



Blood pressure after treatment with sodium–glucose cotransporter 2 inhibitors influences renal composite outcome: Analysis using propensity score-matched models

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Keywords

Blood pressure, Diabetic nephropathy, Sodium–glucose cotransporter 2 Inhibitors

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ABSTRACT

Aims/Introduction: Sodium–glucose cotransporter 2 inhibitors (SGLT2i) improve renal outcome in patients with type 2 diabetes mellitus, but the mechanism is not fully understood. The aim of this retrospective study was to assess the association of achieved blood pressure with renal outcomes in Japanese type 2 diabetes mellitus patients with chronic kidney disease.

Materials and Methods: We assessed 624 Japanese type 2 diabetes mellitus patients with chronic kidney disease taking SGLT2i for >1 year. The patients were classified as those with post-treatment mean arterial pressure (MAP) of ≥ 92 mmHg ($n = 344$) and those with MAP of < 92 mmHg ($n = 280$) for propensity score matching (1:1 nearest neighbor match with 0.04 of caliper value and no replacement). The end-point was a composite of progression of albuminuria or a decrease in the estimated glomerular filtration rate by $\geq 15\%$ per year.

Results: By propensity score matching, a matched cohort model was constructed, including 201 patients in each group. The incidence of renal composite outcome was significantly lower among patients with MAP of < 92 mmHg than among patients with MAP of ≥ 92 mmHg ($n = 11$ [6%] vs $n = 26$ [13%], respectively, $P = 0.001$). The change in estimated glomerular filtration rate was similar in the two groups; however, the change in the albumin-to-creatinine ratio was significantly larger in patients with MAP of < 92 mmHg.

Conclusions: In Japanese type 2 diabetes mellitus patients with chronic kidney disease, blood pressure after SGLT2i administration influences the renal composite outcome. Blood pressure management is important, even during treatment with SGLT2i.

INTRODUCTION

Sodium–glucose cotransporter 2 inhibitors (SGLT2i) are new, oral glucose-lowering agents that act by inhibiting SGLT2 in

the renal proximal tubules and increasing urinary glucose excretion. The Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients—Removing Excess Glucose (EMPA-REG OUTCOME) trial with empagliflozin¹, the Canagliflozin Cardiovascular Assessment Study/ Canagliflozin Cardiovascular Assessment Study—Renal (CANVAS/

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CANVAS-R) program with canagliflozin² and the Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events (DECLARE-TIMI58) with dapagliflozin³ were primarily cardiovascular outcome trials designed to assess the non-inferiority of cardiovascular outcomes, such as death from cardiovascular causes, non-fatal myocardial infarction or non-fatal stroke. They showed the superiority of SGLT2i with regard to the cardiovascular outcome. The renal protective effects of SGLT2i were also reported in the subanalyses of the aforementioned trials^{4–6}, and the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDESCENCE) study showed the superiority of the renal outcome defined as a composite of end-stage kidney disease, a doubling of the serum creatinine level, or death from renal or cardiovascular causes by canagliflozin⁷. Thus, SGLT2i might have significant beneficial renal outcomes as well.

By increasing urinary glucose excretion, SGLT2i lower blood glucose levels, bodyweight (BW) and blood pressure (BP), and improves liver function⁸. Although the pleiotropic beneficial effects of SGLT2i on cardiovascular and renal outcomes have been discussed in detail⁹, little is known about their mechanism of action. We previously published data that confirmed the beneficial effects of SGLT2i on the albumin-to-creatinine ratio (ACR) in 936 Japanese patients with type 2 diabetes mellitus and chronic kidney disease (CKD)¹⁰. In the same study, we also found that the BP-lowering effect of SGLT2i correlates with their renal effects¹¹. The Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2019) stipulated strict BP management by reducing BP to <130/80 mmHg in patients with CKD with proteinuria or type 2 diabetes mellitus¹². The Japan Diabetes Outcome Intervention Trial (J-DOIT3) study is a Japanese randomized controlled trial that suggested a potential benefit of an intensified intervention to prevent cerebrovascular events and a significant reduction in the renal composite outcome by 32% in patients in whom the systolic BP (SBP) decreased to 125 mmHg¹³. Although BP management is important in patients with diabetes, it is often difficult to achieve the target BP in clinical practice. Yokoyama *et al.*¹⁴ reported that 47% of 9,956 Japanese patients with type 2 diabetes mellitus achieved the target BP of <130/80 mmHg measured at the office. In situations where BP management remains difficult, SGLT2i are certainly effective in BP management. However, there is no report on the relationship between the SGLT2i-associated BP lowering and renal outcome. The aim of the present retrospective cohort study was to assess the association of achieved BP on renal outcomes in Japanese patients with type 2 diabetes mellitus and CKD.

METHODS

Study participants and data collection

The study included 797 registered patients with type 2 diabetes mellitus who visited the clinics of members of the Kanagawa Physicians Association (diabetologists $n = 16$, nephrologists $n = 7$, cardiologists $n = 7$ and miscellaneous $n = 6$) between

October 2018 and December 2018. The inclusion criteria were: patients with type 2 diabetes mellitus and (i) treated with SGLT2i for the first time >1 year before enrolment; (ii) CKD, as defined by the Kidney Disease Outcomes Quality Initiative clinical practice guidelines¹⁵; and (iii) age >20 years. The exclusion criteria were: (i) type 1 diabetes mellitus; (ii) requirement of chronic dialysis; (iii) severe liver dysfunction, such as liver cirrhosis or severe infection; (iv) terminal stage malignancy; (v) pregnancy; (vi) irregular use of SGLT2i, as suggested by poor adherence; and (vii) an intent to opt out during the study. On the basis of the aforementioned criteria, 34 patients were excluded from the study. To evaluate renal outcome, the following parameters were recorded both at the time of initiation of SGLT2i treatment and at the time of the survey: age, sex, BW, BP (SBP and diastolic BP), serum creatinine level, glycated hemoglobin (HbA1c) level and urinary protein test results (ACR [mg/g Cr] or qualitative proteinuria). The estimated glomerular filtration rate (eGFR) was calculated using the formula: $eGFR \text{ (mL/min/1.73 m}^2\text{)} = 194 \times \text{age}^{-0.287} \times \text{serum creatinine}^{-1.094} \times (0.739 \text{ for women})^{16}$. Among the 797 registered patients, we included 624 patients for whom ACR was measured both at baseline and at the end of the survey. The median duration of treatment with SGLT2i was 33 months (range 12–66 months).

Outcomes

The renal composite end-point in the present study was set as either a worsening of ACR or a decrease in eGFR by >15% per year, or both.

Statistical analysis

Multivariable logistic regression analysis was carried out to identify the correlates for the renal composite outcome associated with potential predictors. These included concomitant medications and various clinical parameters, such as age, sex, HbA1c, BW, BP, eGFR and ACR at baseline. The inclusion of variables in the aforementioned models was based on existing knowledge of risk factors for renal disease.

Based on the results of the multivariable logistic regression analysis, we assessed the relationship between the MAP after SGLT2i treatment and the renal composite outcome. The receiver operating characteristic (ROC) curve was used to examine the overall prediction accuracy of MAP after SGLT2i treatment and the renal composite end-point. The result was reported as the area under the curve. The cut-off value of post-treatment MAP for further analysis was determined from the results of the ROC analysis.

We divided the patients into two groups on the basis of post-treatment MAP: patients with a post-treatment MAP of more than the cut-off and those with post-treatment MAP less than the cut-off value determined by ROC analysis. We then calculated the propensity score (PS) for patients with post-treatment MAP of more than the cut-off value using a logistic regression model to estimate the probability of the disease

assignment based on the following baseline variables: age, sex, BW, HbA1c, MAP, eGFR and ACR at baseline, type of SGLT2i, and concomitant use of either other antihypertensive medications, glucose-lowering medications and/or statins.

We established a cohort model using PS matching methods with the following algorithm: 1:1 nearest neighbor match with a 0.040 of the caliper value, width = 0.2 of the standard deviation of PS¹⁷, and no replacement. This was used to investigate the imbalance in the impact of clinical findings and baseline renal function on the outcome of interest, and to compare the renal composite outcome in both patient groups. Although, in general, higher caliper widths might result in reduced variance and an increased number of matched participants, this can also decrease the balance between groups and introduce more bias in estimating treatment effects (trade-off between variance and bias). In the present study, we used a lower caliper of width 0.040 to maximize correct matching and reduce bias. The absolute standardized difference <0.1 for measured covariates suggested an appropriate balance between the groups (Table 1). We analyzed the differences in the clinical, laboratory and pathological profiles between these two groups by the unpaired *t*-test or the Mann–Whitney rank-sum test for continuous variables in the unmatched cohort. In the PS-matched cohort, the paired *t*-test or the Wilcoxon signed-rank test was used. We used the χ^2 -test for categorical data for the unpaired cohort, and McNemar's test for the paired cohort.

We also established another cohort model using PS stratification. All patients were stratified into quintiles on the basis of the corresponding PS and were included in the analysis. We used the Mantel–Haenszel method to analyze these five categorical variables, and calculated the odds ratio (OR) and 95% confidence interval (CI).

All results are reported as the mean \pm standard deviation or median with interquartile range for continuous data, and as percentages for categorical data. Statistical tests were considered significant at $P < 0.05$ (two-tailed). All statistical analyses were carried out using the IBM SPSS Statistics 25.0 software program (IBM Corporation, Armonk, NY, USA).

This study was approved by the special ethics committee of the Kanagawa Medical Association, Japan (Krec304401.6 March 2018).

RESULTS

Multivariable logistic regression analysis for the renal composite outcome

In the analyzed model, the *P*-value of the omnibus test for the model coefficient was <0.001, and that of the Hosmer–Lemeshow test was 0.73. These values suggest the significance and effectiveness of the model, and that it deserves further analysis. However, the value of Nagelkerke's R^2 was 0.09, showing that the weight of the independent variable is small. Among the 624 patients, 71 (11%) had the renal composite outcome. Canagliflozin, insulin, MAP after SGLT2i treatment and patient age were significantly associated with the renal composite outcome,

with ORs of 2.42 (95% CI 1.26–4.68, $P < 0.01$), 2.15 (95% CI 1.27–3.65, $P < 0.01$), 1.05 (95% CI 1.03–1.08, $P < 0.01$), and 1.03 (95% CI 1.00–1.05, $P = 0.04$), respectively.

ROC curve

ROC analysis (Figure 1) showed that the estimated optimal cut-off value for MAP after SGLT2i treatment (i.e., a marker for renal composite outcome) was 92 mmHg, with a sensitivity of 72%, specificity of 47% and area under the curve of 0.62 (95% CI 0.55–0.69, $P < 0.001$). Accordingly, we divided the participants into two groups on the basis of post-treatment MAP: patients with post-treatment MAP of ≥ 92 mmHg (MAP ≥ 92 group) and patients with MAP <92 mmHg (MAP <92 group).

PS-matched cohort model

The clinical characteristics at baseline and after SGLT2i treatment before and after PS matching are given in Tables 1 and 2, respectively. There was a significant difference in age, body mass index, MAP and eGFR, as well as the use of dipeptidyl peptidase-4 inhibitors, metformin and insulin between the two groups in the unmatched cohort model (P -values <0.001, <0.001, <0.001, 0.005, 0.002 and 0.04, respectively). There was no significant difference between the two groups in the PS-matched model. Among 402 patients in the PS-matched model, age, BW, HbA1c, and eGFR were 61.2 ± 11.3 years, 78.4 ± 15.5 kg, 63.3 ± 14.5 mmol/mol ($7.9 \pm 1.3\%$) and 79 ± 21 mL/min/1.73 m², respectively.

The standardized background differences in PS-matched patients were calculated to evaluate the balance in this model, and were <0.1.

Comparison of the renal composite outcome of 201 propensity-matched patients in each group

Table 3a shows that the incidence of renal composite outcome was significantly lower in patients with MAP <92 mmHg after SGLT2i treatment than in those with MAP ≥ 92 mmHg. The numbers of events were 11 (6%) versus 26 (13%), respectively, and the estimated OR by the Mantel–Haenszel method was 2.57 (95% CI 1.23–5.35) in patients with MAP ≥ 92 mmHg ($P = 0.001$). Table 3b shows the incidence of renal composite outcome and changes in the logarithmic value of the ACR and eGFR. There was no significant difference in changes in eGFR between the two groups. However, the post-SGLT2i decrease in the logarithmic value of the ACR was significantly higher in the group with MAP <92 mmHg than in the group with MAP ≥ 92 mmHg ($P = 0.03$).

Cohort model using PS stratification

The patients were stratified into quintiles on the basis of the corresponding propensity score: Q1, PS ≤ 0.36 ; Q2, $0.36 < PS \leq 0.50$; Q3, $0.50 < PS \leq 0.60$; Q4, $0.60 < PS \leq 0.75$; and Q5 $0.75 < PS$. Figure 2 shows the mean incidence of renal composite outcomes based on these quintiles. The results of the

Table 1 | Baseline characteristics before and after propensity score matching

	Unmatched cohort (n = 624)		Matched cohort (n = 402)		P-value	Standardized difference	95% CI of the difference
	MAP ≥92 (n = 344)	MAP <92 (n = 280)	MAP ≥92 (n = 201)	MAP <92 (n = 201)			
Age (years)	58 ± 11	63 ± 12	61 ± 10	61 ± 12	0.94	0.01	-2.3,2.1
Sex (male)	237 (69%)	173 (62%)	136/65	135/66	0.92†	0.01	-0.44,0.39‡
Body mass index (kg/m ²)	28.5 ± 4.9	27.1 ± 4.5	27.4 ± 4.6	27.6 ± 4.4	0.67	0.04	-0.69,1.06
Bodyweight(kg)	82.2 ± 17.1	76.1 ± 14.8	78.4 ± 14.5	78.5 ± 14.6	0.92	0.01	-2.9,3.2
MAP (mmHg)	100.2 ± 11.6	93.0 ± 11.8	96.2 ± 10.7	96.0 ± 10.9	0.85	0.02	-2.3,1.9
HbA1c, mmol/mol (%)	64.6 ± 15.9 (8.1 ± 1.4)	63.3 ± 14.2 (8.0 ± 1.3)	63.5 ± 13.4 (8.0 ± 1.3)	63.1 ± 14.6 (7.9 ± 1.3)	0.79	0.03	-3.23, 2.45 (-0.30,0.22)
eGFR (mL/min/1.73 m ²)	82 ± 22	75 ± 22	78 ± 20	80 ± 22	0.37	0.09	-2.2,5.9
LNACR	1.62 ± 0.66	1.57 ± 0.63	1.59 ± 0.62	1.60 ± 0.64	0.91	0.01	-0.12,0.13
Duration of treatment (month)	31.7 ± 10.5	33.4 ± 10.7	32.2 ± 10.2	33.1 ± 10.4	0.38	0.09	-1.1,2.9
Types of SGLT2 inhibitor							
Ipragliflozin	78 (22.7%)	58 (21%)	39 (19%)	42 (21%)	0.71†	0.05	-0.58,0.40‡
Dapagliflozin	55 (16.0%)	47 (17%)	32 (16%)	35 (17%)	0.70†	0.05	-0.63,0.42‡
Tofogliflozin	45 (13.1%)	31 (11%)	28 (14%)	24 (12%)	0.69†	0.09	-0.41,0.76‡
Luseogliflozin	33 (9.6%)	21 (8%)	20 (10%)	16 (8%)	0.55†	0.12	-0.44,0.93‡
Canagliflozin	41 (11.9%)	37 (13%)	25 (12%)	25 (12%)	1.0†	0	-0.59,0.59‡
Empagliflozin	45 (13.1%)	45 (16%)	30 (15%)	30 (15%)	1.0†	0	-0.55,0.55‡
Change in SGLT2 inhibitors§	47 (13.7%)	41 (15%)	27 (13%)	29 (14%)	0.77†	0.04	-0.65,0.48‡
Concomitant treatment (at survey)							
DPP4 inhibitors	171 (49.7%)	171 (61%)	111 (55%)	120 (60%)	0.36†	0.09	-0.58,0.21‡
GLP1RA	58 (16.9%)	44 (16%)	31 (15%)	30 (15%)	0.89†	0.02	-0.51,0.58‡
Metformin	226 (65.7%)	159 (57%)	124 (62%)	128 (64%)	0.68†	0.04	-0.49,0.32‡
SU	102 (29.7%)	88 (31%)	60 (30%)	63 (31%)	0.75†	0.04	-0.50,0.35‡
Insulin	82 (23.8%)	87 (31%)	55 (27%)	54 (27%)	0.91†	0.01	-0.42,0.47‡
Pioglitazone	58 (16.9%)	58 (21%)	39 (19%)	35 (17%)	0.61†	0.07	-0.37,0.64‡
RAS inhibitors	186 (54.1%)	139 (50%)	99 (49%)	107 (53%)	0.43†	0.08	-0.55,0.23‡
Ca channel blocker	162 (47.1%)	115 (41%)	80 (40%)	90 (45%)	0.31†	0.10	-0.60,0.19‡
β-Blocker	41 (11.9%)	35 (13%)	27 (13%)	21 (10%)	0.36†	0.14	-0.32,0.89‡
Statins	210 (61.0%)	172 (61%)	124 (62%)	126 (63%)	0.84†	0.02	-0.45,0.36‡

Values are mean ± standard deviation or n/total n (%). *P-values by unpaired t-test or χ^2 -test on unmatched cohort model. †P-values by paired t-test or McNemar's test on the matched cohort model. ‡95% confidence interval (CI) of the logarithmic value of odds ratio calculated by the Mantel-Haenszel method. §Change in sodium-glucose cotransporter 2 (SGLT2) inhibitors during the study period. DPP4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration; GLP1RA, glucagon-like peptide 1 receptor agonist; HbA1c, glycated hemoglobin; LNACR, logarithmic value of albumin-to-creatinine ratio; MAP, mean arterial pressure; RAS, renin-angiotensin system inhibitor.

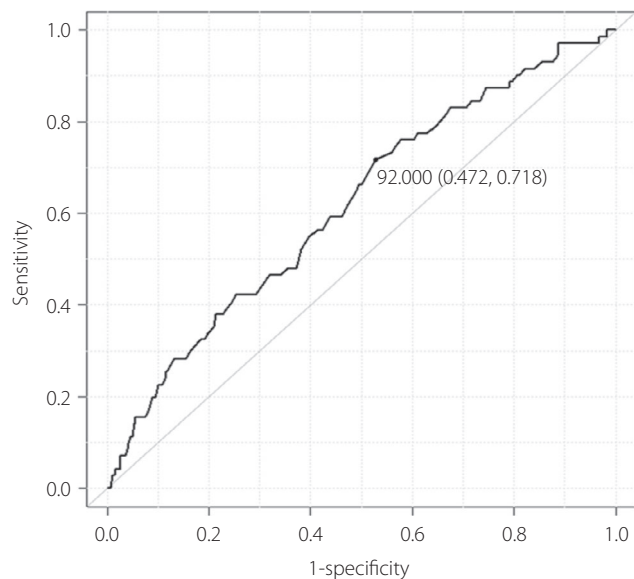


Figure 1 | Receiver operating characteristic curve of mean arterial pressure after treatment with sodium–glucose cotransporter 2 inhibitors for renal composite end-point. It shows the receiver operating characteristic curve of mean arterial pressure after treatment with sodium–glucose cotransporter 2 inhibitors for renal composite end-point.

Mantel–Haenszel analysis showed a significant difference between the two groups ($P = 0.002$). The OR for the renal composite outcome was 2.99 (95% CI 1.56–5.73, $P = 0.001$) in patients with MAP ≥ 92 mmHg after SGLT2i treatment.

DISCUSSION

According to the Standards of Medical Care in Diabetes 2019, BP targets should be individualized for patients with DM and hypertension by a shared decision-making process that addresses cardiovascular risk, potential adverse effects of antihypertensive medications and patient preferences. For individuals at high cardiovascular risk (existing atherosclerotic cardiovascular disease or 10-year atherosclerotic cardiovascular disease risk $>15\%$), a BP target of $<130/80$ mmHg at the office might be appropriate¹⁸. In Japan, the Japan Society of Hypertension 2019

guidelines defined the target BP as 130/80 mmHg at the office or 125/75 mmHg early in the morning at home¹². In the present study, the cut-off value of MAP after SGLT2i treatment was 92 mmHg (equivalent to $\sim 125/75$ mmHg), which is lower than the target BP of 130/80 mmHg. The results of the present study suggest that achieving a lower BP ($<130/80$, as recommended by some guidelines) is associated with a lower incidence of composite renal outcome.

A few trials have evaluated the renal outcome by achieved BP as their primary end-point. The results of the African American Study of Kidney Disease and Hypertension trial reported by Wright *et al.*¹⁹ suggest no additional benefit in the progression of hypertensive nephrosclerosis with a lower achieved BP. Ruggenenti *et al.*²⁰ reported no additional benefit from further BP reduction by felodipine in patients with non-diabetic nephropathy with proteinuria on background therapy with angiotensin-converting enzyme inhibitor (the Ramipril Efficacy in Nephropathy 2 [REIN-2] trial).

Several studies discussed the advantage of a better renal outcome with a BP of $<130/80$ mmHg in patients with type 2 diabetes mellitus. The randomized controlled trial J-DOIT3 study suggested improvement in type 2 diabetes mellitus-related complications in Japanese patients with type 2 diabetes mellitus treated aggressively as compared with those treated in a conventional manner¹³. In patients subjected to aggressive treatment, a reduction in SBP to 123 mmHg was associated with a significant decrease in the renal composite outcome (worsening of ACR status, doubling of serum creatinine, progression to end-stage kidney disease [ESKD] or the initiation of renal replacement therapy) by 32%¹³. The Irbesartan Diabetic Nephropathy Trial (IDNT) study suggested that the decrease in SBP to <120 mmHg is associated with the best renal outcome (doubling of serum creatinine level, progression to ESKD or initiation of renal replacement therapy)²¹. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, however, reported a significant decrease of eGFR in patients with SBP <120 mmHg, despite a decrease in ACR¹⁶. Sim *et al.*¹⁷ reported an insignificant decrease in the incidence of ESKD in patients with an SBP <110 mmHg in a USA cohort. Interestingly, a cohort study from Taiwan reported that an SBP of 110–120 mmHg was associated with the lowest incidence of ESKD, better than that of 96–110 mmHg¹⁸. The results from

Table 2 | Characteristics after sodium–glucose cotransporter 2 inhibitor treatment in both cohort models

	Unmatched cohort ($n = 624$)			Matched cohort ($n = 402$)		
	MAP ≥ 92 ($n = 344$)	MAP <92 ($n = 280$)	P -value	MAP ≥ 92 ($n = 201$)	MAP <92 ($n = 201$)	P -value
Bodyweight (kg)	78.9 \pm 16.4	72.9 \pm 14.1	<0.001	75.0 \pm 15.8	75.2 \pm 13.5	0.89
MAP (mmHg)	100.9 \pm 7.4	84.5 \pm 5.8	<0.001	99.3 \pm 6.4	85.2 \pm 5.5	<0.001
HbA1c, mmol/mol (%)	58.1 \pm 13.4 (7.5 \pm 1.2)	55.7 \pm 10.0 (7.3 \pm 0.9)	0.02	56.8 \pm 10.6 (7.3 \pm 1.0)	55.4 \pm 9.8 (7.2 \pm 0.9)	0.18

MAP, mean arterial pressure; SGLT2, sodium–glucose co-transporter 2.

Table 3 | Incidence of renal composite outcome and changes in logarithmic value of the albumin-to-creatinine ratio and estimated glomerular filtration rate

Incidence of renal composite outcome					
	Observed		Not observed	<i>P</i> -value (McNemar's test)	
MAP <92	11 (6%)		190 (95%)	0.001	
MAP ≥92	26 (13%)		175 (87%)		
Changes in LNACR and eGFR					
	At baseline	At survey	Change from baseline to survey	<i>P</i> -value of comparison of baseline vs survey (unpaired <i>t</i> -test)	<i>P</i> -value of comparison at survey (unpaired <i>t</i> -test)
eGFR					
MAP <92	80.0 ± 21.6	74.6 ± 20.5	-5.4 ± 10.5	<0.001	0.67
MAP ≥92	78.1 ± 19.5	73.7 ± 19.8	-4.4 ± 11.1	<0.001	
LNACR					
MAP <92	1.60 ± 0.64	1.43 ± 0.63	-0.17 ± 0.46	<0.001	0.03
MAP ≥92	1.59 ± 0.62	1.57 ± 0.66	-0.02 ± 0.46	0.54	

Values are mean ± standard deviation. eGFR, estimated glomerular filtration; LNACR, logarithmic value of albumin-to-creatinine ratio; MAP, mean arterial pressure; SGLT2, sodium–glucose c-transporter 2.

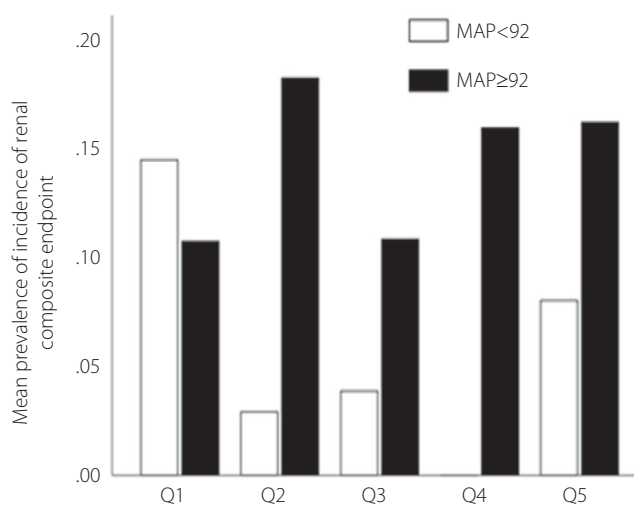


Figure 2 | Mean incidence of renal composite end-point based on the quintiles of all patients. Patients were stratified into quintiles (Q) based on the corresponding propensity score (PS): Q1, PS ≤0.36; Q2, 0.36 < PS ≤ 0.50; Q3, 0.50 < PS ≤ 0.61; Q4, 0.61 < PS ≤ 0.75; and Q5, 0.75 < PS) and it shows the mean incidence of renal composite end-point based on the quintiles of all patients. MAP; mean arterial pressure.

the aforementioned studies suggest that a target SBP of <110 mmHg has no beneficial effect on renal outcomes. However, it is not clear from the aforementioned studies which SBP level (110, 120 or 130 mmHg) is the best with regard to renal outcome. SGLT2i was not used in those studies. The MAP after SGLT2i treatment in the group with MAP <92 mmHg in the

matched cohort model was 85.2 ± 5.5 mmHg (equivalent to approximately 120/70 mmHg), and it appears to be lower than that recorded in the J-DOIT3 study¹³. The results of the present study suggest that BP reduction with SGLT2i is associated with an improved renal outcome.

An excess decrease in BP by antihypertensive medication is a serious problem. The Japan Society of Hypertension 2019 guidelines warn that if SBP has been reduced to <120 mmHg, there might be adverse events associated with falling BP¹². No prospective interventional study has evaluated the effects of excess BP reduction on renal function. However, Weber *et al.*²² reported that the renal end-point of a sustained >50% increase in serum creatinine was significantly lower in those with an SBP <140 mmHg than higher or lower BP ranges. The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) evaluated the benefit of combination treatment with telmisartan and ramipril. A sub-analysis of this study for renal outcomes suggested worse major renal outcomes (dialysis or doubling of serum creatinine) with the combination treatment, and more adverse events, such as hypotensive symptoms or renal impairment with BP of 132.1/75.8 mmHg, which was only slightly lower than that in the ramipril only group^{23,24}. In contrast, a meta-analysis suggests that SGLT2i reduce end-stage kidney disease and acute kidney injury with consistent benefits across studies²⁵.

In the present study, changes in BP were surveyed both at the office and at home for 102 patients with type 2 diabetes mellitus and CKD. The BP significantly decreased from 137 ± 17/78 ± 12 mmHg to 133 ± 15/76 ± 11 mmHg at the office, and 129–126 mmHg in the morning at home (*P* < 0.05 for both). In the same group of patients, SGLT2i treatment significantly decreased home MAP in patients with baseline home

BP of $\geq 125/75$ mmHg (from 97 ± 9 to 94 ± 8 mmHg, $P < 0.001$), but not in those with baseline home BP of $< 125/75$ mmHg. These results suggest that SGLT2i do not induce an excessive decrease in BP. It is well known that SGLT2i do not change the heart rate. As the heart rate increases with an excess decrease in BP as a result of the physiological reflex, tachycardia, we can argue that there is no increase in heart rate with SGLT2i because there is no excess decrease in BP. It is possible that lowering BP to safe levels without causing excessive hypotension is related to the better renal outcome associated with the use of SGLT2i. There are, however, no studies of SGLT2i to prove this hypothesis. Further studies are required to determine whether SGLT2i administration improves renal outcome at a lower target BP compared with the current target of 130/80 mmHg.

The present study had certain limitations. First, it was a retrospective observational study. Second, the study design was one arm without a placebo. Diet, exercise or additional BP-lowering medications might lead to variations in the achieved MAP, and this could confound the results. Third, although PS methods offer certain advantages over more traditional regression methods to control for confounding, nearly half or more of the collected cases will not be analyzed on the PS matching cohort model and important clinical data could be missed. We also analyzed the cohort model using PS stratification. This quintile analysis includes all cases, and there is a possibility to complement the cases that have been missed during PS matching. Similar results from two different analytic methods using PS give strength to our conclusions. Further larger prospective studies are required to confirm the present findings that reducing BP with SGLT2i to 125/75 mmHg ($< 130/80$) can improve renal outcome.

We showed that in Japanese type 2 diabetes mellitus patients with CKD, BP after SGLT2i treatment influences a renal composite outcome. However, the significant finding of the present study was that BP after SGLT2i treatment is associated with albuminuria, but not with eGFR. This confirms the importance of BP management in type 2 diabetes mellitus patients with CKD, even for those receiving SGLT2i treatment.

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DISCLOSURE

The authors declare no conflict of interest.

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