# Comparison of the blood pressure management between sodium glucose co-transporter 2 inhibitors and glucagon-like peptide 1 receptor agonists

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**Article**

**Keywords:** sodium-glucose cotransporter 2 inhibitors, glucagon-like peptide 1 receptor agonist, blood pressure

**Posted Date:** June 17th, 2022

**DOI:** https://doi.org/10.21203/rs.3.rs-1728274/v1

# Abstract

Reduction in blood pressure (BP) contributes to the cardiovascular and renal protective effects of sodium-glucose co-transporter 2 inhibitors (SGLT-2is) and glucagon-like peptide 1 receptor agonists (GLP-1Ras). However, there has been no direct comparison in terms of BP-lowering efficacies. We compared the rates of achieving a target BP with SGLT-2i and GLP-1Ra treatments administered to Japanese patients with type 2 diabetes mellitus (T2DM). This retrospective study included 384 SGLT-2i- and 160 GLP-1Ra-treated patients with a BP > 130/80 mmHg before treatment. Inverse probability weighting methods using propensity scores were applied in this study. The integrated odds ratios (OR) for BP control rates were calculated and clinical changes were analyzed using a generalized linear model. SGLT-2i treatment resulted in significantly higher BP control rates than the GLP1Ra treatment (integrated OR = 2.09 [1.80, 2.43]). Compared with GLP-1Ra, SGLT-2i treatment determined significantly larger decreases in diastolic BP, mean arterial pressure, and body weight (-3.8 mmHg, $P$ = 0.006; -4.1 mmHg, $P$ = 0.01; and -1.5 kg, $P$ = 0.008, respectively) and increased annual estimated glomerular filtration rate (eGFR; 1.5 mL/min/1.73 $m^2$/year, $P$ = 0.04). In T2DM patients with poorly controlled BP, compared with GLP-1Ra, SGLT-2i treatment significantly improved BP management along with increasing eGFR.


# 1 | Introduction

After rosiglitazone treatment was associated with increased cardiovascular risk, especially heart failure and myocardial infarction (1), the United States Food and Drug Administration (FDA) requires non-inferiority randomized placebo-controlled trials, known as cardiovascular outcome trials (CVOT), to assess the cardiovascular risk of new types of drugs used for treating type 2 diabetes mellitus (T2DM). (2) Compared to placebo, treatment with dipeptidyl peptidase-4 inhibitors (DPP4is) demonstrated non-inferiority for major adverse cardiac outcomes (3–6), however, treatment with saxagliptin was associated with an increased risk of heart failure (5). In contrast several CVOTs demonstrated the superiority of sodium-glucose co-transporter inhibitors (SGLT-2is) (7–9) and glucagon-like peptide-1 receptor agonists (GLP-1Ra) in preventing major cardiovascular events compared with placebo (10–13). Furthermore, in several CVOTs, both SGLT-2i and GLP-1Ra treatments have been found to be associated with superior renal outcomes (7–9, 14). Based on these findings, which support the cardiovascular and renal protective effects of SGLT-2i and GLP-1Ra, these two types of antidiabetics are highly recommended by guidelines (15, 16). The mechanisms involved in the cardiovascular and renal protective effects are not completely understood. It seems that not only their hypoglycemic effect, but also other effects such as lowering blood pressure (BP), body weight (BW) loss, and improvement of insulin resistance or lipid profile are involved thereof. The hypoglycemic effects of SGLT-2i are not essential for its organ-protective effects. A DAPA-HF study investigating dapagliflozin (17) and EMPEROR-reduced clinical trials investigating empagliflozin (18) demonstrated their superiority in cardiovascular outcomes, while a DAPA-CKD trial showed their superiority in renal outcomes in patients with or without diabetes compared to placebo (19).

We previously performed a retrospective observational survey of 624 T2DM patients with chronic kidney disease (CKD) and demonstrated that SGLT2i treatment decreased the urine albumin-to-creatinine ratio (ACR) in clinical practice (20). We observed that the BP-lowering effect correlated with the renoprotective effect of SGLT-2i treatment(21) (22) (23) (24). We also performed a retrospective observational survey which included 547 GLP-1Ra-treated T2DM patients (data not published). Using these two reports, we directly compared the renal and cardioprotective effects of SGLT-2i and GLP-1Ra using the propensity score (PS) matching method (25). This analysis demonstrated the significant superiority of SGLT-2i versus GLP-1Ra on the renal composite outcome in

T2DM patients and that, in SGLT2i-treated patients, the decrease in BP is significantly correlated with the decrease in ACR (P = 0.04) (25).

Using actual clinical databases, we posit that appropriate BP control is an important mechanism underlying the renoprotective effects of these new antidiabetics. However, a direct comparison between the BP-lowering effects of these two types of antidiabetic drugs has not been sufficiently reported. Therefore, this study aimed to compare the differences in BP control rates induced by SGLT-2i and GLP-1Ra treatment in Japanese T2DM patients.

# 2 | Results

### 2.1 | Clinical characteristics of SGLT-2i- and GLP-1Ra-treated patients at baseline

Supplementary Fig. S1 shows a schematic of the subject selection procedure. We included 384 SGLT-2i - and 160 GLP-1Ra-treated patients in the comparative analysis. The median duration of treatment was 32 months (range, 12–55 months) for the SGLT-2 group and 48.5 (range, 12–123 months) for the GLP-1Ra group. Table 1 presents the clinical characteristics of the SGLT-2i- and GLP-1Ra-treated patients at baseline. No significant differences were observed between the groups in terms of SBP and ACR values, logarithmic value of ACR (LnACR), and concomitant use of pioglitazone, calcium channel blockers, and statins. However, significant differences were observed between the groups in other clinical characteristics: age, sex, BW, body mass index (BMI), diastolic BP, mean arterial pressure (MAP), glycated hemoglobin $A_{1c}$ ($HbA_{1c}$), estimated glomerular filtration rate (eGFR), duration of treatment, use of sulphonylurea metformin, insulin, renin-angiotensin system inhibitors, and β-blockers (P <0.001, =0.003, <0.001, =0.003, =0.003,=0.01, <0.001, <0.001, <0.001,=0.01, <0.001, <0.001, =0.04, and =0.02, respectively).

### 2.2 | Cohort models using inverse probability weighting estimation

The clinical characteristics of SGLT-2i- and GLP-1Ra-treated patients after inverse probability weighting (IPW) are shown in Tables 2, 3, and 4, where the utilized weighting methods were average treatment effect (ATE), average treatment effect on the treated (ATT), and stabilized ATE, respectively. Furthermore, two different methods were used for the adjustment of IPW: “weight truncation” that consisted in the exclusion of weights larger than 99 percentiles (model A), or “weight trimming” that consisted in excluding extreme PS values and including only the patients with PS ranging from 0.05 to 1.0 (model B), who were selected for further analysis. The distribution of PS in each group is shown in Supplementary Fig. S3. The C-index value for the calculated PS was 0.90.

Trimming using the PS value determined the exclusion of 204 patients from the analysis (166 patients had PS values > 0.95 and 38 patients had values < 0.05). When using the other method, five weights were larger than 99 percentiles and were trimmed.

### 2.3 | Primary outcome assessment

Comparisons between the rates of achieving the target BP with SGLT-2i and GLP-1Ra treatments based on the generalized linear model and integrated odds ratio (OR) analyses are shown in Table 5 and Fig. 1, respectively. No significant differences were observed in primary outcome between treatment groups when employing model A (P value was 0.06 using ATE weighting, 0.14 using ATT weighting, and 0.06 using stabilized ATE weighting). However, when using model B, the difference was statistically significant (P value was 0.03 using ATE weighting, 0.04 using ATT weighting, and 0.03 using stabilized ATE weighting). Figure 1 illustrates the integrated OR

calculated using the meta-analysis method (2.09; 95% confidence interval [CI]; 1.80–2.43). The weighted numbers of patients who reached the target BP after treatment (events) and the weighted numbers of all patients (total) using the six IPW models are shown on the left side of Fig. 1.

### 2.4 | Evaluation of standardized differences among the six utilized models

The standardized differences among the clinical baseline characteristics depending on the type of weighting model employed are shown in Supplementary Fig. S4. The median value and ranges of the standardized differences obtained when applying ATE weighting with truncation of values > 99 percentiles, ATE weighting with PS-based trimming (trimming by $0.05 \leqq PS \leqq 0.95$), ATT weighting with truncation of values > 99 percentiles, ATT weighting with PS-based trimming, stabilized ATE weighting with truncation of values > 99 percentiles, and stabilized ATE weighting with PS-based trimming were 0.10 (0.01–0.35), 0.06 (0.01–0.20), 0.15 (0.03–0.50), 0.13 (0.02–0.37), 0.11 (0.003–0.35), and 0.07 (0.01–0.20), respectively.

### 2.5 | Changes in clinical characteristics induced by treatment

After examining the variations in standardized differences in the baseline clinical characteristics depending on the utilized weighting model, for further analysis, we adopted the ATE weighting model followed by trimming using a PS value because this model showed the smallest median value of the standardized differences. The changes of the clinical characteristics after SGLT2i treatment compare to GLP1Ra treatment by the analysis of the generalized linear model are shown in Table 6. Significant decreases in DBP, MAP, and BW were observed in SGLT-2i- compared with GLP-1Ra-treated patients.

## 3 | Discussion

We performed two retrospective cohort surveys to assess the effects of two new classes of antidiabetic drugs, SGLT-2i and GLP-1R, on renal function. In our previous analysis, we found that SGLT-2 has superior renoprotective effects compared to GLP-1R and that BP reduction caused by treatment with SGLT-2 contributed to this effect (24, 26). To evaluate the comparative efficacy of the two classes of drugs in lowering BP, we selected patients with poorly controlled baseline BP. SGLT-2i showed a better BP control rate than GLP-1Ra treatment, which underlies the renoprotective effects of SGLT-2i treatment.

Although randomized controlled studies provide high-quality evidence, retrospective cohort studies have serious limitations because of inadequate data on confounding factors. PS is the probability that a case is included in the treated group, calculated using the background characteristics that are considered confounding factors. PS methods have been utilized for controlling confounding factors in clinical studies (27). Statistical methods using PS, such as PS weighting and PS matching, may be useful for estimating treatment effects (28).

Of these, the PS-matching method reduces the effects of confounding factors by selecting only participants with close PS and has been used in some real-world studies, such as CVD-REAL (Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGLT-2 Inhibitors) (29), EMPRISE (Empagliflozin Comparative Effectiveness and Safety) (30), and the J-CKD database (31). These studies evaluated the cardiovascular and renal outcomes of SGLT-2i treatment.

PS weighting is another PS-based statistical method. In this survey, we selected participants who did not achieve the target BP at baseline. Consequently, the sample size of both treatment groups became small. We obtained

extreme propensity scores between the two treatment groups in the present models (the value of c-statistics was 0.904); therefore, PS matching may result in substantial loss of sample size. Consequently, we selected the PS-weighting method for further analysis.

Different weighting methods can be used, depending on the primary treatment effect of interest (ATE, stabilized ATE, or ATT). The formula for the weight calculation using PS is described in Supplementary Fig. S2. When the value of PS approaches zero or one, the value of the weight is extremely high, resulting in biased estimates and excessive variance.

Lee et al. reported that trimming large weights can improve the performance of PS weighting (32). Symmetric trimming that excluded subjects with PS values ranging 0.05–0.95 was reported by Richard (33). The truncation of the weight for values “larger than 99 percentiles was reported by Cole and Hernan (34). Currently, there is no consensus on the best method to choose the right PS-weighting, trimming, or truncation method. We used six statistical models in this survey.

To avoid selecting models that would generate the most favorable results, we assessed the integrated OR as primary outcome, calculated using meta-analysis of data resulting from the six models applied. We conclude that SGLT-2i treatment offers superior control of BP in T2DM patients compared with GLP-1Ra treatment. Some concerns regarding this analysis must be mentioned. The ORs of individual models were calculated using generalized linear model analysis. The integrated OR was calculated by combining the above-mentioned ORs in a meta-analysis and using the weighted number of events. Therefore, the OR values, including the lower and upper values of the 95% CIs, were not completely matched. Further analysis and discussion are warranted to determine the best method for assessing the OR and choosing the optimal PS-weighting model. It may be difficult to define an appropriate method of PS weighting because the standardized differences had a large variance in each utilized model, as illustrated in Supplementary Fig. S4. Further analysis is needed to determine which model is appropriate for this study by using data from clinical practice.

A meta-analysis showed the composite renal outcome superiority of SGLT-2i and GLP-1Ra treatment compared with placebo (45% HR, 0.55; 95% CI, 0.48 to 0.64; $P < 0.0001$) (35); 17% HR, 0.83; 95% CI, 0.78–0.89; $P = 0.098$, respectively) (36). A network meta-analysis concluded that SGLT-2i treatment possesses renal outcome superiority compared with GLP-1Ra treatment (37) (38). The renoprotective mechanism of SGLT-2is may be a result of multiple factors: favorable effects on vascular function by reducing intraglomerular pressure through restoration of tubuloglomerular feedback, improvement of hypoxia in the proximal kidney tubule, and metabolic effects, such as a reduction in BP or BW (39),(40). In turn, GLP-1Ras’ renoprotective effects may be a consequence of increased sodium excretion due to the inhibition of the sodium-hydrogen exchanger isoform 3 (41) or anti-inflammatory and antioxidant effects (42, 43). In our previous studies, we found that SGLT-2i treatment is associated with a larger decrease in BP than GLP-1Ra treatment, and that this effect is strongly correlated with their renoprotective effects (25). Regarding the secondary outcome, we selected the ATE weighting model associated with PS-based trimming for generating minimal standardized differences. Using this model for further analysis, we found that SGLT-2i treatment resulted in a greater decrease in BP and BW and higher eGFR values compared with GLP-1Ra treatment. These results are similar to those of our previous study (25). There was no significant difference in the decrease in LnACR between the two groups. However, a larger sample size may show that SGLT-2i determines a higher decrease in LnACR than GLP-1Ra. Accordingly, the renoprotective effect of SGLT-2i in T2DM patients with poorly controlled BP was superior to that of GLP-1Ra treatment.

The standardized differences in clinical characteristics were below 0.20, with some exceptions, which were higher than 1.0, even in this model. In general, a standardized difference of < 0.10 is associated with a meaningful imbalance between the two groups (44). Austin reported that standardized differences exceeding 0.20 are expected, even when the PS-matched model is correctly specified (45). The model used in the current study (ATE weighting associated with PS-based trimming) could decrease the imbalance between clinical characteristics at baseline. However, bias remains concerning the confounding factors that were not included in the study. This is a major limitation of this study.

### Study limitations

In addition to the above-mentioned point, our comparative study has some other limitations.

Our surveys were small in size, were retrospective, and observational, were not performed simultaneously, and did not have the same inclusion criteria. The subjects of the SGLT-2i survey were patients with T2DM and CKD, whereas those of the GLP-1Ra survey were patients with T2DM. Therefore, there may have been a selection bias. In clinical practice, combining both drugs is becoming a basic strategy for managing T2DM, and only patients with underlying contraindications to one of them receive the other. In this study, we compared patients receiving only one of these treatments. Therefore, our results are not applicable to patients treated with combination therapies. As only 265 GLP-1Ra-treated patients were included in the comparative analysis, selection bias appears to be a major issue in our survey.

Furthermore, our survey included only data from subjects who received continuous treatment. No data on adverse events that emerged during treatment were collected. Adverse events and quality of life (QOL) are important outcomes of any treatment. SGLT-2i drugs are administered orally, while GLP-1Ra drugs are administered by injection (oral semaglutide was not available at the time of the survey in Japan), and this may have resulted in a lower QOL or adherence to GLP-1Ra treatment. These factors may have further influenced our results.

Taken together, our results demonstrate that in T2DM patients with poorly controlled BP, SGLT-2i significantly improved BP management (the integrated OR and 95%CI was 2.09 [1.80, 2.43]) and increased BW loss and eGFR compared with GLP-1Ra treatment (P =0.01, and 0.04, respectively). The efficacy in achieving a target BP rate and the characteristics of antidiabetic drugs should be considered to realize renoprotective effects in clinical practice.

# 4| Methods

### 4.1 | Study patients and data collection

This study is a sub-analysis of our previous study and the methods of this study was already described in our previous report (25). In short, the Kanagawa Physicians Association carried out two retrospective surveys that included patients with T2DM receiving SGLT-2i or GLP-1Ra therapy to investigate their influence on renal function. The studies included patients who visited the clinics of members of the association between October and December 2018 and from July to October 2020 for the SGLT-2i and GLP-1Ra surveys, respectively. Both surveys had the following inclusion criteria: patients with T2DM who were (a) treated with each drug for more than one year, (b) aged over 20 years, and, only for SGLT-2i retrospective study: (c) diagnosed as having CKD, as defined by the K/DOQI clinical practice guidelines (46). The following patients were excluded: (a) undergoing chronic dialysis, or with (b) type 1 DM, (c) severe liver dysfunction (e.g., liver cirrhosis or severe hepatitis), (d) stage IV malignancy, (e) pregnancy, (f) poor adherence to each drug (suggested by irregular use), and (g) intended to opt out during the

study. Applying these criteria, 34 patients in the SGLT-2i survey and 33 patients in the GLP-1Ra survey were excluded.

The following parameters were recorded at the time of initiation of each treatment and at the time of the survey: age, sex, BW, BP (systolic; SBP, diastolic; DBP, mean arterial pressure; MAP), serum creatinine level, glycated hemoglobin $A_{1c}$ ($HbA_{1c}$), and urinary ACR [mg/g Cr] or qualitative proteinuria. The estimated glomerular filtration rate (eGFR) was calculated using the formula: eGFR (mL/min/1.73 $m^2$) = 194 × $age^{-0.287}$ × serum $creatinine^{-1.094}$ × (0.739 for women) (47). The formula reported by Sumida et al. (48) was used to convert qualitative proteinuria values to albuminuria values. Documentation of patients' medical records was extracted by medical doctors, and anonymized patient forms were used. A total of 140 patients in the SGLT-2i survey and 29 patients in the GLP-1Ra survey were excluded because of missing ACR values at any point during data collection. Patients concomitantly treated with both drugs were excluded. Thus, 541 and 265 patients were included in the SGLT-2i survey (SGLT-2i group) and GLP-1Ra survey (GLP-1Ra group) surveys, respectively. Patients with poorly controlled BP (>130/80 mmHg) (determined in the clinical setting before the initiation of therapy) were further selected. In total, 384 and 160 patients were included in the SGLT-2i and GLP-1Ra groups, respectively.

### 4.2 | Outcomes

In accordance with the Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2019), the target BP for T2DM patients is < 130/80 mm Hg (49). The primary endpoint of this study was the rate of achievement of the target BP.

### 4.3 | Statistical analysis

When different retrospective surveys are utilized to appropriately analyze the differences in the outcomes of the two treatments, adjusting for confounding factors is needed. PS analysis is useful for balancing confounding factors between the two groups. PS values for SGLT-2i-treated patients were calculated using a logistic regression model to estimate the probability of treatment efficacy when considering the following variables: age, sex, BW, $HbA_{1c}$, SBP, DBP, eGFR, and the logarithmic value of LnACR at baseline, as well as the concomitant use of antihypertensive drugs, other glucose-lowering drugs, and statins. All of these factors are considered common confounding factors when assessing the efficacy of antihypertensive treatment.

In this study, the IPW method was used for comparative analysis. Several methods of weighting and trimming the values may be utilized when the IPW method is applied. As no method is currently considered the best, we utilized three methods for weighting, depending on the primary treatment effect of interest: ATE weighting, ATT weighting, or stabilized ATE weighting. Supplementary Fig. S2 illustrates the calculation method for each weight using PS. Two methods were further used for the adjustment of IPW: "weight truncation" that consisted in the exclusion of weights larger than 99 percentiles (model A), or "weight trimming" that consisted in excluding extreme PS values and including only the patients with PS ranging from 0.05 to 1.0 (model B). Accordingly, six models were used in the IPW method. Regarding the primary outcome, ORs were calculated using the data obtained from the six models, and a meta-analysis of the data was conducted to calculate the integrated OR, using EZR version 1.55 (Saitama Medical Center, Jichi Medical University, Saitama, Japan).

Regarding the other comparative analyses, the model leading to the smallest standardized differences between the clinical characteristics at baseline was selected, and a generalized linear model analysis was performed for

the comparison between groups.

An unpaired *t*-test was used to analyze differences in the clinical and laboratory pathological profiles between the two groups, the Mann-Whitney rank-sum test was used for continuous variables, and the chi-square test was used for categorical data in the cohort model before applying IPW. After applying IPW, a generalized linear model was used for comparative analysis.

The results are presented as mean ± standard deviation, mean (lower and upper 95% CI), or median with interquartile range (IQR) for continuous data and as percentages for categorical data. Statistical significance was set at $P < 0.05$. All statistical analyses, except for the calculation of the integrated OR for the primary outcome, were performed using the IBM SPSS Statistics software (version 28.0; IBM Inc., Armonk, NY, USA).

This retrospective study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the special ethics committee of the Kanagawa Medical Association, Japan (approval Krec202005 on March 23, 2020, for the GLP-1Ra survey and this comparison survey; approval Krec304401 on March 6, 2018, for the SGLT-2i survey). Informed consent was waived by the special ethics committee of the Kanagawa Medical Association, Japan, owing to the retrospective and observational nature of the study.

# Declarations


### Acknowledgments

We are grateful to all participants and acknowledge the support of Yutaka Hatori, Masaaki Miyakawa, Keiichi Chin, Moritsugu Kimura, Nobumichi Saito, Tomohiko Kanaoka, Togo Aoyama, Tomoya Umezono, Shun Ito, Daisuke Suzuki, Hiroshi Takeda, Fuyuki Minagawa, Hisakazu Degawa, Hideo Machimura, Toshimasa Hishiki, Shinichi Umezawa, Hidetoshi Shimura, Shinichi Nakajima, Hareaki Yamamoto, Masaaki Miyauchi, Noriko Kanayama, Kouta Aoyama, Masahiro Takihata, Kohsuke Minamisawa, Yoshiro Hamada, Masahiro Hayashi, Satoshi Suzuki, Sanae Takeichi, Yoshiro Suzuki, Mitsuo Obana, Atsuko Mokubo, Noriyuki Asaba, and Satoshi Suzuki, who contributed considerably to data collection.


### Author contributions

Design;

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Data collection

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Analysis

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Writing manuscript

Kazuo Kobayashi, Masao Toyoda, Nobuo Hatori, and Kouichi Tamura.

### Data availability

Data are available from the Kanagawa Physicians Association Data Access/Ethics Committee for investigators and are bound by confidentiality agreements. Contact details: Kazuo Kobayashi MD, Kanagawa Physicians Association, 3-1Fujimicho Naka-ku, Yokohama City, Kanagawa Prefecture, Japan E-mail: k-taishi@xc4.so-net.ne.jp

### Conflict of interest

The authors declare no conflicts of interest in association with the present study.

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# Tables

**Table 1**

**The clinical characteristics of SGLT2i-treated and GLP1Ra-treated patients at baseline**

| | SGLT2i-treated patients (n=384) | GLP1Ra-treated patients (n=160) | P-value |
|---|---|---|---|
| Age (year-old) | 57.9±11.2 | 63.5±13.5 | <0.001† |
| Sex (female (%)) | 126 (32.8%) | 74 (46.3%) | 0.003† |
| BW (kg) | 80.1±16.2 | 73.4±17.7 | <0.001† |
| BMI | 29.3±4.9 | 28.0±5.4 | 0.003† |
| SBP (mmHg) | 141.1±12.8 | 140.9±11.9 | 0.44† |
| DBP (mmHg) | 81.6±11.2 | 78.6±11.2 | 0.003† |
| MAP (mmHg) | 101.4±9.5 | 99.4±8.9 | 0.01† |
| $HbA_{1c}$ (mmol/mol (%)) | 62.5±13.5<br>(7.9±1.2) | 68.6±17.9<br>(8.4±1.6) | <0.001† |
| eGFR (mL/min/1.73m$^2$) | 79.4±21.4 | 66.7±25.2 | <0.001† |
| ACR (mg/gCr) | 38.4 [13.0, 125.5] | 28.2 [13.5, 142.5] | 0.88♯ |
| LnACR | 1.62±0.66 | 1.66±0.78 | 0.27† |
| Duration of the treatment (month) | 31.9±10.7 | 55.2±31.4 | <0.001† |
| The concomitant treatment | | | |
| SU | 114 (29.7%) | 30 (18.8%) | 0.01‡ |
| Metformin | 231 (60.2%) | 61 (38.1%) | <0.001‡ |
| Insulin | 87 (22.7%) | 72 (45.0%) | <0.001‡ |
| Pioglitazone | 75 (19.5%) | 23 (14.4%) | 0.15‡ |
| RAS inhibitor | 213 (55.5%) | 104 (65.0%) | 0.04‡ |
| CCB | 189 (49.2%) | 91 (56.9%) | 0.10‡ |
| Bblocker | 46 (12.0%) | 31 (19.4%) | 0.02‡ |
| Statin | 234 (60.9%) | 97 (60.6%) | 0.95‡ |

Values represent the mean±standard difference, n (n/total %), or medium [25% quantile, 75% quantile].

‡Chai square test, †unpaired t test, ♯Mann-Whitney rank-sum test

Abbreviation; BMI, body mass index; BW, body wight; CCB, calcium channel blocker; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration; GLP1Ra, glucagon-like-1 receptor agonist; $HbA_{1c}$, glycated hemoglobin $A_{1c}$;

LnACR, logarithmic value of urine albumin-to-creatinine ratio; MAP, mean arterial pressure; RAS, renin aldosterone system; SBP, systolic blood pressure; SGLT2i, sodium glucose cotransporter inhibitor; SU, sulphonyl urea

**Table 2**

**The clinical characteristics of SGLT2i-treated and GLP1Ra-treated patients after ATE weighting**

| | Model A (the truncation on 99 percentiles) | | | Model B (the trimming by 0.05≦ PS ≦0.95) | | |
|---|---|---|---|---|---|---|
| | SGLT2i (n=501) | GLP1Ra (n=513) | Standardized difference | SGLT2i (n=338) | GLP1Ra (n=309) | Standardized difference |
| Age (year-old) | 59.7±11.5 | 63.2±12.4 | 0.29 | 62.8±11.0 | 64.8±12.4 | 0.17 |
| Sex(female (%)) | 34.1 (%) | 41.9 (%) | 0.16 | 38.9 (%) | 45.0(%) | 0.13 |
| BW (kg) | 78.2±15.9 | 72.7±15.5 | 0.35 | 74.3±14.4 | 71.9±18.0 | 0.14 |
| BMI | 28.8±4.8 | 27.5±4.8 | 0.29 | 27.9±4.3 | 27.6±5.6 | 0.06 |
| SBP (mmHg) | 141.1±13.1 | 142.9±13.8 | 0.14 | 140.9±13.5 | 141.1±12.0 | 0.01 |
| DBP (mmHg) | 81.0±11.3 | 79.0±11.8 | 0.17 | 79.2±11.4 | 76.9±11.5 | 0.20 |
| MAP (mmHg) | 101.0±9.5 | 100.3±9.8 | 0.08 | 99.8±9.6 | 98.3±8.9 | 0.16 |
| $HbA_{1c}$ (mmol/mol (%)) | 64.4±14.8 (8.0±1.4) | 64.7±15.3 (8.1±1.4) | 0.02 | 8.0±1.4 | 8.1±1.4 | 0.05 |
| eGFR (mL/min/1.73m$^2$) | 76.4±21.6 | 72.9±22.0 | 0.16 | 71.0±19.9 | 69.3±22.0 | 0.08 |
| LnACR | 1.66±0.67 | 1.62±0.68 | 0.06 | 1.67±0.71 | 1.65±0.82 | 0.03 |
| Duration of the treatment (month) | 33.4±10.7 | 35.3±25.7 | 0.10 | 36.4±9.6 | 37.9±21.9 | 0.09 |
| The concomitant treatment | | | | | | |
| SU | 25.5 (%) | 25.2 (%) | 0.01 | 18.4 (%) | 21.4 (%) | 0.08 |
| Metformin | 55.1 (%) | 56.1 (%) | 0.02 | 46.6 (%) | 45.0 (%) | 0.03 |
| Insulin | 29.7 (%) | 34.1 (%) | 0.09 | 40.2 (%) | 41.4 (%) | 0.02 |
| Pioglitazone | 17.6 (%) | 9.4 (%) | 0.24 | 15.1 (%) | 13.6 (%) | 0.04 |
| RAS inhibitor | 58.7 (%) | 63.2 (%) | 0.09 | 63.6 (%) | 58.9 (%) | 0.10 |
| CCB | 48.6 (%) | 47.3 (%) | 0.03 | 50.0 (%) | 51.8 (%) | 0.04 |
| Bblocker | 16.1 (%) | 15.0 (%) | 0.03 | 20.8 (%) | 22.1 (%) | 0.03 |
| Statin | 57.2 (%) | 52.2 (%) | 0.10 | 55.2 (%) | 52.4 (%) | 0.05 |

Values represent the mean±standard difference, or n (n/total %).

 Calculated number of subjects after weighting.

Abbreviation; ATE, average treatment effect; BMI, body mass index; BW, body wight; CCB, calcium channel blocker; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration; GLP1Ra, glucagon-like-1 receptor agonist; $HbA_{1C}$, glycated hemoglobin $A_{1C}$; LnACR, logarithmic value of urine albumin-to-creatinine ratio; MAP, mean arterial pressure; PS, propensity score; RAS, renin aldosterone system; SBP, systolic blood pressure; SGLT2i, sodium glucose cotransporter inhibitor; SU, sulphonyl urea

**Table 3**

**The clinical characteristics of SGLT2i-treated and GLP1Ra-treated patients after ATT weighting**

| | Model A (the truncation on 99 percentiles) | | | Model B (the trimming by 0.05≦ PS ≦0.95) | | |
|---|---|---|---|---|---|---|
| | SGLT2i (n=384) | GLP1Ra (n=353) | Standardized difference | SGLT2i (n=224) | GLP1Ra (n=193) | Standardized difference |
| Age (year-old) | 57.9±11.2 | 63.0±11.9 | 0.44 | 61.2±10.8 | 65.4±11.9 | 0.37 |
| Sex(female (%)) | 32.8 (%) | 39.9 (%) | 0.15 | 38.8 (%) | 45.6 (%) | 0.14 |
| BW (kg) | 80.1±16.2 | 72.4±14.4 | 0.50 | 75.5±14.9 | 70.9±17.6 | 0.29 |
| BMI | 29.3±4.9 | 27.2±4.5 | 0.43 | 28.2±4.5 | 27.4±5.6 | 0.16 |
| SBP (mmHg) | 141.1±12.8 | 143.9±14.5 | 0.20 | 140.8±13.1 | 141.3±11.9 | 0.03 |
| DBP (mmHg) | 81.6±11.2 | 79.2±12.1 | 0.21 | 79.3±11.5 | 76.4±11.3 | 0.26 |
| MAP (mmHg) | 101.4±9.5 | 100.7±10.2 | 0.07 | 99.8±9.7 | 98.0±8.7 | 0.20 |
| $HbA_{1c}$ (mmol/mol (%)) | 62.5±13.5 (7.9±1.2) | 92.9±13.6 (7.9±1.2) | 0.03 | 8.0±1.4 | 8.0±1.4 | 0.02 |
| eGFR (mL/min/1.73m$^2$) | 79.4±21.4 | 75.7±19.9 | 0.18 | 73.4±20.1 | 71.2±19.9 | 0.11 |
| LnACR | 1.62±0.66 | 1.60±0.63 | 0.04 | 1.62±0.71 | 1.64±0.82 | 0.03 |
| Duration of the treatment (month) | 31.9±10.7 | 26.2±15.8 | 0.43 | 35.4±9.7 | 33.0±18.0 | 0.18 |
| The concomitant treatment | | | | | | |
| SU | 29.7 (%) | 28.1 (%) | 0.04 | 22.3 (%) | 23.8 (%) | 0.04 |
| Metformin | 60.2 (%) | 64.3 (%) | 0.09 | 51.3 (%) | 48.7 (%) | 0.05 |
| Insulin | 22.7 (%) | 29.2 (%) | 0.15 | 33.0 (%) | 39.4 (%) | 0.13 |
| Pioglitazone | 19.5 (%) | 7.1 (%) | 0.37 | 17.4 (%) | 13.0 (%) | 0.12 |
| RAS inhibitor | 55.5 (%) | 62.3 (%) | 0.14 | 60.3 (%) | 58.5 (%) | 0.04 |
| CCB | 49.2 (%) | 42.9 (%) | 0.13 | 51.8 (%) | 50.8 (%) | 0.02 |
| Bblocker | 12.0 (%) | 13.0 (%) | 0.03 | 16.1 (%) | 23.4 (%) | 0.18 |
| Statin | 60.9 (%) | 48.4 (%) | 0.25 | 60.7 (%) | 47.2 (%) | 0.27 |

Values represent the mean±standard difference, or n (n/total %).

 Calculated number of subjects after weighting.

Abbreviation; ATT, average treatment effect on the treated; BMI, body mass index; BW, body wight; CCB, calcium channel blocker; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration; GLP1Ra, glucagon-like-1 receptor agonist; $HbA_{1c}$, glycated hemoglobin $A_{1c}$; LnACR, logarithmic value of urine albumin-to-creatinine ratio;

MAP, mean arterial pressure; PS, propensity score; RAS, renin aldosterone system; SBP, systolic blood pressure; SGLT2i, sodium glucose cotransporter inhibitor; SU, sulphonyl urea

**Table 4**

**The clinical characteristics of SGLT2i-treated and GLP1Ra-treated patients after stabilized ATE weighting**

| | Model A (the truncation on 99 percentiles) | | | Model B (the trimming by 0.05≦ PS ≦0.95) | | |
|---|---|---|---|---|---|---|
| | SGLT2i (n=351) | GLP1Ra (n=150) | Standardized difference | SGLT2i (n=240) | GLP1Ra (n=89) | Standardized difference |
| Age (year-old) | 59.6±11.6 | 63.1±12.5 | 0.30 | 62.8±11.0 | 64.8±12.4 | 0.18 |
| Sex (female (%)) | 34.8 (%) | 42.0 (%) | 0.15 | 38.9 (%) | 44.9 (%) | 0.13 |
| BW (kg) | 78.2±16.0 | 72.7±15.5 | 0.35 | 74.3±14.4 | 71.9±1.8 | 0.15 |
| BMI | 28.8±4.8 | 27.5±4.8 | 0.29 | 27.9±4.3 | 27.6±5.6 | 0.07 |
| SBP (mmHg) | 141.3±13.2 | 142.9±13.8 | 0.12 | 140.9±13.5 | 141.1±12.1 | 0.01 |
| DBP (mmHg) | 80.9±11.3 | 79.0±11.9 | 0.17 | 79.2±11.4 | 76.9±11.5 | 0.20 |
| MAP (mmHg) | 101.1±9.6 | 100.3±9.8 | 0.08 | 99.8±9.6 | 98.3±9.0 | 0.16 |
| $HbA_{1c}$ (mmol/mol (%)) | 64.1±14.6 (8.0±1.3) | 64.7±15.3 (8.1±1.4) | 0.04 | 66.5±16.0 (8.2±1.5) | 65.8±16.4 (8.2±1.5) | 0.05 |
| eGFR (mL/min/1.73m$^2$) | 76.7±21.6 | 64.7±5.3 | 0.17 | 71.0±20.0 | 69.3±22.1 | 0.08 |
| LnACR | 1.65±0.67 | 1.62±0.68 | 0.05 | 1.67±0.71 | 1.65±0.82 | 0.03 |
| Duration of the treatment (month) | 33.3±10.7 | 35.1±25.7 | 0.11 | 36.4±9.6 | 37.9±22.0 | 0.11 |
| The concomitant treatment | | | | | | |
| SU | 25.9 (%) | 25.3 (%) | 0.01 | 18.4 (%) | 21.3 (%) | 0.08 |
| Metformin | 55.8 (%) | 56.0 (%) | 0.003 | 46.7 (%) | 44.9 (%) | 0.03 |
| Insulin | 28.8 (%) | 34.0 (%) | 0.11 | 40.2 (%) | 41.6 (%) | 0.03 |
| Pioglitazone | 17.7 (%) | 9.3 (%) | 0.25 | 15.1 (%) | 13.5 (%) | 0.04 |
| RAS inhibitor | 58.1 (%) | 63.3 (%) | 0.11 | 63.6 (%) | 58.9 (%) | 0.08 |
| CCB | 49.3 (%) | 47.3 (%) | 0.04 | 50.0 (%) | 51.7 (%) | 0.03 |
| Bblocker | 14.8 (%) | 14.7 (%) | 0.004 | 20.8 (%) | 22.2 (%) | 0.04 |
| Statin | 58.1 (%) | 52.0 (%) | 0.12 | 55.2 (%) | 52.2 (%) | 0.04 |

Values represent the mean±standard difference, or n (n/total %).

 the calculated numbers of subjects after weighting

Abbreviation is same in Table 2.

**Table 5**

**The achievement ratio for BP control after SGLT2i treatment compare to GLP1Ra treatment by the analysis of the generalized linear model**

| | OR[95%CI] | P-value |
|---|---|---|
| ATE (model A) | 2.01 [0.97, 4.20] | 0.06 |
| ATE (model B) | 2.09 [1.08, 4.03] | 0.03 |
| ATT (model A) | 2.11 [0.78, 5.73] | 0.14 |
| ATT (model B) | 2.35 [1.03, 5.36] | 0.04 |
| Stabilized ATE (model A) | 2.06 [0.98, 4.31] | 0.06 |
| Stabilized ATE (model B) | 2.09 [1.08, 4.03] | 0.03 |

Odds ratio for SGLT2i treatment compared with GLP1Ra treatment

The truncation on 99 percentiles is utilized in model A, and ) the trimming by 0.05≦PS≦0.95 is utilized in model B.

**Table 6**

**The changes of the clinical characteristics after SGLT2i treatment compare to GLP1Ra treatment by the analysis of the generalized linear model**

| | ATE | | ATT | | Stabilized ATE | |
|---|---|---|---|---|---|---|
| Truncation/trimming | model A | model B | model A | model B | model A | model B |
| ΔSBP | -5.8 [-12.6, 1.0] / 0.09 | -4.5 [-10.6, 1.5] /0.14 | -7.1 [-15.0, 0.9] / 0.08 | -5.8 [-9.8, -1.7] / 0.006 | -6.5 [-13.0, -0.0] / 0.049 | -4.5 [-10.6, 1.5] / 0.14 |
| ΔDBP | -3.2 [-6.9, 0.6] / 0.10 | -3.8 [-6.6, -1.1] /0.006 | -3.3 [-8.2, 1.7] / 0.20 | -4.2 [-7.2, -1.1] / 0.008 | -3.2 [-7.0, 0.6] / 0.10 | -3.8 [-6.6, -1.1] / 0.006 |
| ΔMAP | -4.0 [-8.3, 0.2] / 0.06 | -4.1 [-7.2, -1.0] /0.01 | -4.5 [-9.9, 0.9] / 0.10 | -4.7 [-7.6, -1.8] / 0.001 | -4.3 [-8.5, -0.1] / 0.046 | -4.1 [-7.2, -1.0] / 0.01 |
| ΔBW | -1.7 [-2.7, -0.7] / 0.001 | -1.5 [-2.7, -0.4] /0.008 | -2.0 [-3.3, -0.8] / 0.002 | -1.9 [-0.6, -0.6] / 0.003 | -1.7 [-2.7, -0.6] / 0.001 | -1.5 [-2.7, -0.4] / 0.008 |
| ΔHbA1c | 0.6 [-3.4, 4.6] (0.1 [-0.3, 0.4]) / 0.78 | -1.5 [-5.8, 2.8] (-0.14[-0.53, 0.26]) /0.49 | 0.6 [-4.2, 5.5] (0.1 [-0.4, 0.5]) /0.79 | -2.0 [-6.7, 2.6] (-0.2 [-0.6, 0.2]) / 0.39 | 0.7 [-3.4, 4.7] ( 0.1 [-0.3, 0.4]) / 0.74 | -1.5 [-5.8, 2.8] (-0.1 [-0.5, 0.3]) / 0.49 |
| ΔeGFR per year | 2.6 [-0.7, 5.8] / 0.12 | 1.5 [0.05, 2.9] /0.04 | 3.4 [-0.1, 2.3] / 0.13 | 1.9 [0.1, 3.6] / 0.04 | 2.6 [-0.7, 5.9] / 0.12 | 1.5 [0.1, 2.9] / 0.04 |
| ΔLNACR | -0.11 [-0.23, 0.01] / 0.07 | -0.13 [-0.27, 0.02] /0.08 | -0.08 [-0.23, 0.06] / 0.27 | -0.14 [-0.32, 0.03] / 0.11 | -0.12 [-0.24, 0.002] / 0.054 | -0.13 [-0.27, 0.02] / 0.08 |

Data present as the difference [95%CI] / P-value.

The truncation on 99 percentiles is utilized in model A, and ) the trimming by 0.05≦ PS ≦0.95 is utilized in model B.

Abbreviation; Δ, change; BW, body wight; CI, confidence interval; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration; $HbA_{1c}$, glycated hemoglobin $A_{1c}$; LnACR, logarithmic value of urine albumin-to-creatinine ratio; MAP, mean arterial pressure; SBP, systolic blood pressure

# Figures

**Figure 1**

**The integrated OR using six models by meta-analysis method**

 Calculated number of subjects after weighting.

Abbreviations: ATE, average treatment effect; ATT, average treatment effect on the treated; BP, blood pressure; CI, confidence interval; GLP1Ra, glucagon-like-1 receptor agonist; SGLT2i, sodium glucose cotransporter inhibitor

# Supplementary Files

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