the urine within 24 h of single and multiple doses. No significant differences were observed in mean maximum concentration (C_{max}) of ipragliflozin between the T2DM patient cohorts (1,448–1,626 ng/mL in Europeans; 1,045–1,161 ng/mL in Japanese) and the nondiabetic subjects (1,277 ng/mL; Supplementary Table 1). In European T2DM patients with moderate and severe renal impairment, the area under the curve from time zero to infinity (AUC_{inf}) of ipragliflozin was, respectively, 40% and 47% higher compared with T2DM patients with normal renal function (Supplementary Table 1). In Japanese patients, mean AUC_{inf} was 21% higher in T2DM patients with moderate renal impairment compared with normal renal function (Supplementary Table 1).

Pharmacodynamics

At baseline, urinary glucose excretion rate and fractional glucose excretion (FGE) were generally small, with no significant difference across eGFR class (Table 1). Neither parameter was different between diabetic and nondiabetic participants.

After a single dose of ipragliflozin, the glucose excretion rate and FGE both increased in all groups compared with baseline ($P < 0.0001$ for all; Table 1). In absolute terms (i.e., mg/min), glucose

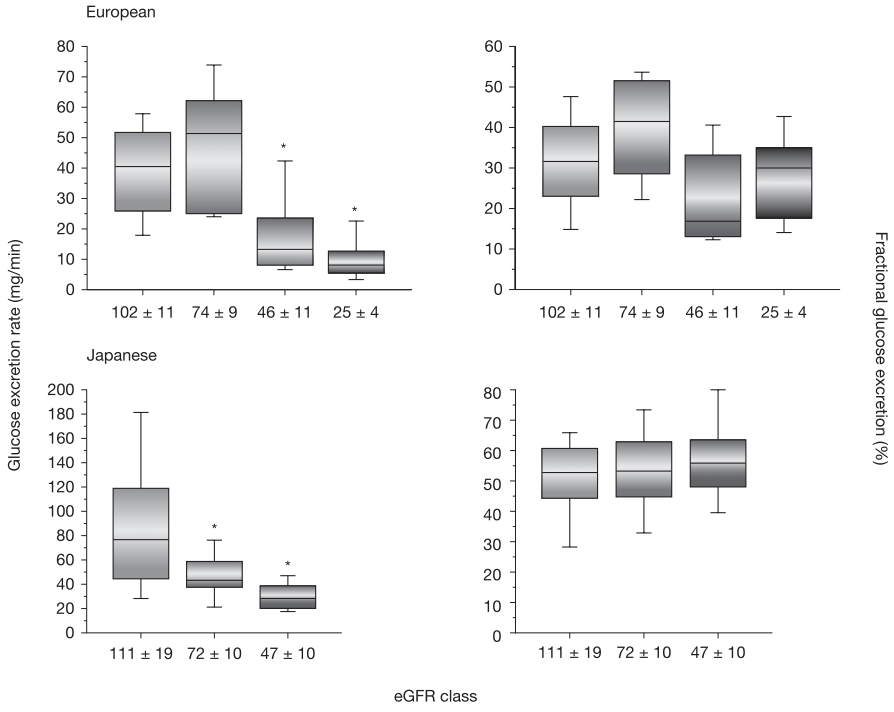

Figure 1—*Box-plots of postdose glucose excretion rates* (left panels) *and FGE* (right panels) *in European* (upper panels) *and Japanese subjects* (lower panels) *by eGFR class (eGFR$_1$ through eGFR$_4$ coded by gray intensity). The numbers at the bottom of the boxes are eGFR values (mean ± SD) for the corresponding class. Patient 5004 in the European group had greater excretion than filtration and was therefore excluded from this analysis.*

excretion was significantly lower in $eGFR_3$ and $eGFR_4$ than in $eGFR_1$ or $eGFR_2$ in European patients. In Japanese patients, ipragliflozin-induced glucose excretion was already significantly reduced in $eGFR_2$ compared with $eGFR_1$; this was the result, however, of the high intersubject variability in the $eGFR_1$ class, because glucose excretion in $eGFR_2$ was similar to the corresponding class of European patients (Table 1, Fig. 1). In contrast, FGE did not change significantly across eGFR class, and was comparable between European and Japanese patients. In the pooled data from both study sites, the median ipragliflozin-induced glucose excretion rate was 47 mg/min in the 41 subjects with an eGFR ≥60 mL/min and 18 mg/min in the 24 subjects with an eGFR <60 mL/min, which extrapolate to 68 and 26 g over 24 h, respectively. Ipragliflozin-induced FGE (excretion/filtration) was 39 [27]% in the T2DM patients, similar to that of the nondiabetic subjects (37 [17]%, P = ns).

The individual measurements of all study subjects show baseline glucose absorption follows the expected linear dependency on filtered glucose, with a splayed threshold and an apparent tubular transport maximum for glucose (Tm_G)

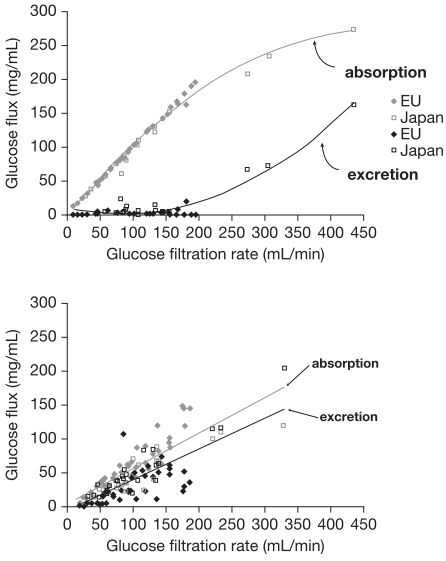

Figure 2—*Individual baseline* (upper panel) *and postdose* (lower panel) *values of glucose absorption and urinary excretion for European (EU) and Japanese cohorts are plotted against the corresponding values of glucose filtration rate. The line of best fit is* $y = -0.5 + 1.1x - 0.001x^2$ ($r^2 = 0.96$) *for baseline absorption, and* $y = 7.5 - 0.2x + 0.001x^2$ ($r^2 = 0.93$) *for baseline excretion. The corresponding line of best fit for postdose absorption is* $y = 3.3 + 0.5x$ ($r^2 = 0.65$) *and the one for postdose excretion is* $y = -4.9 + 0.5x$ ($r^2 = 0.59$).

of >300 mg/min. Glycosuria starts at a filtration rate of 225–250 mg/min, which corresponds in this dataset to a FPG of 200–225 mg/dL. European and Japanese subjects fall on the same curves (Fig. 2).

The same plot of the individual postdose data shows that absorption is decreased and excretion is increased versus baseline throughout the range of glucose filtration rates. Absorption and excretion both increase with increasing filtered glucose in parallel, linear fashion, with no apparent threshold for glycosuria or saturation of absorption (i.e., Tm_G; Fig. 2).

Finally, in the whole dataset, ipragliflozin-induced urinary glucose excretion was a direct function of eGFR and fasting glucose levels (Fig. 3), with no separate influence of sex or age. In a bivariate model, 24-h glycosuria was predicted by eGFR and fasting glucose [glycosuria (g/day) = $-87 \pm 14 + 0.77 \pm 0.12 \cdot$ eGFR (mL · min^{-1} · 1.73 m^{-2}) + $0.70 \pm 0.10 \cdot$ fasting glucose (mg/dL); $r = 0.81$, $P < 0.0001$).

Safety and tolerability

Three treatment-emergent adverse events (TEAEs) occurred in 3 Europeans (1 healthy subject and 2 T2DM patients in $eGFR_3$ class), and 14 TEAEs occurred in 9 Japanese patients (3 patients in each group). All TEAEs were mild in severity, and none was considered drug-related in European patients. Seven TEAEs in Japanese patients were considered drug-related, including vertigo ($n = 1$), elevated blood potassium ($n = 1$), bacteriuria ($n = 3$), pollakiuria ($n = 1$), and eczema ($n = 1$). No hypoglycemic episodes were reported in Europeans; one event related to hypoglycemia (cold sweat) in a Japanese patient in $eGFR_2$ class was not considered to be drug-related. In the European and Japanese patients, no apparent relationship was found between the severity of renal impairment and the incidence of TEAEs. In general, no clinically significant changes from baseline were observed in laboratory tests (hematology, biochemistry, and urinalysis parameters) or vital signs.

CONCLUSIONS

—The main finding of this study is that after a single dose of the SGLT2 inhibitor, ipragliflozin, renal glucose excretion increases in proportion to the GFR and the plasma glucose concentration, with little evidence for other factors related to renal disease or drug efficacy. This conclusion requires specification.

Firstly, the absolute rates of ipragliflozin-induced glucose excretion were progressively reduced in patient groups with increasing severity of renal dysfunction, whether European or Japanese. As a fraction of the filtered glucose, however, ipragliflozin-induced glucose excretion was not affected to a detectable extent in either ethnic group (Fig. 1). That the ipragliflozin-induced increase in glycosuria was comparable in European and Japanese patients, despite the twofold higher dose and exposure in the former than the latter, is in line with the findings of our pharmacokinetic/pharmacodynamic model, that doses of 50 and 100 mg are above the effective dose for 50% of people given it, with an only ~10% difference in response (14).

Secondly, the absorption and excretion functions derived from our individual data at baseline (Fig. 2) very closely match the relationships derived from intraindividual measurements obtained using hyperglycemic steps (15–19): namely, renal glucose absorption rises linearly with the glucose filtration rate up to an apparent splayed threshold (≥300 mg/min) marking the onset of glycosuria (at a plasma glucose concentration typically in the vicinity of 200 mg/dL). In our dataset, the European and Japanese patients and controls all fall on the same regression lines (Fig. 2). Postdose, absorption and excretion both rise in parallel and linearly with glucose filtration rate. A saturation level (Tm_G) is no longer evident because it is shifted way to the right; likewise, a threshold at which glycosuria ensues is no longer discernible, some glucose being detectable in the urine even at very low glucose filtration rates. Clearly, a formal glucose titration protocol in each subject is required to measure Tm_G and the renal glucose threshold. Nonetheless, this finding is compatible with a drug-induced reduction in the affinity of glucose for SGLT2 rather than a decrease in maximal glucose reabsorption, as previously argued (6).

Thirdly, we found that ipragliflozin-induced glycosuria could be described as a dual function of the GFR and plasma glucose levels with a coefficient of determination of 65% (or a multiple $r = 0.74$). This strong association makes it unlikely that the kind of chronic renal disease impairing GFR or an interference of renal dysfunction with the drug mechanism of action were additional factors. More importantly, this relationship may help develop an allometric equation enabling the physician to predict the amount of glycosuria in the individual patient with

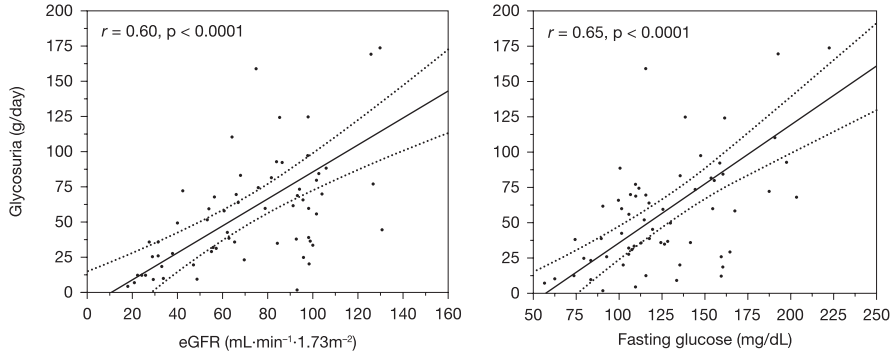

Figure 3—*Dependency of postdose glycosuria on eGFR and FPG concentration. Line of best fit and 95% CIs are shown. The model parameter estimates are glycosuria (g/day) = −11 + 0.96 × eGFR (mL · min^{-1} · 1.73 m^{-2}), and glycosuria (g/day) = −48 + 0.83 × fasting glucose (mg/dL).*

reasonable accuracy using only fasting creatinine and glucose measurements. Our relationship (Fig. 3) calculates a decrease in glycosuria of 15 g/day for each 20 mL · min^{-1} · 1.73 m^{-2} drop in eGFR, and an increase of 7 g/day for each 10 mg/dL increase in fasting glucose. By way of example, the equation predicts that a patient taking ipragliflozin with an eGFR of 45 mL/min and a fasting glucose of 200 mg/dL will excrete 61 mg/min of glucose (or 88 g/day), a similar amount to that of a patient with an eGFR of 90 mL/min and a glucose level of 150 mg/dL. Assuming that robust exposure data rule out specific adverse effects in diabetic patients with impaired renal function, one can judge whether the predicted glycosuria translates into meaningful clinical benefit in terms of glycemic control (20–24).

Finally, the reason(s) why complete inhibition of SGLT2-mediated glucose absorption is not achieved with ipragliflozin—or, for that matter, any other orally active inhibitor (6,24)—remain to be elucidated. Whereas to our knowledge this is the first attempt at quantifying the pharmacodynamics of a SGLT2 inhibitor in T2DM patients with chronic kidney disease, there are clear limitations. Firstly, the group size was relatively small, there were no nondiabetic Japanese participants or Japanese patients in eGFR$_4$ class, and only a few patients had fasting glucose levels >200 mg/dL. Thus, whether the drug effect would be significantly different between T2DM patients and nondiabetic subjects remains to be firmly established in light of the evidence suggesting an upregulation of SGLT2 in diabetes (14,24). Secondly, our Tm_G and threshold values were population estimates and not direct measurements. Thirdly, we used FPG concentrations to calculate glucose filtration rates, whereas in reality, the mean plasma glucose concentration over 24 h determines daily glycosuria. Our calculated glucose filtration rates therefore likely underestimate the actual filtration rates, and our fractional excretion values are overestimates. Finally, our results apply to a single-dose situation, but relationships may change with long-term SGLT2 inhibition.

With these provisos, it is of considerable interest that SGLT2 inhibition is the only pharmacological approach to hyperglycemia in which the primary effect (i.e., glycosuria) can be predicted in the individual patient with a good degree of reliability. Even though our mechanistic analysis demonstrates significant glycosuria in renal impairment, it is the lowering of glucose/HbA_{1c} together with the adverse effect profile, that will ultimately determine whether this class of drugs is useful in patients with diabetes and renal impairment.

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E.F., S.A.V., R.A.S., and T.K. contributed to the research of the data, discussion, and writing of the manuscript. E.F. 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.

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