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# Sodium–glucose cotransporter 2 inhibitor-induced reduction in the mean arterial pressure improved renal composite outcomes in type 2 diabetes mellitus patients with chronic kidney disease: A propensity score-matched model analysis in Japan

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**Keywords**
Blood pressure, Chronic kidney disease, Sodium–glucose cotransporter 2 inhibitors

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## ABSTRACT

**Aims/Introduction:** Large-scale clinical trials have reported that, in patients with type 2 diabetes mellitus, sodium–glucose cotransporter 2 (SGLT2) inhibitor treatment affords favorable renal outcomes; the underlying mechanisms, however, remain unclear. Thus, this study investigated how SGLT2 inhibitor-induced changes in the mean arterial pressure (MAP; denoted as ΔMAP) are associated with renal outcomes in type 2 diabetes mellitus patients with chronic kidney disease (CKD).

**Materials and Methods:** We retrospectively assessed the data of 624 Japanese type 2 diabetes mellitus patients with CKD who had been using SGLT2 inhibitors for >1 year. For propensity score matching (1:1 nearest neighbor match, with caliper value = 0.053, no replacement), patients were categorized into two groups based on the ΔMAP (>−4 mmHg [*n* = 329] and ≤−4.0 mmHg [*n* = 295]). Composite albuminuria progression or a ≥15% annual reduction in the estimated glomerular filtration rate was regarded as the end-point.

**Results:** Per group, 173 propensity-matched patients were compared. Patients with ΔMAP ≤−4 mmHg had a significantly lower incidence of composite renal outcomes than those with ΔMAP ≥−4 mmHg (5.8% [*n* = 10] vs 15.6% [*n* = 27], *P* = 0.003). Although the between-group differences in the estimated glomerular filtration rates were non-significant, patients with a ΔMAP ≤−4 mmHg had significantly larger reductions in the logarithmic urine albumin-to-creatinine ratio (*P* = 0.005).

**Conclusions:** The degree of blood pressure reduction after SGLT2 inhibitor treatment influenced renal composite outcomes in Japanese type 2 diabetes mellitus patients with CKD, confirming the importance of blood pressure management in type 2 diabetes mellitus patients with CKD, even when they are under SGLT2 inhibitor treatment.

## INTRODUCTION

Sodium–glucose cotransporter 2 (SGLT2), present on the renal proximal tubules, is responsible for the reabsorption of urinary glucose. Thus, the administration of SGLT2 inhibitors leads to reductions in plasma glucose levels. Clinical trials, such as the Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI58)[1], Canagliflozin Cardiovascular Assessment Study/Renal Endpoints in Adult Participants With Type 2 Diabetes Mellitus (CANVAS/CANVAS-R)[2] and (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME)[3], reported favorable cardiovascular outcomes with the

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SGLT2 inhibitors, dapagliflozin, canagliflozin and empagliflozin, respectively. Furthermore, the subanalyses of these trials[4–6] confirmed their renal protective effects. In the Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) study, Perkovic *et al.* showed the renal outcome superiority of canagliflozin, defined as a composite of end-stage kidney disease (ESKD), a twofold increase in the serum creatinine levels or death due to renal or cardiovascular causes.[7] In addition to reductions in plasma levels of glucose, SGLT2 inhibitors can improve the liver function and alleviate hypertension, as well as obesity and overweight[8]. However, although the favorable pleiotropic effects of SGLT2 inhibitors on renal and cardiovascular outcomes have been discussed[9], their underlying mechanisms remain unknown.

Two Japanese studies[10,11] reported that SGLT2 inhibitors have favorable effects on the urine albumin-to-creatinine ratios (ACRs) of type 2 diabetes mellitus patients with chronic kidney disease (CKD). In addition, we previously showed that blood pressure (BP) management during SGLT2 inhibitor treatment is correlated with ACR improvement[12]. Further analyses using propensity score matching showed a significantly lower renal composite outcome incidence in patients with a <92 mmHg mean arterial pressure (MAP) after treatment with SGLT2 inhibitors, which is equivalent to 125/75 mmHg[13]. Although BP management is crucial, reaching the target BP is often difficult in clinical practice. SGLT2 inhibitor treatment effectively regulates BP when BP management remains challenging. Baker *et al.*[14] reported that SGLT2 inhibitor use in patients with type 2 diabetes mellitus led to a 4-mmHg reduction in systolic BP (SBP) and a 3.76- and 1.83-mmHg (significant) reduction in 24-h ambulatory SBP and diastolic BP (DBP), respectively[15]. Thus, the BP-reducing effect of SGLT2 inhibitors is comparable to that of antihypertensive agents; however, studies evaluating the relationship between the degree of BP reduction and renal outcomes are warranted.

In this retrospective cohort study, the influence of SGLT2 inhibitor-induced BP-lowering effects on renal outcomes in Japanese type 2 diabetes mellitus patients with CKD was investigated.

## MATERIALS AND METHODS

### Patients and data collection

The present study was a subanalysis of our previous reports; therefore, we have described the data collection method used here previously[11]. In brief, the participants were 797 type 2 diabetes mellitus patients who visited Kanagawa Physicians Association-affiliated medical institutions during the final 3 months of 2018. Patients who received first-time SGLT2 inhibitor treatment for >1 year, as well as a diagnosis of CKD, as defined by the clinical practice guidelines of the Kidney Disease Outcomes Quality Initiative[16], were included in the present study. A total of 34 patients were excluded in accordance with the exclusion criteria described in our previous report[11]. The patients included in this retrospective study received SGLT2 inhibitor treatment as part of the standard treatment for type 2 diabetes mellitus. The sex, age, bodyweight (BW), DBP, SBP, hemoglobin $A_{1c}$ ($HbA_{1c}$) level, serum creatinine levels and urinary protein indicators (i.e., ACR [in mg/gCr] or qualitative proteinuria) at the start of SGLT2 inhibitor treatment and those at the renal outcome evaluation were recorded for all patients. In addition, we calculated the estimated glomerular filtration rate (eGFR) as follows:

eGFR (mL/min/1.73 $m^2$) = 194 × $age^{-0.287}$ × serum creatinine$^{-1.094}$ × (0.739 from women).

Of the 797 included patients, we analyzed the data of 624 whose ACRs were collected at SGLT2 inhibitor initiation and at the time of the evaluation.[17] Their median duration of SGLT2 inhibitor treatment was 33.0 months (range 12–66 months).

The present study was carried out in compliance with the Declaration of Helsinki, with the approval of the special ethics committee of the Kanagawa Medical Association, Japan (Krec304401.6 March 2018).

### Outcomes

An annual eGFR reduction by >15%, worsened ACR category, or both, was defined as the primary renal composite outcome. We also analyzed the change in the natural logarithm of ACR (ΔLNACR) and the change in the eGFR (ΔeGFR) as the secondary outcomes.

### Statistical analysis

The statistical analysis using propensity scores (PSs) carried out in this study, which focused on ΔMAP, is basically identical to our previously reported procedure[13]. The current study assessed the relationship between the change in the MAP (ΔMAP) and renal composite outcome after SGLT2 inhibitor treatment. We collected the BP data only at two points: (i) at the initiation of the treatment of SGLT2 inhibitor; and (ii) at the survey. We defined the change in the MAP at these two points as the ΔMAP.

The overall prediction accuracy of the ΔMAP and renal composite outcome after SGLT2 inhibitor treatment was evaluated using a receiver operating characteristic (ROC) curve analysis. We also identified the ΔMAP cut-off for further analyses using the ROC curve analysis. A comparison analysis was also carried out between two groups of patients with ΔMAPs above and below the cut-off value. We then used a logistic regression model (continuous variables: age, BW, ACR, MAP, $HbA_{1c}$ and eGFR at baseline; categorical variables: sex, SGLT2 inhibitor type and concomitant BP-lowering agent-hypoglycemic agent-statin use) to calculate the PSs of patients with ΔMAP values above the cut-off. The following algorithm was used for PS matching: 1:1 nearest neighbor matching with a caliper value of 0.053, which was equal to a width of 0.2 for the standard deviation of PS[18], and without replacement. We compared the clinical backgrounds of the two groups using the Mann-Whitney rank-sum or unpaired *t*-test for the unmatched cohort model and Wilcoxon's signed-rank and paired *t*-test for the matched cohort model. Regarding categorical data, chi-square and McNemar's tests were used for the unmatched and matched cohort models, respectively. The incidence of the number of renal composite outcomes was analyzed in the PS-matched cohort model by McNemar's test.

We developed an additional PS-stratified cohort model. According to their corresponding PSs, we stratified all patients into quintiles and used the Mantel–Haenszel method to analyze the five categorical variables, and calculated odds ratios (ORs) and their 95% confidence intervals (CIs).

Medians (interquartile ranges) or means ± standard deviations are used to present continuous data, whereas percentages are used to express categorical data. A two-tailed $P < 0.05$ was considered to show significance. Statistical analyses were carried out using the SPSS Statistics software program (version 25.0; IBM Inc., Armonk, NY, USA).

### Supplementary cohort model

Further analyses focusing on the MAP at baseline were carried out. Two statistical analyses involving PS matching and stratification were carried out as described previously in the Materials and Methods section. In particular, the patients were grouped according to the baseline MAP: those with baseline MAPs higher and lower than the MAP cut-off value based on the ROC analysis results. The same indicators, except for the MAP at baseline, were used to calculate PSs. PS matching was then carried out as follows: 1:1 nearest neighbor match, caliper value of 0.035, which was equal to a width of 0.2 for the standard deviation of PS, and without replacement.

## RESULTS

### ROC curve analyses

Of the 624 patients, 71 (11.4%) achieved the renal composite outcome, corroborating our previous results[13]. Table S1 shows the ΔeGFR after SGLT2 inhibitor treatment in the 12 patients who showed >15% annual eGFR reduction. The ACR category of 59 patients worsened, whereas no patients achieved the renal outcome of both eGFR and ACR change. These two renal outcomes were thus deemed independent of each other in the present study.

In the ROC analysis, the optimal ΔMAP cut-off was −4.0 mmHg (a marker of the renal composite outcome), with a sensitivity of 66%, specificity of 48% and area under the ROC curve of 0.58 (95% CI 0.51–0.65, $P < 0.01$; Figure 1). In total, 295 and 329 patients had a reduction in the MAP from the baseline ≥4 mmHg (ΔMAP of ≤−4.0) and a reduction in the MAP from the baseline <4 mmHg (ΔMAP of >−4.0), respectively; of them, 26 and 45, respectively, achieved the renal composite outcome. The univariate regression analysis showed a non-significant relationship of the renal composite outcome with a ΔMAP >−4.0 mmHg (OR 1.64; 95% CI 0.98–2.73; $P = 0.056$).

### PS-matched cohort model

The age, MAP, BW, $HbA_{1c}$ and eGFR of the 346 patients in the PS-matched model were 60.2 ± 11.4 years, 97.7 ± 8.6 mmHg, 79.3 ± 15.8 kg, 63.6 ± 14.2 mmol/mol (8.0 ± 1.3%) and 79 ± 22 mL/min/1.73 $m^2$, respectively.

Table 1 presents the baseline clinical characteristics before and after PS matching, and Table 2 presents the clinical characteristics after SGLT2 inhibitor treatment in both cohort models. The respective values of ΔMAP, ΔSBP, ΔDBP (mmHg) were 5.6 ± 7.1, 5.2 ± 12.6 and 5.8 ± 7.5 in patients with ΔMAP >−4 mmHg, and −13.4 ± 8.5, −18.2 ± 14.3 and −11.1 ± 8.4 in patients with ΔMAP ≤−4 mmHg in the unmatched cohort model, and 3.6 ± 6.0, 2.1 ± 11.8 and 4.4 ± 6.9 in patients with ΔMAP >−4 mmHg, and −11.5 ± 6.6, −15.2 ± 12.2 and −9.7 ± 7.1 in patients with ΔMAP ≤−4 mmHg in the matched cohort model (Table 2). The two groups differed significantly in the unmatched cohort model in terms of the body mass index, MAP, $HbA_{1c}$, dapagliflozin, glucagon-like peptide-1 receptor agonist and statin use ($P$ = 0.049, <0.001, 0.015, 0.027, 0.019 and 0.025, respectively); however, the two groups did not differ significantly in the PS-matched model. The absolute standardized difference of $<1.96 \times \sqrt{2/n}$ for measured covariates showed that the balance between the groups was appropriate[19]. This borderline in the present matched cohort model ($n = 173$) in each group was 0.21 ($=1.96 \times \sqrt{2/173}$), and all standardized differences in clinical characteristics were <0.21 in this matched cohort model.

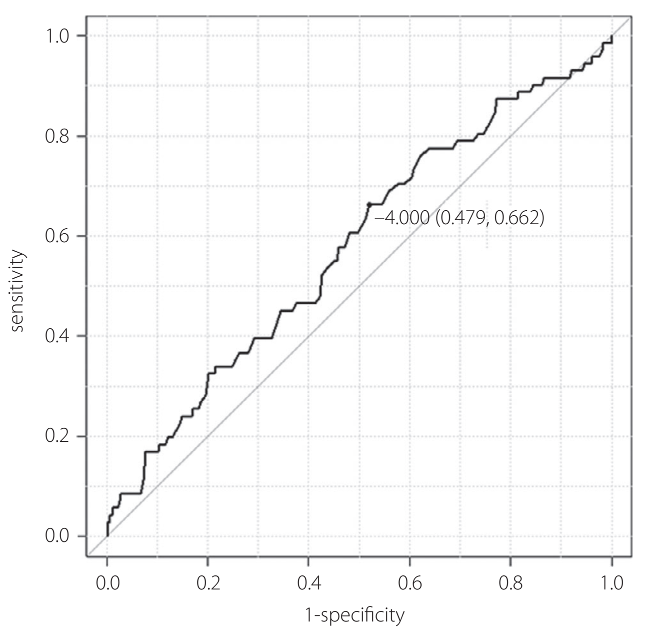


**Figure 1** | Receiver operating characteristic curve of mean arterial pressure reduction for the renal composite outcome after sodium–glucose cotransporter 2 inhibitor treatment. The receiver operating characteristic curve of mean arterial pressure reduction for the renal composite outcome after sodium–glucose cotransporter 2 inhibitor treatment is shown.

**Table 1** | Baseline characteristics before and after propensity score matching for model 1

| | Unmatched cohort ($n$ = 624) | | | | | |
|---|---|---|---|---|---|---|
| | ΔMAP >−4 mmHg ($n$ = 329) | ΔMAP ≤−4 mmHg ($n$ = 295) | $P$-value | ΔMAP >−4 mmHg ($n$ = 173) | ΔMAP ≤−4 mmHg ($n$ = 173) | Standardized difference |
| Age (years) | 60.6 ± 11.0 | 60.3 ± 12.0 | NS (0.72) | 60.3 ± 10.2 | 60.1 ± 12.5 | 0.019 |
| Sex (male) | 216 (65.7%)9 | 194 (65.8%) | NS (0.98)* | 118 (68.2%) | 113 (65.3%) | 0.065 |
| Body mass index (kg/m$^2$) | 28.3 ± 5.1 | 27.5 ± 4.4 | 0.049 | 27.7 ± 4.7 | 27.8 ± 4.1 | 0.021 |
| Bodyweight (kg) | 80.0 ± 17.3 | 78.8 ± 15.4 | NS (0.35) | 79.1 ± 17.0 | 79.6 ± 14.5 | 0.032 |
| MAP (mmHg) | 91.8 ± 10.7 | 102.7 ± 11.2 | <0.001 | 97.7 ± 8.9 | 97.8 ± 8.3 | 0.005 |
| Systolic BP (mmHg) | 128.4 ± 14.4 | 141.9 ± 16.1 | <0.001 | 136.1 ± 12.4 | 135.6 ± 13.4 | 0.009 |
| Diastolic BP (mmHg) | 73.5 ± 11.0 | 83.2 ± 11.0 | <0.001 | 78.5 ± 10.0 | 78.8 ± 9.4 | 0.028 |
| HbA$_{1c}$ (mmol/mol [%]) | 62.6 ± 15.5 (7.88 ± 1.42) | 65.6 ± 14.6 (8.15 ± 1.34) | 0.015 | (7.96 ± 1.39) | (7.98 ± 8.33) | 0.017 |
| eGFR (mL/min/1.73 m$^2$) | 78.2 ± 21.4 | 80.3 ± 22.4 | NS (0.23) | 78.5 ± 20.2 | 80.2 ± 24.0 | 0.076 |
| LNACR | 1.57 ± 0.67 | 0.63 ± 0.61 | NS (0.20) | 1.62 ± 0.69 | 1.61 ± 0.62 | 0.014 |
| Administration period (months) | 32.3 ± 10.5 | 32.6 ± 10.6 | NS (0.73) | 31.5 ± 10.5 | 32.3 ± 10.1 | 0.073 |
| Type of SGLT2 inhibitor | | | | | | |
| Ipragliflozin | 76 (231%) | 60 (79.7%) | NS (0.40)* | 33 (19.1%) | 35 (20.2%) | 0.037 |
| Dapagliflozin | 64 (19.5%) | 38 (12.9%) | 0.027* | 29 (16.8%) | 29 (16.8%) | 0 |
| Tofogliflozin | 36 (10.9%) | 40 (13.6%) | NS (0.32)* | 21 (12.1%) | 21 (12.1%) | 0 |
| Luseogliflozin | 25 (7.6%) | 29 (9.8%) | NS (0.32)* | 15 (8.7%) | 13 (7.5%) | 0.078 |
| Canagliflozin | 37 (11.2%) | 41 (13.9%) | NS (0.32) * | 23 (13.3%) | 25 (14.5%) | 0.048 |
| Empagliflozin | 41 (12.5%) | 49 (16.6%) | NS (0.14)* | 27 (15.6%) | 24 (13.9%) | 0.069 |
| SGLT2 inhibitors were changed | 50 (15.2%) | 38 (12.9%) | NS (0.41)* | 25 (14.5%) | 26 (15.0%) | 0.022 |
| Concomitant treatment (at the survey) | | | | | | |
| DPP4 inhibitor | 185 (56.2%) | 157 (53.2%) | NS (0.45)* | 92 (53.2%) | 93 (53.8%) | 0.011 |
| GLP1RA | 43 (13.1%) | 56 (20.0%) | 0.019* | 23 (13.3%) | 30 (17.3%) | 0.157 |
| Metformin | 201 (61.1%) | 184 (62.4%) | NS (0.74)* | 108 (62.4%) | 106 (61.3%) | 0.024 |
| SU | 98 (29.8%) | 92 (31.2%) | NS (0.71)* | 48 (27.7%) | 52 (30.1%) | 0.056 |
| Insulin | 90 (27.4%) | 79 (26.8%) | NS (0.87) * | 47 (27.2%) | 43 (24.9%) | 0.060 |
| Pioglitazone | 61 (18.5%9 | 55 (18.6%) | NS (0.97)* | 36 (20.8%) | 35 (20.2%) | 0.018 |
| RAS inhibitors | 170 (51.7%) | 155 (52.5%) | NS (0.83)* | 91 (52.6%) | 87 (50.3%) | 0.046 |
| Ca channel blocker | 146 (44.4%) | 131 (44.4%) | NS (0.99)* | 74 (40.5%) | 77 (42.8%) | 0.035 |
| β-blocker | 41 (12.5%) | 35 (11.9%) | NS (0.82) * | 27 (15.6%) | 19 (11.0%) | 0.20 |
| Statins | 215 (65.3%) | 167 (56.6%) | 0.025* | 109 (63.0%) | 104 (60.1%) | 0.061 |

Values are expressed as the mean ± standard deviation or $n$/total $n$ (%), and analyses were carried out using the unpaired $t$-test or $\chi^2$-test* with an unmatched cohort model. ΔMAP, change in the mean atrial pressure; BP, blood pressure; Ca, calcium; CI, confidence interval; DPP4, dipeptidyl peptidase-4; eGFR; estimated glomerular filtration rate; GLP1RA; glucagon-like peptide-1 receptor agonist; HbA$_{1c}$, hemoglobin A1c; LNACR; logarithmic value of albumin-to-creatinine ratio; MAP, mean atrial pressure; NS, not significant; RAS, renin–angiotensin system inhibitor; SGLT2, sodium–glucose cotransporter 2; SU, sulphonylurea.

### Renal composite outcome comparison

After SGLT2 inhibitor treatment, the incidence of the renal composite outcome was significantly lower in patients with ΔMAP ≤−4 mmHg than in those with ΔMAP >−4 mmHg (Table 3a); the number of events in each group was 10 (5.8%) and 27 (15.6%), respectively (OR 3.01, 95% CI 1.41–6.44, $P$ = 0.003). The incidence of renal composite outcome and the ΔLNACR and ΔeGFR are presented in Table 3b. The two groups did not differ significantly with regard to eGFR changes; however, the reductions in the LNACR were significantly larger in patients with ΔMAP ≤−4 mmHg than in those with ΔMAP >−4 mmHg ($P$ = 0.005).

### PS-stratified cohort model

Patient stratification into five quintiles (Q) was carried out based on PSs as follows: Q1 (PS ≤0.26), Q2 (PS = 0.26–0.45), Q3 (PS = 0.45–0.60), Q4 (PS = 0.60–0.80) and Q5 (PS >0.80). The mean incidence of renal composite outcomes for these quintiles is presented in Figure 2. In the Mantel–Haenszel analysis, the two groups differed significantly with regard to the renal composite outcome incidence after SGLT2 inhibitor treatment ($P$ = 0.038), with an OR of 2.05 (95% CI 1.09–3.85; $P$ = 0.025) among patients with ΔMAP >−4 mmHg.

**Table 2** | Clinical characteristics after sodium–glucose cotransporter 2 inhibitor treatment in both cohort models

| | Unmatched cohort ($n$ = 624) | | | Matched cohort ($n$ = 356) | | |
|---|---|---|---|---|---|---|
| | ΔMAP >−4 mmHg ($n$ = 329) | ΔMAP ≤−4 mmHg ($n$ = 295) | $P$-value | ΔMAP >−4 mmHg ($n$ = 173) | ΔMAP ≤−4 mmHg ($n$ = 173) | $P$-value |
| Bodyweight (kg) | 76.9 ± 16.7 | 89.3 ± 9.6 | NS (0.24) | 75.8 ± 16.3 | 76.3 ± 13.8 | NS (0.75) |
| MAP (mmHg) | 97.4 ± 9.9 | 89.3 ± 9.6 | <0.001 | 101.3 ± 9.4 | 86.2 ± 8.1 | <0.001 |
| Systolic BP (mmHg) | 133.6 ± 14.6 | 123.8 ± 13.2 | <0.001 | 138.2 ± 15.0 | 120.5 ± 12.8 | <0.001 |
| Diastolic BP (mmHg) | 79.3 ± 10.4 | 72.1 ± 10.3 | <0.001 | 82.9 ± 9.1 | 69.1 ± 9.1 | <0.001 |
| ΔMAP (mmHg) | 5.6 ± 7.1 | −13.4 ± 8.5 | <0.001 | 3.6 ± 6.0 | −11.5 ± 6.6 | <0.001 |
| ΔSystolic BP (mmHg) | 5.2 ± 12.6 | −18.2 ± 14.3 | <0.001 | 2.1 ± 11.8 | −15.2 ± 12.2 | <0.001 |
| ΔDiastolic BP (mmHg) | 5.8 ± 7.5 | −11.1 ± 8.4 | <0.001 | 4.4 ± 6.9 | −9.7 ± 7.1 | <0.001 |
| $HbA_{1c}$ (mmol/mol [%]) | 57.0 ± 12.5 (7.37 ± 1.15) | 57.0 ± 11.5 (7.37 ± 1.05) | NS (0.96) | 58.6 ± 13.1 (7.51 ± 1.19) | 56.1 ± 10.7 (7.28 ± 0.98) | NS (0.05) |
| eGFR (mL/min/1.73 $m^2$) | 74.2 ± 22.2 | 74.8 ± 21.4 | NS (0.72) | 73.9 ± 19.9 | 74.7 ± 22.1 | NS (0.70) |
| LNACR | 1.26 ± 0.71 | 1.44 ± 0.61 | 0.032 | 1.60 ± 0.72 | 1.40 ± 0.55 | 0.005 |

Values are expressed as the mean ± standard deviation. ΔMAP, change in mean arterial pressure; BP, blood pressure; eGFR, estimated glomerular filtration rate; $HbA_{1c}$, hemoglobin $A_1c$; LNACR, logarithmic value of albumin-to-creatinine ratio; MAP, mean arterial pressure; NS, not significant; SGLT2, sodium–glucose cotransporter 2.

**Table 3** | The incidence of renal composite outcome and changes in the logarithmic value of albumin-to-creatinine ratio and estimated glomerular filtration rate in the propensity score-matched cohort model

| Group | | Observed | Not observed | $P$-value |
|---|---|---|---|---|
| Incidence number of renal composite outcome | | | | |
| | ΔMAP ≤−4 mmHg | 10 (5.8%) | 163 (94.2%) | 0.003[†] |
| | ΔMAP >−4 mmHg | 27 (15.6%) | 146 (84.4%) | |

| | Group | At baseline | At the survey | Change between baseline and at the survey | Comparison between baseline and at the survey (paired $t$-test) | Comparison at the survey (paired $t$-test) |
|---|---|---|---|---|---|---|
| Changes in LNACR and eGFR | | | | | | |
| eGFR | ΔMAP ≤−4 mmHg | 80.2 ± 24.0 | 74.7 ± 22.1 | −5.5 ± 10.4 | <0.001 | NS (0.70) |
| | ΔMAP >−4 mmHg | 78.5 ± 20.2 | 73.9 ± 19.9 | −4.6 ± 12.0 | <0.001 | |
| LNACR | ΔMAP ≤−4 mmHg | 1.61 ± 0.62 | 1.40 ± 0.55 | −0.20 ± 0.44 | <0.001 | 0.005 |
| | ΔMAP >−4 mmHg | 1.62 ± 0.69 | 1.60 ± 0.72 | −0.02 ± 0.43 | NS (0.60) | |

ΔMAP, change in mean arterial pressure; eGFR, estimated glomerular filtration rate; LNACR, logarithmic value of albumin-to-creatinine ratio; NS, not significant; SGLT2, sodium–glucose cotransporter 2. [†]McNemar's test.

**Supplementary cohort model results**

The optimal baseline MAP cut-off as a renal composite outcome marker estimated in the ROC analysis was 97.7 mmHg, with a sensitivity of 52%, specificity of 54% and area under the ROC curve of 0.53 (95% CI 0.46–0.60, $P$ < 0.01; Figure S1). In total, 34 of the 336 patients with a baseline MAP <97.7 mmHg and 37 of the 298 patients with a baseline MAP ≥97.7 mmHg achieved the renal composite outcome. The univariable regression analysis showed a non-significant relationship between the renal composite outcome and a baseline MAP ≥97.7 mmHg (OR 1.31; 95% CI 0.80–2.15; $P$ = 0.286). Tables S2 and S3 present the baseline characteristics and clinical findings before and after PS matching. The incidence of renal composite outcome did not differ significantly between the patients with a baseline MAP of ≥97.7 and those with a baseline MAP of <97.7 mmHg ($n$ = 26 [11.9%] and $n$ = 24 [11.0%], respectively; Table S4). The eGFR and LNACR changes were non-significant between the groups. Figure S2 presents the mean prevalence of renal composite outcome incidence by patient quintiles. Patient stratification into five quintiles was carried out on the basis of PSs as follows: Q1 (PS ≤0.30), Q2 (PS = 0.30–0.40), Q3 (PS = 0.40–0.50), Q4 (PS = 0.50–0.63) and Q5 (PS >0.63). Between-group differences were non-significant, and the renal composite outcome OR was 1.11 (95% CI 0.61–2.01, $P$ = 0.74) in the patients with a baseline MAP of ≥97.7 mmHg.

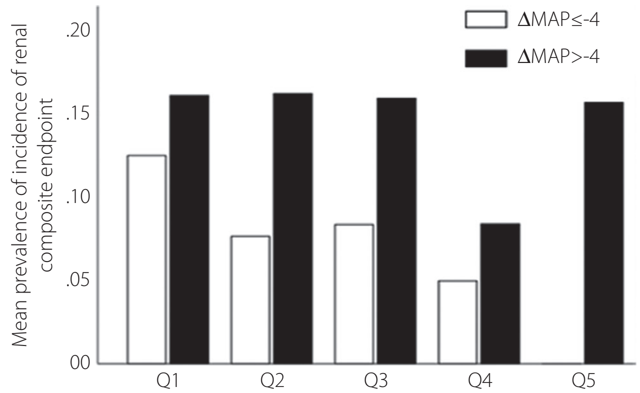


**Figure 2** | Mean prevalence of renal composite outcome stratified by propensity score (PS)-based patient quintiles (Q) in the cohort model: Q1 (PS ≤0.26), Q2 (PS = 0.26–0.45), Q3 (PS = 0.45–0.60), Q4 (PS = 0.60–0.80) and Q5 (PS > 0.80). The mean prevalence of renal composite outcome stratified by PS-based patient quintiles in the cohort model is shown. MAP, mean arterial pressure.

## DISCUSSION

Proteinuria and ACR are reported independent risk factors for renal dysfunction progression and ESKD, and high proteinuria or ACR levels increase the risk of renal dysfunction[20,21]. According to Drey *et al.*,[22] the proteinuria level is significantly related to the renal composite outcomes, which include progression to ESKD (eGFR <15 mL/min/$m^2$) and a twofold increase in serum creatinine levels, and the risk increases even when the proteinuria level remains constant after antihypertensive treatment. Lambers Heerspink *et al.*[23] reported intertrial variability in treatment effects on ESKD (range −55% to +35% risk change) and albuminuria (range −1.3% to −32.1%). According to these results, although the ACR is the surrogate renal outcome marker, treatment that reduces the ACR is appropriate for CKD management. Many surveys have shown that antihypertensive treatment effectively mitigates progression to ESKD in patients who have CKD[24,25]. The Japanese Society of Hypertension Guidelines for the Management of Hypertension recommends that BP be strictly maintained at <130/80 mmHg in CKD patients with proteinuria or type 2 diabetes mellitus[26]. The Japanese randomized controlled trial, Japan Diabetes Outcome Intervention Trial (J-DOIT3), showed that intensified intervention with an SBP reduction to 125 mmHg could prevent cerebrovascular events and significantly reduce the prevalence of a renal composite outcome to 32%[27]. Accordingly, strict BP management is required in clinical practice for patients with type 2 diabetes mellitus; however, Yokoyama *et al.*[28] showed that the target BP (measured at the office) of <130/80 mmHg was achieved in 47% of 9,956 Japanese patients with type 2 diabetes mellitus.

In the present study, SGLT2 inhibitor treatment increased the number of patients who achieved the target BP from 177 (28%) to 261 (42%) of 624 patients; however, more than half of the patients showed insufficient BP control. We previously reported that baseline BP is an independent factor of BP reduction[29]. In the present study, the MAP of 383 patients (61%) decreased after SGLT2 inhibitor treatment. The relationship of the ΔMAP with renal outcomes, even in patients achieving target BP, is difficult to research. The present findings show a lower renal outcome prevalence in patients with a ΔMAP ≤−4 mmHg than in those with a ΔMAP >−4 mmHg. According to the results of the analysis of the ΔMAP in the two groups divided by the baseline BP of 130/80 mmHg (target BP), the ΔMAP was 4.9 ± 9.9 mmHg (95% CI 3.4–6.4 mmHg) in patients with baseline BP <130/80 mmHg ($n$ = 177) and −6.7 ± 11.6 mmHg (95% CI −7.8 to −5.6 mmHg) in those with a baseline BP ≥130/80 mmHg ($n$ = 447). These results suggest that treatment with an SGLT2 inhibitor does not cause excessive hypotension.

Makino *et al.*[30] reported that treatment with telmisartan reduced microalbuminuria not only in patients with hypertension, but also in those with normotension. Significant decreases in BP were observed in both groups after administration of telmisartan (40 mg): from 140 ± 14.1/79 ± 10.2 to 129 ± 12.7/72 ± 10.3 mmHg in patients with hypertension, and from 131 ± 13.0/75 ± 9.5 to 122 ± 15.1/70 ± 8.7 mmHg in patients with normotension. Furthermore, the changes in ACR were significantly correlated with the ΔSBP in patients with hypertension. Burnier *et al.* carried out a meta-analysis on how angiotensin receptor blockers affect the renal function and BP in hypertension patients with CKD. The authors found that after ≥1 year angiotensin receptor blocker monotherapy, proteinuria and hypertension were significantly alleviated (Δproteinuria = −0.90 [95% CI −1.22 to −0.59] g/L, ΔSBP = −14.84 [95% CI −17.82 to −11.85] and ΔDBP = −10.27 [95% CI −12.26 to −8.27] mmHg, $P$ < 0.01), but there were no significant changes in the eGFR[31]. These results were consistent with those of combination therapy. Takahashi *et al.*[32] reported a meta-analysis on whether or not the use of mineralocorticoid receptor antagonists as an adjuvant agent for renin–angiotensin system (RAS) inhibitors can engender antihypertensive effects in type 2 diabetes mellitus patients with hypertension. The authors obtained mean differences of −9.4 mmHg (95% CI −12.9 to −5.9 mmHg) in office SBP and −3.8 mmHg (95% CI −5.5 to −2.2 mmHg) in office DBP between the MRA and placebo groups, with a consistent albuminuria reduction across the studies that they surveyed. In the present study, the ΔMAP was −13.4 ± 8.5 and 5.6 ± 7.1 mmHg in the patients with a ΔMAP of ≤−4 and >−4 mmHg, respectively. The weak area under the ROC curve value of 0.58, which was calculated to determine the cut-off value of ΔMAP, might be concerning, but given that SGLT2 inhibitor-induced BP reduction was comparable to that induced by angiotensin receptor blockers and mineralocorticoid receptor antagonists treatment in patients with ΔMAP ≤−4 mmHg, BP might be involved in the mechanism underlying the ACR reduction. Furthermore, the mechanism by which SGLT2 inhibitor treatment exerts renoprotective effects remains insufficiently clarified; dapagliflozin itself mainly contributed to the ACR reduction, whereas BP and $HbA_{1c}$ reduction did not significantly contribute to this effect[33]. Therefore, the relationship between the renoprotective effect of SGLT2 inhibitors and the magnitude of BP reduction warrants clarification in future studies.

To evaluate the renal outcomes, the twofold increase of serum creatinine level, the progress to ESKD or the induction of renal replacement therapy is often used as a hard end-point in large-scale clinical studies. These events are reliable and have a strong relationship with the progression to ESKD; however, large sample sizes or long observational periods are often required. Indeed, just four patients showed a twofold increase in the serum creatine level, and no cases of progression to ESKD were observed in the present study. The National Kidney Foundation and the US Food and Drug Administration sponsored a scientific workshop to identify alternative GFR-based end-points for clinical trials in CKD patients, and the workshop concluded that a 30–40% reduction in the eGFR over a period of 2–3 years might be an acceptable surrogate end-point[34]. KDIGO discussed the appropriate trial design and proposed several reliable surrogate end-points, such as a 30–40% reduction in the eGFR or a decline in the eGFR[35]. Chang *et al.*[36] reported that a 30% reduction in the eGFR over a period of 2 years is the best predictor for the incidence of ESKD in Japanese CKD patients. The Japanese Society of Nephrology also discussed the renal surrogate end-point and stated that a 30–40% reduction in the eGFR over a period of 2 or 3 years is acceptable as a surrogate end-point for Japanese CKD patients[37]. In addition, the Japanese Society of Nephrology mentioned that the power of the evidence for the cut-off value of the reduction in the eGFR might be insufficient, and appropriate cut-off values might vary depending on the study design or type of CKD[37]. In the present study, which included some patients who had been treated with SGLT2 inhibitors for <2 years, we defined an annual eGFR reduction of >15% as a renal end-point for the change in the eGFR (i.e., a total of 30% reduction in the eGFR over a period of 2 years for patients with 2-year observation). In the present study, 12 of 624 patients showed a >15% annual eGFR reduction, and the details are shown in Table S4; the patients showed a reduction in the eGFR that could not be ignored in clinical practice. In contrast, 23 patients showed a >30% reduction in the eGFR over the observation period, so we selected a harder end-point to represent a reduction in the eGFR in the present study.

Our analysis using PS showed the baseline MAP-renal composite outcome relationship. The matched cohort model was developed with well-balanced parameters; however, no significant difference was observed in this model. We were unable to draw a final conclusion that the difference in renal composite outcome prevalence between the high- and low-baseline MAP groups was non-significant because of the limitations of the PS-matching analysis; however, the model using PS stratification did not show a significant difference either. When baseline BP is irrelevant to the renoprotective effect of an SGLT2 inhibitor, both the BP level and magnitude of reduction after SGLT2 inhibitor treatment might be crucial.

We already reported the independent factors influencing the ΔMAP after treatment with an SGLT2 inhibitor using a multiple regression analysis[38], and the ΔLNACR, use of insulin, LNACR at baseline, baseline MAP, ΔBW and BW at baseline were identified. Accordingly, patients with a higher baseline MAP are suspected to show a larger decrease in MAP after SGLT2 inhibitor treatment than those with lower baseline MAP values. We therefore evaluated the relationship between the baseline MAP and the renal composite outcome; however, no significant difference was found between the two groups divided by the baseline MAP (see the supplementary analysis). These findings suggest that the ΔMAP is more closely related to the renal composite outcome than is the MAP at baseline. The ΔMAP has components of the ΔSBP and ΔDBP, so the degree of contribution by the ΔSBP and ΔDBP to the renal composite outcome was analyzed using a logistic analysis. The ORs were 1.019 (95% CI 1.004–1.034; $P = 0.012$) for ΔSBP and 1.010 (95% CI 0.989–1.033; $P = 0.347$) for ΔSBP. Accordingly, the ΔSBP might be a stronger determinant than the ΔDBP.

Several limitations associated with the present study warrant mention. First, the study design was retrospective, observational and single arm without a placebo group. This survey included only patients who were able to be continuously treated with SGLT2 inhibitors and did not include patients who discontinued treatment with SGLT2 inhibitors or started renal replacement therapy during the treatment period. Therefore, renal events might not have been confirmed accurately. Second, there was no strict regulation of the measurement of the ACR in this study. We collected the data on the ACR from general practitioners, and the measurement of the ACR in diabetes patients suspected of having diabetic nephropathy is permitted only once every 3 months by the Medicare system legislated by the Government of Japan. This study consisted of a real-world data analysis, so there are limitations on frequent measurements of the ACR. Furthermore, the timing of ACR measurements was not regulated. It therefore cannot be denied that these methods of ACR measurements might have influenced the result of this study. Third, additional modalities for reducing the BP, such as exercise and diet restrictions, might have produced variations in the achieved MAPs, potentially confounding the results. In the present study, there was no regulation regarding the use of antihypertensive treatment to reach the target BP; however, we collected information on concomitant antihypertensive treatment only at the survey. An accurate evaluation of the effect of concomitant antihypertensive treatment could, therefore, not be carried out. Furthermore, the ratio of RAS inhibitor use was 53% among patients with diabetes and CKD. Several reasons regarding the lack of RAS inhibitor use might be speculated, including the possibility that GPs simply did not use RAS inhibitors despite the recommendation of the guideline. Fourth, although PS methods can be useful compared with conventional statistical analyses in confounding adjustment, 45% of our included patients were not selected in our PS-matched cohort model. To address these limitations, a PS-stratified cohort model including all cases was analyzed to complement the patients excluded from the PS-matched model. Our conclusion was strengthened by the fact that we obtained similar results between the two analytical methods using PS.

MAP changes after treatment with SGLT2 inhibitors in Japanese patients with type 2 diabetes and CKD influenced renal composite outcomes. Given these results, general practitioners should recognize the importance of BP management, even during SGLT2 inhibitor treatment, in these patients.

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## DISCLOSURE

The authors declare no conflict of interest.

## REFERENCES

1. Wiviott SD, Raz I, Bonaca MP, *et al*. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2019; 380: 347–357.
2. Neal B, Perkovic V, Mahaffey KW, *et al*. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017; 377: 644–657.
3. Zinman B, Wanner C, Lachin JM, *et al*. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015; 373: 2117–2128.
4. Wanner C, Inzucchi SE, Lachin JM, *et al*. Empagliflozin and progression of kidney disease in type 2 diabetes. *N Engl J Med* 2016; 375: 323–334.
5. Mosenzon O, Wiviott SD, Cahn A, *et al*. Effects of dapagliflozin on development and progression of kidney disease in patients with type 2 diabetes: an analysis from the DECLARE-TIMI 58 randomised trial. *Lancet Diabetes Endocrinol* 2019; 7: 606–617.
6. Perkovic V, de Zeeuw D, Mahaffey KW, *et al*. Canagliflozin and renal outcomes in type 2 diabetes: results from the CANVAS program randomised clinical trials. *Lancet Diabetes Endocrinol* 2018; 6: 691–704.
7. Perkovic V, Jardine MJ, Neal B, *et al*. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med* 2019; 380: 2295–2306.
8. Scheen AJ. Beneficial effects of SGLT2 inhibitors on fatty liver in type 2 diabetes: a common comorbidity associated with severe complications. *Diabetes Metab* 2019; 45: 213–223.
9. Heerspink HJL, Perkins BA, Fitchett DH, *et al*. Sodium glucose cotransporter 2 inhibitors in the treatment of diabetes mellitus. *Circulation* 2016; 134: 752–772.
10. Kobayashi K, Toyoda M, Kimura M, *et al*. Retrospective analysis of effects of sodium-glucose co-transporter 2 inhibitor in Japanese type 2 diabetes mellitus patients with chronic kidney disease. *Diab Vasc Dis Res* 2019; 16: 103–107.
11. Kobayashi K, Toyoda M, Hatori N, *et al*. Retrospective analysis of the renoprotective effects of long-term use of six types of sodium-glucose cotransporter 2 inhibitors in Japanese patients with type 2 diabetes mellitus and chronic kidney disease. *Diabetes Technol Ther* 2020. https://doi.org/10.1089/dia.2020.0165
12. Kobayashi K, Toyoda M, Kaneyama N, *et al*. Relation between blood pressure management and renal effects of sodium-glucose cotransporter 2 inhibitors in diabetic patients with chronic kidney disease. *J Diabetes Res* 2019; 2019: 1–7.
13. Kobayashi K, Toyoda M, Hatori N, *et al*. Blood pressure after treatment with sodium-glucose cotransporter 2 inhibitors influences renal composite outcome: analysis using propensity score matched models. *J Diabetes Investig* 2021; 12: 74–81.
14. Baker WL, Smyth LR, Riche DM, *et al*. Effects of sodium-glucose co-transporter 2 inhibitors on blood pressure: a systematic review and meta-analysis. *J Am Soc Hypertens* 2014; 8: 262–275.e269.
15. Baker WL, Buckley LF, Kelly MS, *et al*. Effects of sodium-glucose cotransporter 2 inhibitors on 24-hour ambulatory blood pressure: a systematic review and meta-analysis. *J Am Heart Assoc* 2017; 6: e005686.
16. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis* 2002; 39(2 Suppl 1): S1–266.
17. Matsuo S, Imai E, Horio M, *et al*. Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis* 2009; 53: 982–992.
18. Austin PC. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. *Pharm Stat* 2011; 10: 150–161.
19. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med.* 2009; 28: 3083–3107.
20. Brown JH, Hunt LP, Vites NP, *et al*. Comparative mortality from cardiovascular disease in patients with chronic renal failure. *Nephrol Dial Transplant* 1994; 9: 1136–1142.
21. Nakayama M, Metoki H, Terawaki H, *et al*. Kidney dysfunction as a risk factor for first symptomatic stroke

events in a general Japanese population – the Ohasama study. *Nephrol Dial Transplant* 2007; 22: 1910–1915.
22. Drey N, Roderick P, Mullee M, *et al*. A population-based study of the incidence and outcomes of diagnosed chronic kidney disease. *Am J Kidney Dis* 2003; 42: 677–684.
23. Lambers Heerspink HJ, Kröpelin TF, Hoekman J, *et al*. Drug-induced reduction in albuminuria is associated with subsequent renoprotection: a meta-analysis. *J Am Soc Nephrol* 2015; 26: 2055–2064.
24. Bakris GL, Williams M, Dworkin L, *et al*. Preserving renal function in adults with hypertension and diabetes: a consensus approach. National Kidney Foundation Hypertension and Diabetes Executive Committees Working Group. *Am J Kidney Dis* 2000; 36: 646–661.
25. Jafar TH, Stark PC, Schmid CH, *et al*. Progression of chronic kidney disease: the role of blood pressure control, proteinuria, and angiotensin-converting enzyme inhibition: a patient-level meta-analysis. *Ann Intern Med* 2003; 139: 244–252.
26. Umemura S, Arima H, Arima S, *et al*. The Japanese Society of Hypertension guidelines for the management of hypertension (JSH 2019). *Hypertens Res* 2019; 42: 1235–1481.
27. Ueki K, Sasako T, Okazaki Y, *et al*. Effect of an intensified multifactorial intervention on cardiovascular outcomes and mortality in type 2 diabetes (J-DOIT3): an open-label, randomised controlled trial. *Lancet Diabetes Endocrinol* 2017; 5: 951–964.
28. Yokoyama H, Oishi M, Takamura H, *et al*. Large-scale survey of rates of achieving targets for blood glucose, blood pressure, and lipids and prevalence of complications in type 2 diabetes (JDDM 40). *BMJ Open Diabetes Res Care* 2016; 4: e000294.
29. Kobayashi K, Toyoda M, Kimura M, *et al*. Renal effects of sodium glucose co-transporter 2 inhibitors in Japanese type 2 diabetes mellitus patients with home blood pressure monitoring. *Clin Exp Hypertens* 2019; 41: 637–644.
30. Makino H, Haneda M, Babazono T, *et al*. Microalbuminuria reduction with telmisartan in normotensive and hypertensive Japanese patients with type 2 diabetes: a post-hoc analysis of the Incipient to Overt: Angiotensin II Blocker, Telmisartan, Investigation on Type 2 Diabetic Nephropathy (INNOVATION) study. *Hypertens Res* 2008; 31: 657–664.
31. Burnier M, Lin S, Ruilope L, *et al*. Effect of angiotensin receptor blockers on blood pressure and renal function in patients with concomitant hypertension and chronic kidney disease: a systematic review and meta-analysis. *Blood Press* 2019; 28: 358–374.
32. Takahashi S, Katada J, Daida H, *et al*. Effects of mineralocorticoid receptor antagonists in patients with hypertension and diabetes mellitus: a systematic review and meta-analysis. *J Hum Hypertens* 2016; 30: 534–542.
33. Heerspink HJ, Johnsson E, Gause-Nilsson I, *et al*. Dapagliflozin reduces albuminuria in patients with diabetes and hypertension receiving renin-angiotensin blockers. *Diabetes Obes Metab* 2016; 18: 590–597.
34. Levey AS, Inker LA, Matsushita K, *et al*. GFR decline as an end point for clinical trials in CKD: a scientific workshop sponsored by the National Kidney Foundation and the US Food and Drug Administration. *Am J Kidney Dis* 2014; 64: 821–835.
35. Baigent C, Herrington WG, Coresh J, *et al*. Challenges in conducting clinical trials in nephrology: conclusions from a Kidney Disease-Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int* 2017; 92: 297–305.
36. Chang WX, Asakawa S, Toyoki D, *et al*. Predictors and the Subsequent Risk of End-Stage Renal Disease – Usefulness of 30% Decline in Estimated GFR over 2 Years. *PLOS ONE* 2015; 10: e0132927.
37. field Rgotfocegfcditr. Endpoints in clinical trials of CKD patients. *Jpn J Nephrol* 2018; 60: 67–100.
38. Furuki T, Kobayashi K, Toyoda M, *et al*. The influence of long-term administration of SGLT2 inhibitors on blood pressure at the office and at home in patients with type 2 diabetes mellitus and chronic kidney disease. *J Clin Hypertens (Greenwich)* 2020; 22: 2306–2314.

## SUPPORTING INFORMATION

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

**Figure S1** | Receiver operating characteristic curve of baseline mean arterial pressure (MAP) for the renal composite outcome.
**Figure S2** | Mean prevalence of renal composite outcome stratified by propensity scores (PS)-based patient quintiles (Q) in the supplementary cohort model: Q1 (PS $\leq$0.30), Q2 (PS = 0.30–0.40), Q3 (PS = 0.40–0.50), Q4 (PS = 0.50–0.63), and Q5 (PS >0.63).
**Table S1** | Change in the estimated glomerular filtration rate after treatment with an sodium–glucose cotransporter 2 inhibitor in 12 patients with >15% annual estimated glomerular filtration rate reduction.

**Table S2** | Baseline characteristics pre- and post-propensity score matching: The supplementary model.

**Table S3** | Clinical findings after sodium–glucose cotransporter 2 inhibitor treatment in both cohorts in the supplementary model.

**Table S4** | Incidence of renal composite outcome and changes in the natural logarithm of the urine albumin-to-creatinine ratio and sodium–glucose cotransporter 2 in the supplementary propensity score-matched model.