

ARTICLE

Polypharmacy influences the renal composite outcome in patients treated with sodium-glucose cotransporter 2 inhibitors

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Funding information

No funding was received for this work.

Abstract

Polypharmacy is a serious concern in general practice, especially among elder patients; however, the evidence showing significantly poor renal outcomes is not sufficient. This survey was performed to evaluate the effect of polypharmacy on the incidence of the renal composite outcome among a sample of patients with sodium-glucose cotransporter 2 inhibitor (SGLT2i) treatment. We assessed 624 Japanese patients with type 2 diabetes mellitus (T2DM) and chronic kidney disease who received SGLT2i treatment for greater than 1 year. The patients were classified as those with concomitant treatment, that was limited to the medications for hypertension, T2DM, and dyslipidemia, with greater than or equal to seven medications ($n = 110$) and those with less than seven medications ($n = 514$). Evaluation of the renal composite outcome was performed by propensity score matching and stratification into quintiles. A subgroup analysis of patients of greater than or equal to 62 years of age and less than 62 years of age was also performed. The incidence of the renal composite outcome was larger in patients with greater than or equal to seven medications than in those with less than seven medications in the propensity score-matched cohort model (6% vs. 17%, respectively, $p = 0.007$) and also in the quintile-stratified analysis (odds ratio [OR], 2.23, 95% confidence interval [CI], 1.21–4.12, $p = 0.01$). The quintile-stratified analysis of patients of less than 62 years of age—but not those of greater than or equal to 62 years of age—also showed a significant difference (OR, 3.29, 95% CI, 1.41–7.69, $p = 0.006$). Polypharmacy appears to be associated to the incidence of the renal composite outcome, especially in young patients.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Polypharmacy is an unaddressed concern and may worsen prognosis in clinical practice, especially in elderly patients.

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WHAT QUESTION DID THIS STUDY ADDRESS?

The evidence that polypharmacy correlates with poor cardiovascular or renal outcomes is insufficient in clinical practice.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

This study clarified the relationship between polypharmacy and a renal composite outcome in patients with type 2 diabetes mellitus and chronic kidney disease receiving sodium-glucose cotransporter 2 inhibitor treatment, especially in young patients.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

Both specialists and general practitioners should pay attention to polypharmacy to improve renal outcomes in clinical practice.

INTRODUCTION

Evidence-based medicine has now gained widespread acceptance, and guidelines have been established to promote appropriate global standards in clinical practice regarding many diseases. These guidelines often provide evidence-based recommendations for medications. Elderly patients have many diseases or experience many complications, and the number of medications that they use inevitably increases. On the contrary, potentially inappropriate medication (PIM) is sometimes observed in clinical practice and thought to be related to polypharmacy. PIMs are defined by the Beers criteria¹ or the Screening Tool of Older Persons' Potentially Inappropriate Prescription (STOPP)/Screening Tool to Alert doctors to Right Treatment (START) criteria,² and the frequency of PIMs, as defined by the STOPP criteria, was found to be 21%–79% in a systemic review.³ The risk of adverse effects increases when many medications are administered, and unexpected toxicity can occur due to multiple drug interactions. These are thought to be issues of polypharmacy and cannot be ignored in clinical practice, especially in an aging society. However, studies on the epidemiology, mechanisms, and management of polypharmacy have been insufficient.

There is a gap between the evidence obtained in randomized controlled trials and medical findings from clinical practice, which is recognized as the evidence–practice gap.⁴ An understanding of this evidence–practice gap is necessary for providing quality medical care as a patient-centered medical therapy. Many cardiovascular outcome trials of sodium-glucose cotransporter 2 inhibitors (SGLT2is) have confirmed strong evidence of cardiovascular and renal events; however, whether SGLT2i treatment in clinical practice can have the same organ-protective effect as shown by randomized controlled trials has not been investigated enough. Consequently, we started this research using our real-world data. Our clinical question

is “Can an SGLT2i have the organ-protective effects in all patients, or may some clinical conditions worsen these effects?” If such conditions become clear, then general practitioners (GPs) can refrain from administering an SGLT2i or can strive to improve these conditions; therefore, it is important for GPs to perform a study to answer such a clinical question. We conducted a retrospective study that included patients treated with SGLT2is that showed reduced albuminuria in type 2 diabetes mellitus (T2DM) with chronic kidney disease (CKD) as a high-risk group for renal outcomes.

Despite the limited information about the concomitant medications for hypertension, T2DM, and dyslipidemia in our survey, the patients used an average of 4.9 (minimum, 1; maximum, 10) medications, and this number was larger than we expected; therefore, medication use of many patients was assumed to fulfil the criteria of polypharmacy. Such polypharmacy is a serious concern for GPs; however, the risk of cardiovascular or renal outcomes has not been evaluated in cardiovascular outcome trials involving SGLT2is. At the same time, the large numbers of concomitant medications are not limited to elderly patients; consequently, it is quite natural to wonder whether the effects of polypharmacy differ between elderly and younger patients. Our hypothesis in this study is that polypharmacy deteriorates the renoprotective effect of an SGLT2i not only in elderly but also in younger patients with T2DM. If this is true, then GPs must address polypharmacy, for example, by reducing the number of concomitant medications via better lifestyle management. Our interest is not only in the effect of polypharmacy; we have already analyzed the conditions under which the renoprotective effect of an SGLT2i is deteriorated (e.g., some levels of blood pressure management after SGLT2i treatment,^{5,6} differences among dissimilar types of SGLT2i treatments,⁷ and effects of an SGLT2i with or without dipeptidyl peptidase 4 (DPP4) inhibitors during SGLT2i treatment (Journal of Diabetes Research, in press).

In view of this background information, we chose the following aim for this study to clarify the relationship between renal events and polypharmacy using an actual clinical database on the treatment with SGLT2i. Furthermore, in our study, not only the elderly but also some young patients experienced polypharmacy, and the association between age and polypharmacy was evaluated too.

MATERIALS AND METHODS

Study participants and data collection

This study is a subanalysis of our previous study, and the details of the entire study population have been described previously.⁸ In brief, the study included 797 registered patients with T2DM who visited the clinics of the members of the Kanagawa Physicians Association between October and December 2018, with the following inclusion criteria: (i) first-time treatment with an SGLT2i more than 1 year before the enrollment; (ii) CKD, as defined by the Kidney Disease Outcomes Quality Initiative clinical practice guidelines⁹; and (iii) age greater than 20 years. Thirty-four patients were excluded based on the following exclusion criteria: (i) type 1 diabetes mellitus; (ii) required chronic dialysis; (iii) severe liver dysfunction, such as liver cirrhosis or severe infection; (iv) terminal-stage cancer; (v) pregnancy; (vi) irregular use of an SGLT2i as evidenced by poor adherence; and (vii) an intention to opt out during the study. Furthermore, to evaluate a renal outcome, 624 patients whose albumin-to-creatinine ratio (ACR) was measured both at baseline and at the end of the survey were included in this study.

The median duration of treatment with SGLT2is was 33.0 months (range 12–66 months). The following parameters were recorded both at the time of the initiation of SGLT2i treatment and during the survey: age, sex, body weight (BW), systolic blood pressure (SBP), diastolic blood pressure (DBP), the serum creatinine level, glycated hemoglobin (HbA1c) level, and the ACR (mg/g Cr). The estimated glomerular filtration rate (eGFR) was calculated using the formula¹⁰: $eGFR \text{ (ml/[min} \times 1.73 \text{ m}^2])} = 194 \times \text{age}^{-0.287} \times \text{serum creatinine}^{-1.094} \times (0.739 \text{ for women})$.

We conducted a survey on the medications taken concomitantly with SGLT2is, including hypoglycemic and hypotensive agents and statins. Hypoglycemic agents included DPP4 inhibitors, glucagon-like peptide 1 receptor agonists, sulfonylureas, metformin, insulin, and pioglitazone. Hypotensive agents were renin–angiotensin system inhibitors, including angiotensin II receptor blockers or angiotensin-converting-enzyme inhibitors, calcium channel blockers, β blockers, direct aldosterone blockers, thiazide diuretics, and loop diuretics. In this study, data on

the use of antiplatelet or anticoagulant agents and gastrointestinal medications were not collected. The number of concomitant medications was calculated as the number of these medications plus an SGLT2i.

Outcomes

In recent large-scale clinical trials involving SGLT2is,^{11–16} composite outcomes, including the induction of renal replacement therapy, the progression of end-stage kidney disease, the doubling of serum creatinine levels, renal death, or worsening owing to macroalbuminuria were commonly used as renal end points. Because the incidence of these hard end points is low, a surrogate renal end point, such as a 30%–40% decrease of the eGFR per 2 or 3 years, is advocated.^{17–20} However, the appropriate end points are not completely agreed upon and should be chosen depending on the study design or participants. According to our previous study,^{5,6} we defined the renal composite outcome as ACR progression, a greater than 15% annual decrease in the eGFR, or both.

Statistical analysis

A receiver-operating characteristic (ROC) curve analysis was used to examine the overall prediction accuracy of the number of concomitant medications—which was limited to the medications for hypertension, T2DM, and dyslipidemia—after SGLT2i treatment in relation to the renal composite end point. The results are reported as the area under the ROC curve (AUC). The cutoff value of the number of concomitant medications for further analysis was determined based on the results of the ROC analysis. We subdivided the patients into two groups according to the cutoff for concomitant medications as determined by the ROC analysis (see the Results for details). We then calculated the propensity score (PS) for patients with a high number of concomitant medications using a logistic regression model to estimate the probability of the disease assignment based on the following variables that are considered confounding factors for the renal composite outcome: age, sex, BW, body-mass index, the HbA1c level, SBP, DBP, eGFR, creatinine clearance, logarithmic value of the ACR (LNACR) at baseline, the type of SGLT2i used, and treatment duration. In this study, we compared the two groups compiled according to the number of concomitant medications; however, the concomitant-medication number was not included as a covariate in the logistic regression model when the PS was determined.

We established a cohort model using PS-matching methods via the following algorithm: a 1:1 nearest-neighbor

match and no replacement. In the present subanalysis, to maximize correct matching and reduce bias, we used a lower caliper of width 0.03, which was equal to 0.2 of the standard deviation of the PS.²¹ We analyzed the differences in the clinical and laboratory profiles between these two groups using the unpaired *t*-test or the Mann–Whitney rank sum test for continuous variables in the unmatched cohort. In the PS-matched cohort, either the paired *t*-test or Wilcoxon signed-rank test was used. The chi-square test was used for the analysis of categorical variables in the unpaired cohort, whereas McNemar's test was used for paired cohorts.

Using the Statistical Package for the Social Sciences (SPSS) software, the hazard ratio (HR) for each outcome was determined using a Cox proportional hazard model instead of a conditional logistic regression analysis.

We also established another cohort model: the one involving PS stratification. The way to balance data through PS stratification is to make the group of participants within a stratum as homogeneous as possible in terms of observed covariates. All patients were stratified into quintiles based on their corresponding PS and were included in the analysis. We used the Mantel–Haenszel method to analyze these five categorical variables and calculated odds ratios (ORs) and 95% confidence intervals (95% CIs).

On the basis of the report by Qato et al.,²² age greater than or equal to 62 years was assumed to be a risk factor for polypharmacy; therefore, we subdivided the patients into two groups: those aged less than 62 years and those aged greater than or equal to 62 years.

For this subgroup analysis by age, we recalculated the PSs for each age group and performed a PS-matching analysis and PS stratification into quintiles using the methods described above within this statistical analysis subsection.

All results are reported as the mean \pm standard deviation or median with an interquartile range for continuous variables and as percentages for categorical variables. The *p* values (2-tailed) of less than 0.05 were assumed to indicate statistical significance. All statistical analyses were performed using the International Business Machine (IBM) SPSS Statistics software (version 25.0; IBM).

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

RESULTS

ROC curves

The ROC analysis (Figure 1) indicated that after SGLT2i treatment, the optimal cutoff for the number of concomitant medications—as an indicator of the renal composite

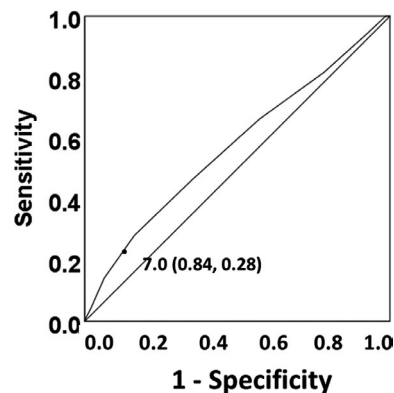


FIGURE 1 Receiver operating characteristic curve of the number of concomitant medications after sodium-glucose cotransporter 2 inhibitor (SGLT2i) treatment for the renal composite outcome

outcome—was 7.0 (sensitivity, 84%; specificity, 28%; and AUC, 0.57, 95% CI, 0.50–0.65, *p* = 0.04). Accordingly, we subdivided the participants into two groups based on the number of concomitant medications: patients with greater than or equal to seven medications and those with less than seven medications.

The PS-matched cohort model

The clinical characteristics at baseline after SGLT2i treatment and before and after PS matching are shown in Tables 1 and 2, respectively. There were significant differences in age, body-mass index, BW, SBP, HbA1c level, eGFR, LNACR, and the use of canagliflozin (*p* < 0.04, 0.001, 0.048, 0.002, 0.04, 0.01, 0.004, < 0.001, and 0.01, respectively). Owing to the significant difference between the two groups in these confounding variables that influence the renal composite outcome in the unmatched cohort model, we next utilized the PS-matching method for the comparisons. The use of all concomitant medications was significantly more frequent in patients with greater than or equal to seven medications (*p* = 0.002 for the use of DPP4 inhibitors, whereas *p* < 0.001 for the use of other concomitant medications). An absolute standardized difference of $< 1.96\sqrt{2/n}$ for the measured covariates was suggestive of an appropriate balance between the groups.²³ This borderline in this matched cohort model was calculated and found to be 0.28 (*n* = 101 in each group, $< 1.96\sqrt{2/n}$ equals 0.28), and all standardized differences in the clinical characteristics were less than 0.16 in this matched cohort model. Histograms before and after the PS distribution matching are shown in Figure S1; the histograms were found to be well balanced after the matching.

TABLE 1 Baseline characteristics before and after propensity score matching in the whole population

	Unmatched cohort (n = 624)			Matched cohort (n = 202)			Standardized difference
	<7 medications (n = 514)	≥7 medications (n = 110)	p value	<7 medications (n = 101)	≥7 medications (n = 101)		
Age at the time of the initiation of SGLT2i treatment, year	57.2 ± 11.6	59.9 ± 10.3	0.04	58.9 ± 11.4	59.8 ± 10.4	0.08	
Sex, male	336 (65%)	74 (67%)	0.70 ^a	73 (72%)	71 (70%)	0.04	
BMI, kg/m ²	27.6 ± 4.8	29.3 ± 4.4	0.001	30.4 ± 5.5	30.0 ± 4.3	0.08	
BW, kg	78.8 ± 16.7	82.2 ± 15.0	0.048	82.9 ± 17.1	81.1 ± 13.6	0.12	
SBP, mmHg	133.9 ± 16.4	139.2 ± 17.0	0.002	138.6 ± 15.3	137.9 ± 15.9	0.05	
DBP, mmHg	78.1 ± 12.0	78.0 ± 13.0	0.98	78.3 ± 12.1	77.5 ± 12.6	0.07	
MAP, mmHg	96.7 ± 12.1	98.4 ± 12.7	0.18	98.4 ± 11.6	97.6 ± 12.0	0.07	
HbA1c, mmol/mol (%)	63.5 ± 15.3 (7.96 ± 1.40)	66.6 ± 14.1 (8.24 ± 1.29)	0.04	65.8 ± 16.2 (8.2 ± 1.5)	65.6 ± 13.2 (8.2 ± 1.2)	0.01	
eGFR, ml/min/1.73 m ²	80.3 ± 22.1	74.2 ± 20.0	0.01	76.4 ± 19.1	75.9 ± 19.0	0.03	
LNACR	1.56 ± 0.62	1.78 ± 0.73	0.004	1.64 ± 0.67	1.72 ± 0.67	0.12	
Duration of treatment, month	32.1 ± 10.5	34.1 ± 10.8	0.08	33.5 ± 9.8	33.9 ± 11.0	0.04	
Number of concomitant medications	4.4 ± 1.3	7.6 ± 0.8	<0.001	4.6 ± 1.2	7.6 ± 0.8	3.0	
Types of SGLT2 inhibitor							
Ipragliflozin	103 (20%)	33 (30%)	0.22 ^a	23 (23%)	30 (30%)	0.16	
Dapagliflozin	80 (16%)	22 (20%)	0.25 ^a	23 (23%)	20 (20%)	0.07	
Tofogliflozin	65 (13%)	11 (10%)	0.44 ^a	11 (11%)	10 (10%)	0.03	
Luseogliflozin	44 (9%)	10 (9%)	0.86 ^a	11 (11%)	10 (20%)	0.03	
Canagliflozin	72 (14%)	6 (6%)	0.01 ^a	4 (4%)	6 (6%)	0.09	
Empagliflozin	76 (15%)	14 (13%)	0.58 ^a	16 (16%)	12 (12%)	0.11	
Change in SGLT2is ^b	74 (14%)	14 (13%)	0.65 ^a	13 (13%)	13 (13%)	0.0	
Concomitant treatment (at survey)							
DPP4 inhibitors	267 (52%)	75 (68%)	0.002 ^a	53 (53%)	70 (70%)	0.35	
GLP1RA	71 (14%)	31 (28%)	<0.001 ^a	20 (20%)	26 (26%)	0.14	
Metformin	297 (58%)	88 (80%)	<0.001 ^a	56 (55%)	83 (82%)	0.60	
SU	131 (26%)	59 (54%)	<0.001 ^a	21 (21%)	55 (55%)	0.74	
Insulin	116 (23%)	53 (48%)	<0.001 ^a	25 (25%)	48 (48%)	0.49	
Pioglitazone	77 (15%)	39 (36%)	<0.001 ^a	19 (19%)	38 (38%)	0.43	
RAS inhibitors	229 (45%)	96 (87%)	<0.001 ^a	53 (53%)	88 (87%)	0.82	

(Continues)

TABLE 1 (Continued)

	Unmatched cohort (n = 624)		p value	Matched cohort (n = 202)		Standardized difference
	<7 medications (n = 514)	≥7 medications (n = 110)		<7 medications (n = 101)	≥7 medications (n = 101)	
Ca channel blocker	179 (35%)	98 (89%)	<0.001 ^a	39 (39%)	91 (90%)	1.27
B blocker	38 (7%)	38 (35%)	<0.001 ^a	10 (10%)	32 (32%)	0.56
Mineral corticoid receptor blocker	19 (4%)	24 (22%)	<0.001 ^a	5 (5%)	22 (22%)	0.51
Loop diuretics	2 (0%)	8 (7%)	0.01 ^a	0 (0%)	7 (7%)	0.39
Thiazide diuretics	10 (2%)	24 (22%)	<0.001 ^a	3 (3%)	20 (20%)	0.55
Statins	292 (57%)	90 (82%)	<0.001 ^a	62 (61%)	83 (82%)	0.47

Abbreviations: BMI, body mass index; BW, body weight; DPP4, Dipeptidyl Peptidase-4; eGFR, estimated glomerular filtration; GLP1RA, glucagon-like peptide 1 receptor agonist; LNACR, logarithmic value of albumin-to-creatinine ratio; MAP, mean arterial pressure; RAS, renin-angiotensin system inhibitor; SGLT2i, sodium-glucose co-transporter inhibitor.

Notes: Values are the mean ± SD or n/total n (%). The p values by unpaired t-test or

^aChi-square test on unmatched cohort model. ^bChange in SGLT2is during the study period.

A comparison of the renal composite outcome at 101 PS-matched patients in each group

In the matched cohort model, the incidence of the renal composite outcome was higher in the “greater than or equal to seven medications” group than in the “less than seven medications” group ($p = 0.007$), and the HR was 6.5 (95% CI, 1.5–28.8, $p = 0.01$). There was also a significant difference in the incidence of albuminuria progression; however, the incidence of a greater than or equal to 15% annual decrease in the eGFR and clinical findings after SGLT2i treatment did not show significant differences (Table 2).

The cohort model with PS stratification

The patients were stratified into quintiles based on the PS: Q1, PS less than or equal to 0.70; Q2, PS greater than 0.70 to less than or equal to 0.12; Q3, PS greater than 0.12 to less than or equal to 0.17; Q4, PS greater than 0.17 to less than or equal to 0.28; and Q5, PS greater than 0.28. Figure 2 shows the mean incidence of the renal composite outcome based on these quintiles. According to the results of the Mantel-Haenszel analysis, the incidence of the renal composite outcome and a greater than or equal to 15% annual decrease in the eGFR were significantly higher in the “greater than or equal to seven medications” group than in the “less than seven medications” group (OR: 2.23, 95% CI: 1.21–4.12, $p = 0.01$, and OR: 5.97, 95% CI: 1.24–28.74, $p = 0.03$, respectively).

The subgroup analysis by age (<62 years and ≥62 years)

The baseline characteristics before and after PS matching in cohorts aged less than 62 years and greater than or equal to 62 years are shown in Tables S1 and 3, respectively. No significant differences were observed in the incidence of the renal composite outcome: the HR was 3.3 (95% CI: 0.9–12.1, $p = 0.07$) in the matched cohort model of the “age less than 62 years” group, whereas it was HR: 1.7, 95% CI: 0.4–7.0, $p = 0.48$) in the matched cohort model of the “age greater than or equal to 62 years” group (Table 4). In the analysis with PS stratification, the “age less than 62 years” group showed a significantly higher incidence of the renal composite outcome than did the “age greater than 62 years” group (OR: 3.29, 95% CI: 1.41–7.69, $p = 0.006$), and the progression of albuminuria was greater in the “greater than

TABLE 2 Incidence of the renal composite outcome and changes in clinical findings after SGLT2i treatment in the whole population

	<7 medications (n = 101)	≥7 medications (n = 101)	p value
(a) The renal outcomes			
(1) Incidence of a renal composite outcome	6 (6%)	17 (17%)	0.007 ^a
(2) Incidence of a progression of albuminuria	3 (3%)	13 (13%)	0.006 ^a
(3) Incidence of a ≥15% annual decrease in eGFR	1 (1%)	4 (4%)	0.38 ^a
(b) Clinical findings after SGLT2i treatment			
eGFR at the survey, ml/min/1.73 m ²	71.2 ± 18.9	70.1 ± 19.6	0.67 ^b
the change in eGFR, ml/min/1.73 m ²	-5.1 ± 12.1	-5.7 ± 11.7	0.71 ^b
the annual eGFR change	-2.1 ± 5.4	-2.3 ± 6.1	0.78 ^b
LNACR at the survey	1.49 ± 0.67	1.59 ± 0.71	0.18 ^b
BMI, kg/m ²	29.0 ± 5.5	29.0 ± 4.2	0.95 ^b
BW, kg	79.2 ± 16.3	78.5 ± 13.1	0.72 ^b
SBP, mmHg	130.6 ± 17.1	133.1 ± 17.1	0.24 ^b
DBP, mmHg	76.8 ± 10.5	75.5 ± 11.0	0.31 ^b
MAP, mmHg	94.8 ± 9.4	94.7 ± 10.9	0.93 ^b
HbA1c, mmol/mol (%)	58.9 ± 14.3 (7.5 ± 1.3)	57.8 ± 12.7 (7.4 ± 1.2)	0.54 ^b

Note: Values are the mean ± SD.

Abbreviations: BMI, body mass index; BW, body weight; eGFR, estimated glomerular filtration; LNACR, logarithmic value of albumin-to-creatinine ratio; SGLT2i, sodium-glucose co-transporter inhibitor.

^aMcNemar' test.

^bPaired *t*-test.

or equal to seven medications” group than in the “less than seven medications” group (OR: 3.72, 95% CI: 1.45–9.56, *p* = 0.006).

DISCUSSION

Definition of polypharmacy

The use of multiple medications to treat various diseases or an inappropriate health status is often observed in clinical practice and is known as polypharmacy. There is no consensus definition of polypharmacy; however, the study by Masnoon et al. is based on a systemic review and suggests that the most common definition of polypharmacy is the numerical definition of greater than five medications daily.¹² Kantor et al. have reported the trends in the use of prescription drugs in the United States of America, and polypharmacy was observed in 39% of patients aged greater than 65 years, with the rate increasing yearly.¹³ According to another report, an average of 4.5 drugs are administered to elderly outpatients in Japan.²⁴ In the present study, we defined polypharmacy as the use of more than seven drugs in accordance with the results of the ROC analysis; however, only hypoglycemic and hypotensive agents and statins were included in the survey. We cannot rule out the possibility

that many patients received other medications, including antithrombotic agents, gastrointestinal drugs, and orthopedic medications. In the quintile analysis shown in Table S2, the incidence in the fifth quintile (with ≥7 medications) seems larger than that in the other quintiles. This finding suggests that the cutoff of seven medications is acceptable; however, this cannot be regarded as the actual clinical cutoff because of the missing information on the number of all medications that the patients used.

Interpretation of the results

This study revealed that the incidence of the renal composite outcome was higher among patients with greater than or equal to seven medications than among patients with less than seven medications not only in the PS-matched model but also in the PS-stratified model (*p* = 0.007 and *p* = 0.001, respectively). The PS-stratified model in the subgroup analysis also revealed that there was a significant association between polypharmacy and the renal composite outcome in young patients (age <62 years, *p* = 0.006).

Many comorbidities can result in polypharmacy and lead to poor cardiovascular or renal outcomes. Table S3 shows the numbers of hypotensive and hypoglycemic

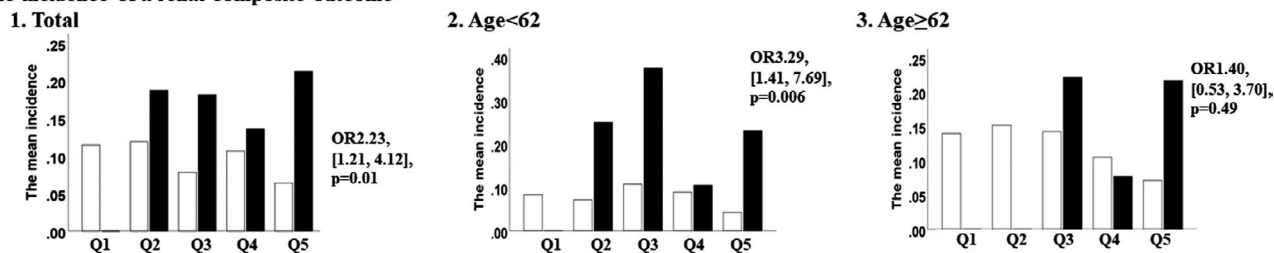
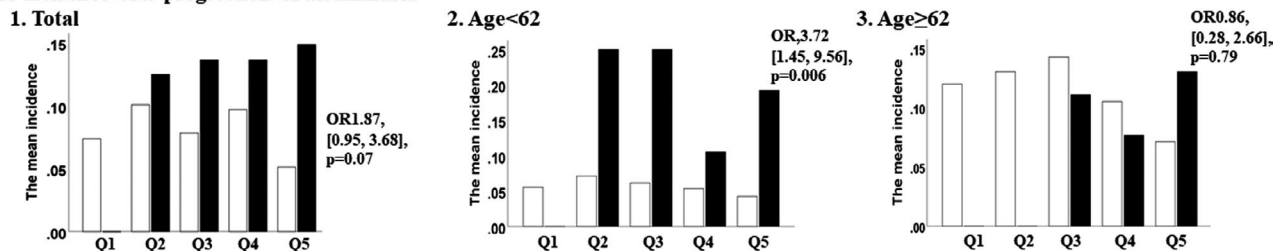
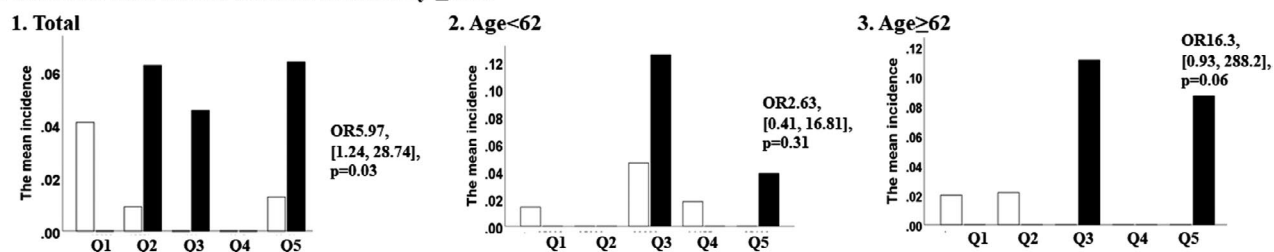
(a) The incidence of a renal composite outcome**(b) The incidence of a progression of albuminuria****(c) The incidence of an annual decrease in eGFR by $\geq 15\%$** 

FIGURE 2 Mean incidence of each renal outcome based on the quintiles of patients in total and in subgroups (age <62 years and age ≥ 62 years). (a) The incidence of the renal composite outcome. (b) The incidence of the progression of albuminuria. (c) The incidence of an annual decrease in eGFR by greater than or equal to 15%. White column shows the patients with less than seven medications, and black column shows the patients with greater than or equal to seven medications. Patients were stratified into quintiles based on the corresponding propensity score; Whole; Q1: PS less than or equal to 0.07, Q2: 0.07 less than PS less than or equal to 0.11, Q3: 0.11 less than PS less than or equal to 0.16, Q4: 0.16 less than PS less than or equal to 0.26, and Q5: 0.26 less than PS. Age less than 62; Q1: PS less than or equal to 0.05, Q2: 0.05 less than PS less than or equal to 0.09, Q3: 0.09 less than PS less than or equal to 0.14, Q4: 0.14 less than PS less than or equal to 0.25, and Q5: 0.25 less than PS. Age greater than or equal to 62; Q1: PS less than or equal to 0.06, Q2: 0.06 less than PS less than or equal to 0.13, Q3: 0.13 less than PS less than or equal to 0.19, Q4: 0.19 less than PS less than or equal to 0.31, and Q5: 0.31 less than PS. Abbreviations: eGFR, estimated glomerular filtration rate; OR, odds ratio; PS, propensity score

medications in the two groups. These data suggest that for one comorbidity, such as hypertension or T2DM, more medications were administered to patients in the “greater than or equal to seven medications” group than to patients in the “less than seven medications” group. Furthermore, patients with characteristics, such as old age or poor control of blood pressure or HbA1c levels, may have experienced comorbidities or needed medications; therefore, we applied the PS-matching method to align the backgrounds of the two groups. We cannot deny that many comorbidities can result in polypharmacy; however, patients tended to need many medications for each comorbidity; therefore, polypharmacy cannot be explained only by the number of comorbidities.

Limitations of this study are its retrospective design and small sample size; however, when polypharmacy is investigated for a long period, a prospective randomized study is not suitable for ethical reasons because a restriction on the number of administered drugs is clearly disadvantageous for the enrolled patients. PS matching was used to adjust the data for confounding factors in this retrospective survey, and the analysis of the PS-matching and PS-stratified models showed a significantly larger number of adverse events among patients with greater than or equal to seven medications than among patients with less than seven medications. This result indicates that polypharmacy was associated with a high risk. However, in the PS-matched model, the frequency of concomitant medications was

TABLE 3 Baseline characteristics in two matched cohort models divided by age (age <62 years; and age ≥62 years) after propensity score matching

	Matched cohort of age <62 years (n = 106)			Matched cohort of age ≥62 years (n = 84)		
	<7 medications (n = 53)	≥7 medications (n = 53)	Standardized difference	<7 medications (n = 42)	≥7 medications (n = 42)	Standardized difference
Age at the time of the initiation of SGLT2i treatment, year	51.2 ± 6.8	52.3 ± 7.4	0.16	69.4 ± 5.7	68.5 ± 5.9	0.16
Sex, male	39 (74%)	38 (72%)	0.04	26 (62%)	28 (67%)	0.10
BMI, kg/m ²	30.9 ± 6.2	31.2 ± 6.2	0.05	27.6 ± 3.7	28.2 ± 3.6	0.16
BW, kg	86.4 ± 17.4	87.1 ± 14.0	0.04	70.9 ± 12.8	74.2 ± 11.2	0.27
SBP, mmHg	138.1 ± 14.6	138.4 ± 14.9	0.02	139.4 ± 17.2	136.0 ± 17.0	0.20
DBP, mmHg	82.9 ± 11.6	82.1 ± 9.9	0.07	73.9 ± 10.8	71.5 ± 12.8	0.21
MAP, mmHg	101.3 ± 11.6	100.8 ± 10.4	0.05	95.7 ± 10.7	93.0 ± 12.5	0.23
HbA1c, mmol/mol (%)	69.6 ± 17.1 (8.5 ± 1.6)	68.2 ± 13.6 (8.4 ± 1.2)	0.09	62.2 ± 11.4 (7.8 ± 1.0)	63.2 ± 12.6 (7.9 ± 1.2)	0.08
eGFR, ml/min/1.73 m ²	83.4 ± 21.0	81.8 ± 16.6	0.08	72.0 ± 19.7	67.8 ± 20.1	0.21
LNACR	1.84 ± 0.67	1.82 ± 0.62	0.03	1.76 ± 0.65	1.73 ± 0.81	0.04
Duration of treatment, month	36.7 ± 10.5	34.4 ± 10.2	0.21	34.3 ± 10.7	32.5 ± 10.5	0.17
Number of concomitant medications	4.6 ± 1.2	7.5 ± 0.9	2.7	4.8 ± 1.1	7.5 ± 0.7	2.8
Types of SGLT2 inhibitor						
Ipragliflozin	9 (17%)	13 (25%)	0.19	14 (33%)	13 (31%)	0.05
Dapagliflozin	11 (21%)	11 (21%)	0.0	9 (21%)	8 (18%)	0.06
Tofogliflozin	9 (17%)	8 (15%)	0.05	0 (0%)	2 (5%)	0.32
Luseogliflozin	2 (4%)	4 (8%)	0.16	6 (14%)	3 (7%)	0.23
Canagliflozin	8 (15%)	6 (11%)	0.11	0 (0%)	0 (0%)	0.0
Empagliflozin	3 (6%)	3 (6%)	0.0	10 (24%)	10 (24%)	0.0
Change in SGLT2 inhibitors ^a	11 (21%)	8 (15%)	0.15	3 (7%)	6 (14%)	0.23
Concomitant treatment (at survey)						
DPP4 inhibitors	11 (21%)	32 (60%)	0.88	33 (79%)	34 (81%)	0.06
GLP1RA	14 (26%)	28 (32%)	0.56	2 (5%)	9 (21%)	0.51
Metformin	37 (70%)	48 (91%)	0.54	24 (57%)	28 (67%)	0.20
SU	15 (28%)	27 (51%)	0.48	13 (31%)	23 (55%)	0.50
Insulin	16 (30%)	26 (49%)	0.39	13 (31%)	15 (36%)	0.10
Pioglitazone	8 (15%)	17 (32%)	0.41	10 (24%)	16 (38%)	0.31
RAS inhibitors	24 (45%)	47 (89%)	1.04	19 (45%)	36 (86%)	0.94

(Continues)

TABLE 3 (Continued)

	Matched cohort of age <62 years (n = 106)		Matched cohort of age ≥62 years (n = 84)		Standardized difference
	<7 medications (n = 53)	≥7 medications (n = 53)	<7 medications (n = 42)	≥7 medications (n = 42)	
Ca channel blocker	15 (28%)	46 (87%)	15 (36%)	39 (93%)	1.49
B blocker	5 (9%)	17 (32%)	2 (5%)	13 (31%)	0.73
Mineral corticoid receptor blocker	4 (8%)	10 (19%)	1 (2%)	13 (31%)	0.83
Loop diuretics	0 (0%)	3 (6%)	0 (0%)	4 (10%)	0.46
Thiazide diuretics	0 (0%)	10 (19%)	0 (0%)	9 (21%)	0.74
Statins	32 (60%)	46 (87%)	27 (64%)	35 (83%)	0.44

Note: Values are the mean ± SD or n/total n (%).

Abbreviations: BMI, body mass index; BW, body weight; DPP4, Dipeptidyl Peptidase-4; eGFR, estimated glomerular filtration; GLP1RA, glucagon-like peptide 1 receptor agonist; LNA CR, logarithmic value of albumin-to-creatinine ratio; MAP, mean arterial pressure; RAS, renin-angiotensin system inhibitor; SGLT2i, sodium-glucose co-transporter inhibitor.

^aChange in SGLT2is during the study period.

significantly higher among patients with greater than or equal to seven medications than among patients with less than seven medications. Because the number of administered drugs and their frequency are closely related to the definition of polypharmacy, we did not include the number of concomitant medications and their frequency as a covariate in the logistic regression analysis when the PS was calculated. A significant difference was observed between the two groups in the use of concomitant medications; however, the influence of concomitant medications on the results of the PS-matched model cannot be ruled out. The PS-matching method could not completely resolve the background differences between the two groups.

The current study suffers from a number of limitations. Several major limitations in the current study include the fact that the unmatched concomitant medications are in the PS-matched model. Another limitation is that insufficient information about other concomitant medications that patients actually used and that may cause nephrotoxicity. Excessive use of diuretics or enin-angiotensin system inhibitors or mineralocorticoid receptor blockers by patients with a severe renal impairment may decrease renal blood flow and cause a further eGFR reduction. In each cohort model, the use of these agents was more significantly frequent among patients with greater than or equal to seven medications than among patients with less than seven medications ($p \leq 0.01$ for each model), and there is a possibility that these agents worsened the renal composite outcome in patients with greater than or equal to seven medications, but the logistic regression analysis could not identify these agents as the independent risk factor for the renal composite outcome in our previous report.⁵ Furthermore, our previous logistic regression analysis identified the use of insulin as an independent risk factor for the incidence of the renal composite outcome.⁵ A meta-analysis suggests that severe hypoglycemia is associated with a higher risk of cardiovascular events.²⁵ In the present study, it is also possible that the use of insulin severely aggravated hypoglycemia and worsened the renal composite outcome; however, the relation between severe hypoglycemia and renal outcomes is not fully understood. Our analysis only reported that the patients who were experiencing polypharmacy showed a high incidence of renal outcomes; however, our results could not clarify any mechanism or cause of outcomes. These major limitations constrain the implication of the current work.

Regarding the age subgroups (<62 years and ≥62 years), the PS-matched model did not show significant differences in either age group. The PS matching was performed to adjust the data for clinical background factors (that could be confounding factors) between the two groups; however, only 106 of the 369 patients aged less than 62 years and 84 of the 255 patients aged

TABLE 4 Incidence of the renal composite outcome and changes in clinical findings after SGLT2i treatment in two matched cohort models divided by age

	Age <62 years			Age ≥62 years		
	<7 medications (n = 53)	≥7 medications (n = 53)	p value	<7 medications (n = 42)	≥7 medications (n = 42)	p value
(a) The renal outcomes						
(1) Incidence of a renal composite outcome	4 (8%)	11 (21%)	0.09 ^a	3 (7%)	5 (12%)	0.73 ^a
(2) Incidence of a progression of albuminuria	2 (4%)	9 (17%)	0.07 ^a	3 (7%)	3 (7%)	1.0 ^a
(3) Incidence of a ≥15% annual decrease in eGFR	2 (4%)	2 (4%)	1.0 ^a	0 (0%)	2 (5%)	0.50 ^a
(b) Clinical findings after SGLT2i treatment						
eGFR at the survey, ml/min/1.73 m ²	77.8 ± 20.6	75.1 ± 18.9	0.44 ^b	66.9 ± 17.6	63.3 ± 20.7	0.41 ^b
The change in eGFR, ml/min/1.73 m ²	-5.6 ± 12.0	-6.8 ± 11.9	0.62 ^b	-5.1 ± 10.4	-4.5 ± 10.9	0.79 ^b
The annual eGFR change, ml/min/1.73 m ²	-2.3 ± 6.3	-2.9 ± 5.7	0.59 ^b	-2.0 ± 5.1	-2.4 ± 6.5	0.76 ^b
LNACR at the survey	1.60 ± 0.68	1.68 ± 0.68	0.48 ^b	1.57 ± 0.59	1.59 ± 0.86	0.90 ^b
BMI, kg/m ²	29.9 ± 6.4	30.0 ± 4.2	0.92 ^b	26.4 ± 3.6	27.4 ± 3.5	0.18 ^b
BW, kg	83.4 ± 17.1	83.6 ± 12.9	0.94 ^b	67.8 ± 12.9	72.2 ± 10.8	0.11 ^b
SBP, mmHg	128.8 ± 14.9	133.9 ± 17.5	0.07 ^b	128.1 ± 14.0	132.0 ± 7.2	0.27 ^b
DBP, mmHg	80.3 ± 10.6	79.5 ± 10.9	0.70 ^b	68.9 ± 10.4	70.6 ± 10.4	0.40 ^b
MAP, mmHg	96.5 ± 11.1	97.6 ± 10.9	0.59 ^b	88.6 ± 9.3	91.1 ± 10.2	0.23 ^b
HbA1c, mmol/mol (%)	61.0 ± 14.0 (7.7 ± 1.3)	59.4 ± 15.6 (7.6 ± 1.4)	0.54 ^b	55.2 ± 9.3 (7.2 ± 0.9)	56.6 ± 9.3 (7.3 ± 0.85)	0.50 ^b

Note: Values are the mean ± SD.

Abbreviations: BMI, body mass index; BW, body weight; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration; LNACR, logarithmic value of albumin-to-creatinine ratio; MAP, mean arterial pressure; SBP, systolic blood pressure; SGLT2i, sodium-glucose co-transporter inhibitor.

^aMcNemar test.

^bPaired *t*-test.

greater than or equal to 62 years were analyzed in the PS-matched model, and this small sample size is another limitation of this study.

In contrast, a significant difference in the incidence of the renal composite outcome was observed in the PS-stratified model that included all patients. Polypharmacy is generally considered a problem in elderly patients. However, young adults with chronic pain or developmental disabilities may reach polypharmacy,²⁶ whereas patients with epilepsy, diabetes mellitus, stroke, osteoporosis, and cancer are at a high risk of polypharmacy.²⁷ Our results show that polypharmacy correlates with adverse events irrespective of age and that our study is very interesting and novel. In the matched model, the HR was higher in patients less than 62 years of age than in patients

aged greater than or equal to 62 years (HR: 3.3, 95% CI: 0.9–12.1, and HR: 1.7, 95% CI: 0.4–7.0, respectively), and these results suggest that polypharmacy in young patients is a serious concern. Polypharmacy should be recognized as a serious clinical problem in any age group; however, this study has some limitations, including the possibility of a mismatch of other comorbidities, and a large sample size is needed to reach definitive conclusions.

Polypharmacy and the risk of adverse events

In Japan, adverse drug reactions are observed frequently in elderly hospitalized patients treated with more than

six drugs,²⁸ and the risk of falls among geriatric outpatients is reported to be high.¹⁶ Sunaga et al. recently reported that PIMs correlate with all-cause mortality and that the mortality rate is significantly higher in patients treated with more than six medications.¹⁷ Few reports have addressed the relationship between polypharmacy and renal outcomes, and this relationship has not been sufficiently discussed. Sakamoto recently reported that polypharmacy is associated with the number of cardiovascular diseases or their risk factors and the deterioration of renal dysfunction.¹⁸ Whitney et al. have reported a significant association between polypharmacy and the progression of severe kidney dysfunction with a fully adjusted HR of 1.66 (95% CI: 1.17–2.36).¹⁹ Our present study is the first cohort study where the PS is used to evaluate polypharmacy, and the findings are related to the progression of the renal composite outcome, consistently with the findings of the studies reported by Sakamoto¹⁸ or Whitney et al.¹⁹ In contrast, by means of background factors, Kang et al. performed a nested case-control study using matching²⁰; a greater incidence of eGFR progression (<60% or >10% decreases in the basal eGFR) was observed in elderly patients with polypharmacy than in those without polypharmacy,²⁰ and both the cohort study and case-control study confirmed that polypharmacy is a significant risk factor for renal outcomes.

The proposed strategy against polypharmacy

There are many causes of polypharmacy; however, this is a serious clinical concern that must be addressed urgently. Few researchers have investigated whether interventions into polypharmacy affect prognosis. Kim et al. have reported that polypharmacy and PIMs are often observed in elderly patients with CKD, and a medication management service by pharmacists significantly reduced the number of medications from 13.5 ± 4.3 to 10.9 ± 3.8 (mean \pm SD) and the number of PIMs from 1.6 ± 1.4 to 1.0 ± 1.2 .²¹ In Japan, the medical insurance agency implemented a project to prevent polypharmacy and started to provide economic incentives to hospitals in 2016 and pharmacies in 2018 when the number of medications was decreased from greater than six to less than four with informed consent of the patients.

Polypharmacy is a new problem that is emerging in aging societies, and social efforts to reduce polypharmacy are still inadequate. The problems of polypharmacy can be clarified by accumulating real-world evidence, as in our present study, and effective strategies against this problem are needed to improve the quality of medical care.

CONCLUSION

Polypharmacy is significantly associated with the incidence of the renal composite outcome, especially in young patients with T2DM and CKD who received SGLT2i treatment; thus, GPs need to pay close attention to polypharmacy in order to improve renal outcomes. However, this study has limitations, including an imperfect study design and PS-matching method, and additional studies are needed to clarify the relationship between polypharmacy and renal outcomes as well as between polypharmacy and age.

ACKNOWLEDGEMENTS

The authors thank all the participants and particularly acknowledge the support of Tomohiko Kanaoka, Nobumichi Saito, Shun Ito, Tomoya Umezono, Hiroshi Takeda, Daisuke Suzuki, Hisakazu Degawa, Fuyuki Minagawa, Hideo Machimura, Hareaki Yamamoto, Toshimasa Hishiki, Keiichi Chin, Kouta Aoyama, Masahiro Takihata, Kohsuke Minamisawa, Shinichi Umezawa, Yoshiro Hamada, Togo Aoyama, Masahiro Hayashi, Yoshiro Suzuki, Mitsuo Obana, Atsuko Mokubo, Noriyuki Asaba, Hidetoshi Shimura, Satoshi Suzuki, and Yutaka Hatori, who contributed considerably to data collection.

CONFLICT OF INTEREST

The authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

K.K., M.T., and N.H. wrote the manuscript. K.K., M.T., N.H., T.F., H.S., Y.H., K.S., M.M., K.T., and A.K. designed the research. K.K., M.T., N.H., T.F., H.S., Y.H., K.S., M.M., K.T., and A.K. performed the research. K.K., M.T., N.H., and H.S. analyzed the data.

REFERENCES

1. American Geriatrics Society 2012 Beers Criteria Update Expert Panel. American Geriatrics Society Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. *J Am Geriatr Soc.* 2012;60:616-631.
2. Gallagher P, Ryan C, Byrne S, Kennedy J, O'Mahony D. STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment). Consensus validation. *Int J Clin Pharmacol Ther.* 2008;46:72-83.
3. Hill-Taylor B, Sketris I, Hayden J, Byrne S, O'Sullivan D, Christie R. Application of the STOPP/START criteria: a systematic review of the prevalence of potentially inappropriate prescribing in older adults, and evidence of clinical, humanistic and economic impact. *J Clin Pharm Ther.* 2013;38:360-372.
4. Liang L. The gap between evidence and practice. *Health Aff (Millwood).* 2007;26:w119-w121.
5. 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(1):74-81.

6. Kobayashi K, Toyoda M, Hatori N, et al. 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. *J Diabetes Investig.* 2021;12(8):1408-1416.
7. Kobayashi K, Toyoda M, Hatori N, et al. The evaluation of noninferiority for renal composite outcomes between sodium-glucose cotransporter inhibitors in Japan. *Prim Care Diabetes.* 2021;15(6):1058-1062.
8. 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.* 2021;23:110-119.
9. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis.* 2002;39:S1-S266.
10. 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.
11. 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.
12. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med.* 2019;380:347-357.
13. 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.
14. 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.
15. Cannon CP, Pratley R, Dagogo-Jack S, et al. Cardiovascular outcomes with ertugliflozin in type 2 diabetes. *N Engl J Med.* 2020;383:1425-1435.
16. Bhatt DL, Szarek M, Pitt B, et al. Sotagliflozin in patients with diabetes and chronic kidney disease. *N Engl J Med.* 2021;384:129-139.
17. 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.
18. 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.
19. 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.
20. Research group on the formulation of clinical evaluation guidelines for chronic diseases in the renal field. Endpoints in clinical trials of CKD patients. *Jpn J Nephrol.* 2018;60(2):67-100.
21. 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.
22. Qato DM, Wilder J, Schumm LP, Gillet V, Alexander GC. Changes in prescription and over-the-counter medication and dietary supplement use among older adults in the United States, 2005 vs 2011. *JAMA Intern Med.* 2016;176:473.
23. 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.
24. Suzuki Y, Akishita M, Arai H, Teramoto S, Morimoto S, Toba K. Multiple consultations and polypharmacy of patients attending geriatric outpatient units of university hospitals. *Geriatr Gerontol Int.* 2006;6:244-247.
25. Goto A, Arah OA, Goto M, Terauchi Y, Noda M. Severe hypoglycaemia and cardiovascular disease: systematic review and meta-analysis with bias analysis. *BMJ.* 2013;347:f4533.
26. Lunskey Y, Modi M. Predictors of psychotropic polypharmacy among outpatients with psychiatric disorders and intellectual disability. *Psychiatr Serv.* 2018;69:242-246.
27. Haider SI, Ansari Z, Vaughan L, Matters H, Emerson E. Prevalence and factors associated with polypharmacy in Victorian adults with intellectual disability. *Res Dev Disabil.* 2014;35:3071-3080.
28. Kojima T, Akishita M, Kameyama Y, et al. High risk of adverse drug reactions in elderly patients taking six or more drugs: analysis of inpatient database. *Geriatr Gerontol Int.* 2012;12:761-762.

SUPPORTING INFORMATION

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How to cite this article: Kobayashi K, Toyoda M, Hatori N, et al. Polypharmacy influences the renal composite outcome in patients treated with sodium-glucose cotransporter 2 inhibitors. *Clin Transl Sci.* 2022;15:1050-1062. doi:[10.1111/cts.13222](https://doi.org/10.1111/cts.13222)