Review Article

Impacts of Sodium/Glucose Cotransporter-2 Inhibitors on Circulating Uric Acid Concentrations: A Systematic Review and Meta-Analysis

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Background. Several trials have assessed the antihyperglycemic effects of sodium/glucose cotransporter-2 inhibitors (SGLT2i) in patients with type 2 diabetes mellitus (T2DM). We conducted a quantitative analysis to assess the impact of SGLT2is on serum uric acid (SUA) in patients with T2DM. Methods. Placebo-controlled trials published before 13 August 2021 were identified by searching PubMed, Embase, Web of Science, and Scopus. The intervention group received SGLT2i as monotherapy or add-on treatment, and the control group received a placebo that was replaced with SGLT2i. Clinical trials providing changes in SUA were included. The mean change of SUA, glycated hemoglobin (HbA1c), fasting plasma glucose (FPG), and body weight were calculated (PROSPERO CRD42021287019). Results. After screening of 1172 papers, 59 papers were included in the systematic review. A total of 55 trials (122 groups) of 7 types of SGLT2i on patients with T2DM were eligible for meta-analysis. All SGLT2is significantly decreased SUA levels compared with the placebo groups: empagliflozin mean difference (MD) = −40.98 μmol/L, 95% CI [−47.63, −34.32], dapagliflozin MD = −35.17 μmol/L, 95% CI [−39.68, −30.66], canagliflozin MD = −36.27 μmol/L, 95% CI [−41.62, −30.93], luseogliflozin MD = −24.269 μmol/L, 95% CI [−33.31, −15.22], tofogliflozin MD = −19.47 μmol/L, 95% CI [−27.40, −11.55], and ipragliflozin MD = −18.85 μmol/L, 95% CI [−27.20, −10.49]. SGLT2i also decreased FPG, body weight, and HbA1c levels. SUA reduction persisted during long-term treatment with SGLT2i (except for empagliflozin), while the SUA reduction was affected by the duration of diabetes. Conclusions. SGLT2i can be a valid therapeutic strategy for patients with T2DM and comorbid hyperuricemia. Besides reducing FPG, body weight, and HbA1c, SGLT2i can significantly decrease SUA levels compared to placebo (Total MD = −34.07 μmol/L, 95% CI [−37.00, −31.14]).

1. Introduction

Sodium/glucose cotransporter-2 inhibitors (SGLT2i) are one of the main classes of medications that are used for the management of patients with type 2 diabetes (T2DM) [1]. They also have significant renoprotective and cardioprotective properties [2–4]. These oral glucose-lowering agents have been shown to reduce the risk of cardiovascular and renal complications in patients with T2DM [2, 3, 5–7] plus several other salutary effects on autophagy pathways, neuromodulatory pathways, oxidative stress pathways, platelet function, blood pressure, and hepatic function [5, 8–12].
Dapaglixflozin, canaglifoizin, ipraglixflozin, empaglifoizin, sitaglixflozin, tofoglixflozin, ertuglixflozin, and luseoglixflozin are some of the established SGLT2Is. The action of SGLT2Is is independent of insulin; they reduce the renal glucose reabsorption mediated by the SGLT2 expressed along the proximal tubules [6]. Several randomized controlled trials (RCTs) with placebo-controlled groups studied the efficacy of SGLT2Is in patients with and without T2DM. The change in serum uric acid (SUA) is one of the parameters which is directly or indirectly assessed in RCTs [13–72]. Increased SUA (hyperuricemia) is an important risk factor for cardiovascular and renal complications of T2DM [73, 74]. Hence, lowering SUA levels with SGLT2Is could be a valid therapeutic strategy in this cohort of patients [9–12]. Di Zhao et al. [75] evaluated the effect of empaglifoizin on SUA levels through a meta-analysis of clinical trials published before December 2017. They found that empaglifoizlin reduced serum uric acid levels and other cardiometabolic risk factors such as glycated hemoglobin (HbA1c), fasting plasma glucose (FPG), systolic and diastolic blood pressures, and body weight. Di Zhao and his team did not review other SGLT2Is. A meta-analysis by Xin et al. [76] showed that SGLT2Is could benefit patients with T2DM with increased SUA levels. However, this manuscript reviewed studies published before August 2017. Several recently published RCTs on the effects of SGLT2Is on SUA need to be evaluated in a new meta-analysis. Moreover, limiting RCTs to placebo-controlled ones may help to identify urate-lowering properties that can be solely attributed to SGLT2i. The present study was aimed at finding any changes in SUA levels in individuals on SGLT2i based on randomized, placebo-controlled trials.

2. Materials and Methods

The current systematic review and meta-analysis were conducted according to the recommendations of the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA) [77]. This review was registered in PROSPERO (registration number: CRD42021287019).

2.1. Data Sources and Searches. The electronic databases of PubMed, Embase, Scopus, and Web of Science were searched to identify eligible clinical trials using relevant search terms to “Sodium-glucose cotransporter-2 inhibitors (SGLT2i)” and “uric acid” by A.A. and M.R.; complete search strategy is available in Table S1. We identified articles published up to May 5, 2021, without restrictions on language and year of publication. In addition, we updated the article on August 13, 2021. Two authors (A.A. and M.R.) did a further manual search of the references lists of all selected papers, previous similar reviews, and pooled analysis studies to look for possible missing papers.

2.2. Study Selection. The two investigators (A.A. and M.R.) selected the studies according to the following criteria: (1) population: subjects (regardless of their disease) using any kind of SGLT2i; (2) intervention: SGLT2i monotherapy or as an add-on to other antidiabetic medications; (3) comparison: SGLT2is were replaced with placebo; (4) outcome: serum uric acid changes; (5) design: clinical trials; and (6) follow-up duration: at least 4 weeks. We excluded from our meta-analysis studies that were not conducted on patients with T2DM. The conference abstracts and pooled analysis studies were carefully assessed for possible duplicate data. Furthermore, several studies assessed serum uric acid at different time points. We chose the time point that was closer to 24 weeks.

2.3. Data Extraction and Quality Assessment. The two investigators (A.A. and M.R.) independently extracted the following data: first author, year of publication, type of study population, number of participants, demographic data, intervention (type of SGLT2i and dose regimen), follow-up duration, duration of diabetes, baseline estimated glomerular filtration rate (eGFR), and outcome (change in SUA, HbA1c, body weight, and FPG from baseline). Moreover, these authors assessed the quality of studies using the quality criteria proposed by the Joanna Briggs Institute (JBI) checklist [40]. If any disagreements existed, these were resolved through discussion or referral to another investigator (A.H.S.). Checklist questions were answered by “yes,” “no,” “unclear,” or “not/applicable.” Each “yes” answer takes 1 point. After adding up the scores, the studies were classified into three groups based on their risk of bias: high risk of bias (scores between 0 and 5), intermediate-risk (scores between 6 and 10), and low-risk groups (scores between 11 and 13).

2.4. Publication Bias and Statistical Analysis. Publication bias was examined using funnel plots, Egger’s test and Begg’s test. Mean differences (MD) and 95% confidence interval (CI) in SUA levels were calculated using a random-effects model to evaluate the effects of SGLT2is on SUA, HbA1c, body weight, and FPG. Heterogeneity was calculated using $I^2$, with $I^2$ values >50% representing moderate heterogeneity. $P$-value less than 0.05 was considered as statistically significant for the outcome and heterogeneity analyses. Random-effect meta-regression analysis was done to assess the effects of the patient’s duration of diabetes, treatment period, and SGLT2i dosage on SUA level changes. Data analysis was done using the Comprehensive Meta-Analysis software (CMA) V.3.

3. Results

A total of 1920 papers were collected during the initial electronic search. Through a manual search, six papers were identified. Among those papers, 754 were duplicates, so the 1172 remaining papers were assessed for eligibility criteria. Finally, 59 trials met the inclusion criteria, and 55 trials were included in the meta-analysis. The screening, assessing, and analyzing steps are shown in Figure 1. Seven types of SGLT2is were assessed, including canagliflozin, dapagliflozin, empagliflozin, ipragliflozin, tofogliflozin, ertugliflozin, and luseogliflozin. Descriptive characteristics of the 59 included trials (9 types of SGLT2is) are presented in Table 1.

3.1. Outcome. Of the 36,215 patients, 23,494 received different SGLT2is in different dosages versus 12,721 patients who
received placebo. The effect size, population, and heterogeneity of SGLT2is included in meta-analysis are shown in Table 2. SGLT2is considerably decreased SUA levels compared with placebo (Total MD, −34.07 μmol/L, 95% CI [−37.00, −31.14], empagliflozin MD, −40.98 μmol/L, 95% CI [−47.63, −34.32], dapagliflozin MD, −35.17 μmol/L, 95% CI [−39.68, −30.66], canagliflozin MD, −36.27 μmol/L, 95% CI [−41.62, −30.93], luseogliflozin MD, −24.26 μmol/L, 95% CI [−33.31, −15.22], tofogliflozin MD, −19.47 μmol/L, 95% CI [−27.40, −11.55], and ipragliflozin MD, −18.85 μmol/L, 95% CI [−27.20, −10.49]) (Figures S1–S3 and Figures 2–7).

Out of 122 comparisons between the different dosages of SGLT2is and placebo, 21 comparisons showed that SGLT2is did not significantly reduce the SUA. After the removal of studies which were conducted only on patients with chronic kidney disease (CKD) [22, 43, 68, 72], the MD of SUA changes of dapagliflozin compared to placebo increased to −36.29 μmol/L (95% CI [−40.53, −32.05], I² = 69.3%), the MD of SUA changes of canagliflozin compared to placebo increased to −37.44 μmol/L (95% CI [−42.90, −31.97], I² = 68.0%), and MD of SUA changes of empagliflozin compared to placebo increased to −43.79 μmol/L (95% CI [−50.75, −36.83], I² = 85.9%).

3.1.1. Canagliflozin. Ten clinical trials evaluated the effect of canagliflozin (range of 50 mg to 600 mg) on SUA. Canagliflozin 300 mg reduced the SUA, FPG, body weight, and HbA1c more than canagliflozin 100 mg (Table 2). Moreover,
| Author          | Size | Females (%) | Dosage (mg) | Treatment duration | SUA I (mg/dL) | SUA P (mg/dL) | HbA1c I (%) | HbA1c P (%) | FPG I (mg/dL) | FPG P (mg/dL) | Duration of diabetes (Y) | eGFR (ml/min/1.73 m²) | Risk of bias |
|-----------------|------|-------------|-------------|--------------------|---------------|---------------|-------------|-------------|---------------|---------------|--------------------------|-----------------------|--------------|
| Rosenstock et al. [48] | 386  | 188 (48.7)  | 50 100 200 300 300 BID | 12 weeks          | —             | —             | 8.01        | 7.81        | 7.91 ± 0.9    | 7.71          | 171.0                   | 167.4                  | Moderate    |
| Ji et al. [28]    | 636  | 314 (46.4)  | 100 300 300 | 18 weeks          | 315.7         | 323.3         | 8.0 ± 0.9   | 8.0 ± 0.9   | 7.9 ± 0.9     | 156.5 ± 33.6  | 160 ± 36.0               | 158.2 ± 32.7           | Low         |
| Sha et al. [56]   | 35   | 5 (13.9)    | 300 12 weeks | 352.6             | 339.7         | 7.6 ± 0.5     | 7.7 ± 0.6   | 154.95 ± 1.1 | 147.74 ± 1.4 | 8.6          | 9.4 ± 0.22               | 9.4 ± 0.22              | Moderate    |
| Wilding et al. [66] | 306  | 230 (49.0)  | 300 100 100 | 26 weeks          | 322.3         | 340.1         | 8.1 ± 0.9   | 8.1 ± 0.9   | 8.1 ± 0.9     | 172.97 ± 2.3   | 167.56 ± 2.1             | 167.56 ± 2.1           | Low         |
| Stenlöf et al. [59] | 584  | 326 (55.8)  | 300 100 100 | 26 weeks          | 320.0         | 326.3         | 8.0 ± 1.0   | 8.0 ± 1.0   | 8.0 ± 1.0     | 169.36 ± 2.6   | 158.55 ± 3.2             | 160.8 ± 4.4            | Moderate    |
| Yale et al. [68]  | 211  | 106 (39.4)  | 300 100 300 | 26 weeks          | 433.7         | 442.2         | 7.9 ± 0.9   | 8.0 ± 0.8   | 8.0 ± 0.9     | 169.36 ± 2.6   | 158.55 ± 3.2             | 160.8 ± 4.4            | Moderate    |
| Rodbard et al. [46] | 171  | 92 (43.2)   | 100 26 weeks | 318.3             | 336.7         | 8.5 ± 0.9     | 8.4 ± 0.8   | 185.5 ± 46.2 | 180.4 ± 37.8 | 9.8          | 16.4 ± 15.7              | 16.4 ± 15.7             | Moderate    |
| Bode et al. [48]  | 584  | 318 (44.5)  | 100 26 weeks | 339.1 ± 34.1      | 343.4         | 7.8 ± 0.8     | 7.7 ± 0.8   | 160.4 ± 38.7 | 156.8 ± 38.9 | 12.3         | 16.4 ± 15.7              | 16.4 ± 15.7             | Moderate    |
| CANVAS [38]       | 10142 | 3629 (36)   | 300/100 26 weeks | 360.95 ± 95.17    | 350.93 ± 95.17 | 8.2 ± 0.9     | 8.2 ± 0.9   | 167.13 ± 42.7 | 167.13 ± 42.7 | 15.3         | 16.4 ± 15.7              | 16.4 ± 15.7             | Moderate    |
| Qiu et al. [44]   | 239  | 149 (53.4)  | 300 50 BID 50 BID | 24 weeks          | 318.7         | 328.2         | 7.6 ± 0.9   | 7.6 ± 0.9   | 7.7 ± 0.9     | 9.0 ± 2.0      | 9.1 ± 1.9                | 9.0 ± 1.9               | Low         |
| Dapagliflozin     | Weber et al. [65] | 402 | 202 (45.0) | 10 12 weeks | 334.95 ± 28.25 | 325.28 ± 76.92 | 8.1 ± 1.0   | 8.0 ± 1.0   | 162.16 ± 45.04 | 160.36 ± 43.24 | 7.7          | 7.3 ± 0.57               | 7.3 ± 0.57              | Moderate    |
| Ji et al. [29]    | 338  | 156 (34.6)  | 5 24 weeks  | 309.3 ± 71.38     | 297.4 ± 77.32 | 8.14 ± 0.74  | 8.28 ± 0.95 | 8.35 ± 0.95 | 154.37 ± 31.6 | 167.13 ± 42.7 | 167.13 ± 42.7           | 167.13 ± 42.7           | Moderate    |
| Jabbour et al. [27] | 292  | 202 (45.1)  | 10 24 weeks | 321.19 ± 78.22    | 317.62 ± 87.50 | 7.8 ± 0.98  | 8.1 ± 1.07 | 7.9 ± 1.03 | 155.49 ± 48.28 | 159.81 ± 51.53 | 157.11 ± 41.62           | 161.62 ± 57.47           | Moderate    |
| Bailey et al. [14] | 282  | 141 (50.0)  | 1 24 weeks  | 321.19 ± 78.22    | 317.62 ± 87.50 | 339.04 ± 96.89 | 7.8 ± 0.98  | 8.1 ± 1.07 | 7.9 ± 1.03 | 155.49 ± 48.28 | 159.81 ± 51.53 | 157.11 ± 41.62           | 161.62 ± 57.47           | Moderate    |
| Ferrannini et al. [21] | 485  | 256 (52.8)  | 1 24 weeks | 25 ± 5 P 2.5 P 5 P 25 E 5 E 10 P E 10 E | 7.92 ± 0.90 | 8.01 ± 0.94 | 8.01 ± 0.96 | 7.99 ± 0.99 | 7.82 ± 0.91 | 7.99 ± 1.05 | 164.1 ± 48.0 | 162.2 ± 45.0 | 166.6 ± 41.5 | 160.6 ± 45.9 | 157.0 ± 50.9 | 168.1 ± 27.9 | 0.50 ± 0.50 | 0.40 ± 0.40 | Moderate |
| Henry et al. [26] | 809  | 438 (53.8)  | 5 24 weeks | 293.9 ± 91.0      | 307.5 ± 87.4  | 301.6 ± 85.1 | 9.21 ± 1.31 | 9.10 ± 1.28 | 9.14 ± 1.32 | 193.87 ± 36.21 | 189.54 ± 58.01 | 197.11 ± 60.36           | 190.45 ± 54.05           | Moderate    |
| Strojek et al. [60] | 596  | 307 (51.5)  | 5 24 weeks | 301.6 ± 81.2      | 303.9 ± 79.8  | 301.0 ± 82.4 | 8.11 ± 0.75 | 8.12 ± 0.78 | 8.07 ± 0.79 | 172.25 ± 38.37 | 174.41 ± 38.19 | 172.07 ± 36.75           | 172.61 ± 37.29           | Moderate    |

**Table 1:** Characteristics of included studies.
Table I: Continued.

| Author                  | Size | Females (%) | Dosage (mg) | Treatment duration | SUA I (mg/dL)† | SUA P (mg/dL)† | HbA1c I (%)† | HbA1c P (%)† | FPG I (mg/dL)† | FPG P (mg/dL)† | Duration of diabetes (Y) | eGFR (ml/min/1.73 m²)† | eGFR (ml/min/1.73 m²)† | Risk of bias |
|-------------------------|------|-------------|-------------|-------------------|----------------|----------------|--------------|--------------|----------------|----------------|--------------------------|--------------------------|--------------------------|-------------|
| Bailey et al. [16]      | 541  | 254 (46.5)  | 5 10        | 24 weeks          | 32.4 ± 80.4   | 32.30 ± 88.3  | 32.30 ± 79.9 | 7.99 ± 0.90 | 8.17 ± 0.96 | 7.92 ± 0.82 | 161.4 ± 43.06 | 169.18 ± 49.00 | 156.03 ± 38.73 | Low         |
| Ramirez-Rodriguez et al. [45] | 24   | 17 (70.8)   | 10          | 12 weeks          | 534 ± 70      | 312 ± 101      | —            | —            | 106.3 ± 7.2 | 108.1 ± 7.2 | —             | —             | —             | Low         |
| Wober et al. [64]       | 557  | 263 (42.9)  | 10          | 12 weeks          | 321.19 ± 83.27| 321.19 ± 77.32| 8.1 ± 1.0    | 8.0 ± 0.9    | 7.19 ± 0.44 | 7.16 ± 0.33 | 148.0 ± 24.7 | 149.6 ± 25.1 | 6.0           | —            | Moderate     |
| Bolinder et al. [19]    | 167  | 80 (40.5)   | 10          | 24 weeks          | 346.8 ± 68.9  | 338.4 ± 61.7  | 8.03 ± 0.70  | 8.37 ± 0.96  | 8.34 ± 1.00 | 168.6 ± 52.1 | 164.9 ± 46.3 | 160.7 ± 47.0 | 5.64         | 5.75         | Moderate     |
| Rosenstock et al. [51]  | 420  | 212 (50.5)  | 5 10        | 24 weeks          | —             | —             | 8.40 ± 1.03  | 8.37 ± 0.96  | —             | —             | —             | —             | —            | Moderate     |
| Fioretto et al. [22]    | 320  | 159 (49.7)  | 10          | 24 weeks          | —             | —             | 8.33 ± 1.08  | 8.03 ± 1.08  | 181.98 ± 66.66 | 172.97 ± 54.05 | 14.3         | 14.5         | 53.3         | 53.6         | Moderate     |
| Wilding et al. [67]     | 660  | 418 (52.2)  | 10          | 24 weeks          | 326.0 ± 89.2  | 323.6 ± 95.2  | 324.8 ± 93.9 | 8.46 ± 0.78  | 8.62 ± 0.89 | 8.57 ± 0.82 | 180.1 ± 59.9 | 185.4 ± 58.7 | 173.1 ± 54.9 | Low          |
| Kohan et al. [36]       | 252  | 88 (34.9)   | 5 10        | 104 weeks         | 434.2 ± 126.1 | 424.09 ± 101.7| 419.33 ± 115.39| 8.30 ± 1.04 | 8.22 ± 0.97 | 8.53 ± 1.29 | 161.0 ± 56 | 165.6 ± 67 | 150.48        | 16.9         | 18.2         | 15.7         | 44.2         | 45.6         | Moderate     |
| List et al. [39]        | 333  | 164 (49.2)  | 2.5 5 10    | 12 weeks          | 327.14 ± 71.38| 309.3 ± 77.32 | 327.14 ± 71.38| 7.6 ± 0.7   | 8.0 ± 0.9   | 7.8 ± 0.9   | 145.3 ± 34 | 153.4 ± 48 | 149.49        | 153.4 ± 34 | 153.4 ± 48 | —            | —            | —            | Moderate     |
| Pollock et al. [43]     | 291  | 86 (29.6)   | 10          | 24 weeks          | 399.4 ± 98.9  | 424.9 ± 102.8 | 414.9 ± 92.6  | 8.44 ± 1.0  | 8.20 ± 1.0  | 8.57 ± 1.2  | —             | —             | 17.55         | 17.71        | 50.2         | 47.7         | Moderate     |
| Schumm-Draeger et al. [55] | 401  | 220 (55.1)  | 5 10        | 16 weeks          | 337.87 ± 72.57| 331.93 ± 81.96| 349.77 ± 89.81| 7.77 ± 0.75 | 7.78 ± 0.76 | 7.71 ± 0.71 | 153.33 ± 33.33 | 155.31 ± 31.89 | 153.31 ± 36.39 | Low          |
| Araki et al. [13]       | 173  | 53 (28.9)   | 5 10        | 16 weeks          | 321.19 ± 77.32| 315.24 ± 83.27| 8.3 ± 0.8    | 8.5 ± 0.9    | 160.7 ± 44.9 | 159.7 ± 38.0 | 15.3         | 14.2         | —            | —            | Moderate     |
| Empagliflozin           |      |             |             |                   |                |                |              |              |                |                |              |              |              |              |              |
| Zanchi et al. [70]      | 45   | 18 (40.0)   | 10          | 4 weeks           | 303 ± 70      | 275 ± 73      | 5.4 ± 0.3    | 5.4 ± 0.3    | 90 ± 12.61  | 90 ± 7.20     | —             | —             | 112.9        | 113.1        | Moderate     |
| Shintu et al. [57]      | 96   | 19 (19.8)   | 10          | 24 weeks          | 344.98 ± 83.27| 339.04 ± 89.22| 6.82 ± 1.00  | 6.89 ± 0.92  | —             | —             | 3.19         | 2.7          | 66.1         | 64.6         | Moderate     |
| Ross et al. [52]        | 965  | 445 (46.1)  | 10 25       | 12.5 BID 5 BID    | 316.12 ± 126  | 328.12 ± 120  | 327.12 ± 131  | 7.78 ± 0.79  | 7.73 ± 0.79  | 7.79 ± 0.88  | 156.75 ± 37.83 | 158.55 ± 32.43 | 162.16 ± 39.63 | Moderate     |
| Kovacs et al. [37]      | 265  | 257 (51.6)  | 10 25       | 76 weeks          | 288 ± 116     | 271 ± 117     | 275 ± 113    | 8.07 ± 0.89  | 8.06 ± 0.82 | 8.16 ± 0.92 | 151.35 ± 37.83 | 151.35 ± 37.83 | 151.35 ± 39.63 | Moderate     |
| Haring et al. [24]      | 671  | 276 (43)    | 10 25       | 24 weeks          | 314.12 ± 127  | 298 ± 115     | 307 ± 110    | 8.07 ± 0.81  | 8.10 ± 0.83 | 8.15 ± 0.83 | 150.99 ± 32.79 | 156.75 ± 33.69 | 151.71 ± 35.85 | Moderate     |

[Note: The table continues with more entries, each representing different authors and studies with their respective data on HbA1c, treatment duration, and other relevant metrics. The data columns include SUA I and SUA P in mg/dL, HbA1c I and HbA1c P in %, FPG I and FPG P in mg/dL, duration of diabetes in years, and eGFR values. The last column indicates the risk of bias, with categories such as Low, Moderate, and High.]
| Author                  | Size | Females (%) | Dosage (mg) | Treatment duration | SUA I (mg/dL) | SUA P (mg/dL) | Hba1c I (%) | Hba1c P (%) | FPG I (mg/dL) | FPG P (mg/dL) | Duration of diabetes (Y) | Duration of diabetes (Y) | eGFR (ml/min/1.73 m²) | eGFR (ml/min/1.73 m²) | Risk of bias |
|------------------------|------|-------------|-------------|--------------------|---------------|---------------|--------------|--------------|----------------|----------------|--------------------------|--------------------------|--------------------------|--------------------------|-------------|
| Kahl et al. [31]       | 84   | 36 (30.9)   | 25          | 24 weeks           | 365.26        | 381.84        | 6.8 ± 0.5    | 6.7 ± 0.7    | 135.13 ± 25.22 | 129.72 ± 23.42 |                          |                          |                          |                          | Low         |
| Kadowaki et al. [30]   | 547  | 137 (25)    | 10          | 25                 | 283 ± 120     | 277 ± 124     | 7.92 ± 0.70  | 7.93 ± 0.71  | 154.0 ± 27.9   | 156.8 ± 28.5   |                          |                          |                          |                          | Moderate    |
| Takahama et al. [62]   | 723  | 328 (39.9)  | 10          | 25                 | 341.85 ± 81.78| 338.27 ± 79.52| 8.02 ± 0.65  | 8.01 ± 0.65  | 156.7 ± 37.83 | 162.16 ± 37.83|                          |                          |                          |                          | Low         |
| Zinnman et al. [71]    | 665  | 2004 (28.5) | 10          | 28 weeks           | 350.93        | 356.88        | —            | —            | —              | —              | —                        | —                        | —                        | —                        | Moderate    |
| Rosenstock et al. [49] | 563  | 307 (55)    | 10          | 25                 | 326 ± 127     | 331 ± 123     | 8.39 ± 0.05  | 8.29 ± 0.05  | 159.09 ± 150.27| 151.35 ± 150.27|                          |                          |                          |                          | Moderate    |
| Mordi et al. [41]      | 23   | 6 (26.1)    | 25          | 6 weeks            | —             | —             | —            | —            | —              | —              | —                        | —                        | —                        | —                        | Moderate    |
| Roden et al. [96]      | 676  | 266 (39.3)  | 10          | 25                 | 293 ± 109     | 307 ± 133     | 7.87 ± 0.88  | 7.91 ± 0.78  | 153.15 ± 32.43 | 154.95 ± 36.03 |                          |                          |                          |                          | Moderate    |
| Heise et al. [25]      | 78   | 11 (14.1)   | 10          | 4 weeks            | —             | —             | 7.2 ± 0.7    | 7.5 ± 0.8    | 186.2 ± 93.9  | 167.5 ± 91.2   |                          |                          |                          |                          | Moderate    |
| Kario et al. [33]      | 131  | 62 (47.6)   | 10          | 12 weeks           | 322.98 ± 89.22| 318.81 ± 89.22| 8.6 ± 0.8    | 8.6 ± 0.8    | 156.75 ± 54.05| 147.74 ± 57.65 |                          |                          |                          |                          | Moderate    |
| Nishimura et al. [42]  | 60   | 13 (21.6)   | 10          | 4 weeks            | 265 ± 155     | 268 ± 84      | 7.99 ± 0.83  | 7.73 ± 0.75  | 151.0 ± 21.6  | 151.9 ± 23.3   |                          |                          |                          |                          | Moderate    |
| Seftelnd et al. [58]   | 327  | 130 (39.7)  | 10          | 25                 | 301 ± 124     | 297 ± 116     | 7.97 ± 0.84  | 7.97 ± 0.87  | 145.94 ± 34.23| 147.74 ± 34.23 |                          |                          |                          |                          | Moderate    |
| Barnett et al. [72]    | 292  | 113 (39.0)  | 10          | 52 weeks           | 341.12 ± 73   | 337 ± 159     | 8.02 ± 0.84  | 8.06 ± 0.84  | 145.94 ± 34.23| 147.74 ± 34.23 |                          |                          |                          |                          | Low         |
| Barnett et al. [72]    | 375  | 161 (43.0)  | 25          | 52 weeks           | 419 ± 138     | 439 ± 135     | 8.02 ± 0.84  | 8.09 ± 0.80  | 142.34 ± 36.03| 144.14 ± 36.58 |                          |                          |                          |                          | Low         |
| Barnett et al. [72]    | 74   | 34 (45.9)   | 25          | 52 weeks           | 559 ± 126     | 583 ± 162     | 8.06 ± 1.07  | 8.16 ± 0.99  | 156.75 ± 54.05| 147.74 ± 57.65 |                          |                          |                          |                          | Low         |

**Ipragliflozin**

| Kashwagi et al. [33]   | 331  | 126 (35.0)  | 25          | 12 weeks           | —             | —             | 8.39 ± 0.90  | 8.32 ± 0.83  | 185.4 ± 40.0   | 170.8 ± 38.8   |                          |                          |                          |                          | Moderate    |
| Kashwagi et al. [34]   | 129  | 39 (30.2)   | 50          | 16 weeks           | 289.07 ± 65.43| 272.42 ± 73.16| 8.40 ± 0.86  | 8.25 ± 0.68  | 155.55 ± 41.44| 153.15 ± 36.03|                          |                          |                          |                          | Moderate    |
| Wålind et al. [66]     | 304  | 167 (48.8)  | 12          | 12 weeks           | —             | —             | 7.78 ± 0.64  | 7.76 ± 0.66  | 154.95 ± 27.02| 154.95 ± 27.02|                          |                          |                          |                          | Moderate    |
**Table 1: Continued.**

| Author | Size  | Females (%) | Dosage (mg) | Treatment duration | SUA I (mg/dL)† | SUA P | HbA1c I (%)† | HbA1c P (%)† | FPG I (mg/dL)† | FPG P (mg/dL)† | Duration of diabetes (Y) I | Duration of diabetes (Y) P | eGFR (ml/min/1.73 m²) I† | eGFR (ml/min/1.73 m²) P† | Risk of bias |
|--------|------|-------------|-------------|--------------------|----------------|-------|--------------|--------------|----------------|----------------|--------------------------|--------------------------|--------------------------|--------------------------|-------------|
| Terachi et al. [61] | 201 | 63 (31.3) | 20 | 16 weeks | 300.37 ± 74.35 | 311.08 ± 84.46 | 8.53 ± 0.75 | 8.40 ± 0.65 | 163.4 ± 47.5 | 162.4 ± 43.2 | 15.02 | 9.36 | 79.7 | 79.5 | Low |
| Kaku et al. [32] | 212 | 76 (33.2) | 10 | 24 weeks | 283.72 ± 60.07 | 297.99 ± 70.78 | 302.75 ± 82.68 | 8.45 ± 0.75 | 8.34 ± 0.81 | 8.37 ± 0.77 | 170.2 ± 32.4 | 168.7 ± 29.6 | 167.9 ± 37.0 | 6.3 | 6.4 | 6.7 | 6.0 | Moderate |
| Haneda et al. [23] | 145 | 34 (23.4) | 2.5 | 24 weeks | 350.93 ± 78.51 | 375.32 ± 85.06 | 7.72 ± 0.68 | 7.69 ± 0.65 | 140.4 ± 30.2 | 141.7 ± 26.7 | 10.4 | 12.6 | 52.0 | 52.4 | Moderate |
| Seino et al. [54] | 158 | 42 (26.6) | 2.5 | 24 weeks | 308.11 ± 70.19 | 295.02 ± 68.4 | 8.14 ± 0.91 | 8.17 ± 0.80 | 160.8 ± 28.7 | 161.9 ± 31.0 | 6.5 | 6.1 | — | — | Moderate |
| Seino et al. [54] | 236 | 66 (32.2) | 0.5 | 12 weeks | 314.65 ± 64.83 | 302.75 ± 88.63 | 302.16 ± 76.73 | 8.16 ± 0.93 | 8.07 ± 0.90 | 8.16 ± 0.96 | 158.7 ± 28.8 | 158.1 ± 30.3 | 159.9 ± 34.7 | 4.90 | 6.15 | 5.77 | — | Moderate |
| Seino et al. [55] | 280 | 81 (29.3) | 1 | 12 weeks | 320.60 ± 74.94 | 306.92 ± 76.13 | 296.81 ± 67.21 | 289.67 ± 70.19 | 7.77 ± 0.79 | 8.05 ± 0.75 | 7.86 ± 0.69 | 7.95 ± 0.67 | 152.0 ± 28.4 | 156.1 ± 28.5 | 149.3 ± 23.1 | 155.3 ± 28.2 | 4.7 | 4.6 | 4.5 | 5.1 | Moderate |
| Budoff et al. [20] | 307 | 83 (25.2) | 5 | 18 weeks | 323.57 ± 83.87 | 328.33 ± 79.7 | 343.57 ± 81.49 | 8.4 ± 1.0 | 8.3 ± 1.0 | 8.3 ± 1.0 | 183.5 ± 49.6 | 174.0 ± 52.8 | 177.3 ± 45.6 | 11.6 | 11.1 | 11.6 | 84.8 | 80.2 | 85.5 | Moderate |
| Yokote et al. [69] | 123 | 48 (38.1) | 2.5 | 12 weeks | — | — | — | — | — | — | — | — | — | 6.9 ± 1.0 | 6.7 ± 0.8 | 6.6 ± 0.7 | 6.6 ± 0.8 | 6.5 ± 0.6 | 133.3 ± 30.63 | 127.92 ± 23.42 | 126.12 ± 25.22 | 126.12 ± 23.42 | 120.72 ± 19.81 | — | — | — | 104.0 | 101.7 | 103.2 | 105.4 | 100.4 | Moderate |
| Van Gaal et al. [63] | 1434 | 779 (54.5) | 24 weeks | 269.44 ± 26.49 | 268.25 | 7.7 ± 0.8 | 7.6 ± 0.8 | 7.7 ± 0.8 | — | — | 21.6 | 21.5 | 21.2 | — | — | — | Moderate |

All studies were randomized, parallel-group and double-blind. *Multicenter studies. †Baseline. Abbreviations: I = intervention; P = placebo; eGFR = estimated glomerular filtration rate; SUA = serum uric acid; FPG = fasting plasma glucose; HbA1c = glycated hemoglobin.
Table 2: The results of meta-analysis for changes in SUA, HbA1c, and FPG derived from SGLT2i treatment in patients with T2DM.

| SGLT2i | Dose | Mean diff. [95% CI] SUA (μmol/L) | P-value | t² | SGLT2i sample size | Placebo sample size | Treatment duration (week)† | Mean diff. [95% CI] HbA1c (%) | P | Mean diff. [95% CI] FPG (mg/dL) | t² | Mean diff. [95% CI] body weight (kg) | P |
|--------|------|--------------------------------|---------|---|----------------|-------------------|----------------|---------------------------|-----------------------------|---|--------------------------|---|--------------------------|---|
| Canagliflazine | 100  | -36.277 [-41.621, -30.933]      | 0.001>  | 66.5%   | 7976 | 5318 | 24.8 | -0.648 | 81.6%   | -26.737 [-29.888, -23.586] | 68.3% | -1.990 [-2.284, -1.697] | 78.7% |
|         | 300  | -40.692 [-47.151, -34.232]      | 0.001>  | 24.8%   | 957  | 893  | 22.3 | -0.594 | 85.4%   | -28.874 [-34.204, -23.545] | 71.4% | -2.286 [-2.777, -1.796] | 84.1% |
| Dapagliflazine | 2.5  | -31.592 [-41.172, -22.012]      | 0.001>  | 66.0%   | 825  | 733  | 23.0 | -0.719 | 94.5%   | -15.368 [-21.375, -9.36] | 97.9% | -1.271 [-1.488, -1.053] | 80.2% |
|         | 5    | -33.595 [-41.071, -26.118]      | 0.001>  | 69.0%   | 1340 | 1269 | 27.7 | -0.873 | 89.1%   | -19.675 [-23.737, -15.612] | 94.6% | -1.405 [-1.762, -1.048] | 99.0% |
|         | 10   | -35.284 [-42.538, -28.029]      | 0.001>  | 78.7%   | 2327 | 2196 | 23.5 | -0.490 | 91.1%   | -20.734 [-24.225, -17.24] | 93.4% | -1.700 [-1.935, -1.464] | 97.5% |
| Empagliflazine | 10   | -40.980 [-47.632, -34.328]      | 0.001>  | 84.9%   | 9039 | 4242 | 28.0 | -0.536 | 96.1%   | -25.911 [-29.100, -22.72] | 80.6% | -1.765 [-2.038, -1.493] | 99.7% |
|         | 25   | -38.791 [-49.643, -27.939]      | 0.001>  | 85.8%   | 4492 | 4154 | 29.08| -0.588 | 97.7%   | -25.345 [-30.581, -20.11] | 83.3% | -1.678 [-2.158, -1.199] | 99.8% |
| Ipragliflazine | Total | -18.850 [-27.202, -10.499]     | 0.001>  | 59.0%   | 583  | 181  | 12.4 | -0.470 | 91.4%   | -31.593 [-42.446, -20.74] | 93.0% | -1.365 [-1.613, -1.098] | 99.3% |
| Tofogliflazine | Total | -19.476 [-27.402, -11.550]     | 0.001>  | 0.0%    | 299  | 114  | 20.3 | -0.543 | -91.9%  | -22.566 [-27.709, -17.24] | 73.9% | -1.528 [-1.909, -1.147] | 76.8% |
| Luseogliflazine | Total | -24.269 [-33.316, -15.223]     | 0.001>  | 66.3%   | 579  | 240  | 15.6 | -0.490 | 71.5%   | -22.566 [-27.709, -17.24] | 73.9% | -1.528 [-1.909, -1.147] | 76.8% |

All* | Total | -34.076 [-37.006, -31.146]     | 0.001>  | 78.8%   | 2349 | 12721 | —     | -0.564 | -81.6%  | -30.516 [-38.357, -22.67] | 92.3% | -1.865 [-2.130, -1.599] | 99.2% |

Abbreviations: SUA = serum uric acid; FPG = fasting plasma glucose; HbA1c = glycated hemoglobin; CI = confidence interval; Diff = difference.
Figure 2: Mean difference and 95% confidence intervals for changes in serum uric acid level for canagliflozin compared to placebo ((a) canagliflozin 50 mg; and (b) canagliflozin 300 mg).

Figure 3: Mean difference and 95% confidence intervals for changes in serum uric acid level for dapagliflozin compared to placebo ((a) dapagliflozin 2.5 mg; (b) dapagliflozin 5 mg; and (c) dapagliflozin 10 mg).
the results of metaregression, shown in Table 3, demonstrated that the amount of SUA change was not significantly correlated with dosage and weeks of treatment. However, SUA change was positively correlated with the duration of diabetes (Coefficient = 1.581 [0.148, 3.014]; P = 0.03) (Table 3). Figure S4 shows the scatter plots of metaregression by week, SGLT2i dosage, and duration of diabetes covariates. Figures S7, S10, and S13 show the
forest plot of HbA1c, FPG, and body weight changes, respectively.

3.1.2. Dapagliflozin. Eighteen clinical trials with a total of 41 comparisons examined the effect of dapagliflozin (range of 1 mg to 50 mg) on SUA levels. The pooled effects of different doses of dapagliflozin on SUA, HbA1c, and FPG are reported in Table 2. MD of HbA1c, body weight, and FPG changes was lower in dapagliflozin studies than other types of SGLT2i. Furthermore, the results of random-effects meta-regression indicated that the amount of SUA change does not correlate with dosage or weeks of treatment, but SUA change was positively correlated with the duration of diabetes (Coefficient = 1.906 [1.218, 2.594]; P < 0.001) (Table 3). Figure S5 shows the scatter plots of metaregression by week, dosage, and duration of diabetes covariates. Figures S8, S11, and S14 show the forest plot of HbA1c, FPG, and body weight changes, respectively. Moreover, one study was removed because it was conducted on prediabetic patients. The findings showed that dapagliflozin reduced SUA levels (MD = −62 ± 47 μmol/L) [45].

3.1.3. Empagliflozin. Seventeen trials assessed the effect of empagliflozin (range of 5 mg to 100 mg) on SUA. Empagliflozin had the highest rate of SUA reduction (MD = −40.98 μmol/L; CI [−47.63, −34.32]; I² = 84.9%). Empagliflozin effects on SUA, HbA1c, body weight, and FPG are shown in Table 2. Scatter plots of metaregression by the week of treatment and dosage covariates are shown in Figure S6. Figures S9, S12, and S15 show the forest plot of HbA1c, FPG, and body weight changes, respectively. We removed the Zanchi et al. study from the meta-analysis. They employed nondiabetic patients to measure the effect of empagliflozin 10 mg; the results also showed a reduction in SUA (MD = −97 ± 36 μmol/L) [70].

3.1.4. Other SGLT2i. The effects of other SGLT2is on SUA, HbA1c, body weight, and FPG are also reported in Table 2. Three studies assessed ipragliflozin (range of 12.5 mg to 300 mg), two studies assessed tofogliflozin (range of 10 mg to 40 mg), and four studies assessed luseogliflozin (range of 0.5 mg to 10 mg) effects on SUA levels. Four studies were removed from the meta-analysis because they did not assess patients with T2DM. A recent study in 2020
assessed the effects of 12 weeks of treatment with licogliplizin on 123 obese patients. MD of SUA change in different doses was between -65.1 and -74.4 μmol/L [69]. Van Raalte et al. in 2019 assessed a 24-week treatment with sotagliflozin 200 mg or 400 mg on 955 type 1 diabetes patients compared with 479 patients in the placebo group; MD of SUA was calculated \(-32.71 \pm 38.95 \mu \text{mol/L} \) [63].

3.2. Publication Bias. Regarding Egger’s test, canagliflozin 100 mg, canagliflozin 300 mg, empagliflozin 10 mg, and empagliflozin 25 mg had publication bias \(P < 0.05 \). However, Begg’s test did not show any publication bias, except for canagliflozin (total).

4. Discussion

The current meta-analysis of 55 placebo-controlled trials analyzed the data of 23,494 patients who received SGLT2is compared with 12,721 patients who received a placebo. The mean difference of SUA changes was about \(-34.07 \mu \text{mol/L} \) (95% CI [-37.00, -31.14], \(I^2 = 78.8\% \)) among T2DM patients. Empagliflozin showed more potential in SUA reduction than other SGLT2is, while ipragliflozin had the least SUA changes.

There are six meta-analyses on this topic, two of which focused specifically on SUA change. Wu et al. assessed the impact of SGLT2i as an add-on treatment to insulin therapy compared to the control group in patients with T2DM, which received a placebo in addition to insulin. They calculated MD of SUA change -26.16 μmol/L (95% CI [-42.14, -10.17], \(I^2 = 80\% \)) through assessment of 5 comparisons [78]. Yumo Zhao et al. specifically focused on SUA changes of 62 trials, which compared the effects of SGLT2is with placebo or active control or standard care. Overall MD of SUA changes was \(-37.73 \mu \text{mol/L} \) (CI [-40.51, -34.95], \(I^2 = 73.5\% \)) [79].

Dapagliflozin was studied more than the other SGLT2is. In accordance with our study, a previous meta-analysis on 4454 patients showed that dapagliflozin can significantly reduce SUA; the weighted mean difference (WMD) of SUA changes was about \(-41.50 \mu \text{mol/L} \) (95% CI [-47.22, -35.79]; \(I^2 = 50\% \)), while it was about \(-35.17 \mu \text{mol/L} \) (95% CI [-39.68, -30.66], \(I^2 = 73.9\% \)) in our study [80]. The effects of dapagliflozin on SUA were also assessed by Zhang et al. on 5302 patients, with results being similar to those of our study (WMD -36.17 μmol/L; 95% CI: -40.99, -31.36; \(I^2 = 64\% \)) [81]. Both studies compared dapagliflozin with a placebo.

In agreement with us, Xin et al. assessed SUA changes obtained with 5 types of SGLT2i compared with placebo or control or standard care. All SGLT2is significantly decreased SUA levels compared with placebo; canagliflozin WMD – 37.02 μmol/L (95% CI [-38.41, -35.63]), dapagliflozin WMD –38.05 μmol/L (95% CI [-44.47, -31.62]), empagliflozin WMD –42.07 μmol/L (95% CI [-46.27, -37.86]), ipragliflozin WMD –18.97 μmol/L (95% CI [-28.79, -9.16]), and ipragliflozin WMD –19.75 μmol/L (95% CI [-28.17, -11.34]) [76]. Furthermore, Yumo Zhao et al. performed a meta-regression and concluded that only the effect of dapagliflozin depended on the administration dosage. In addition, the meta-regression of Yumo Zhao et al. showed that the reduction of SUA could be persistent with long-term, 104-week administration of SGLT2is [79]. Conversely, our study showed no relationship between SUA reduction and duration (except for empagliflozin) and dosage of SGLT2i. However, our data showed that SUA was reduced more in the canagliflozin and dapagliflozin groups, with a more pronounced reduction observed in patients with a longer duration of diabetes. Perhaps, longer duration of diabetes may alter the expression of SGLT2, glucose transporter 9 (GLUT9), or related unknown pathways in the kidney, thus favouring uric acid excretion. Di Zhao et al. specifically reviewed the effect of empagliflozin on some cardiometabolic risk factors [75]. In accordance with our review, they showed that empagliflozin could significantly reduce SUA level, HbA1c, and FPG. However, there are some differences: the mean change of HbA1c and FPG, unlike SUA, was higher in their study. The differences may be due to the mean treatment period, the number of patients, and different analysis tools.

Increased SUA causes inflammation in adipocytes as well as endothelial dysfunction, which reduces nitric oxide bioavailability and leads to insulin resistance. Moreover, uric acid impairs glucose uptake in skeletal muscle, which reduces insulin-stimulated glucose uptake [82]. Uric acid excretion is more pronounced reduction observed in patients with a longer duration of diabetes. Perhaps, longer duration of diabetes may alter the expression of SGLT2, glucose transporter 9 (GLUT9), or related unknown pathways in the kidney, thus favouring uric acid excretion. Di Zhao et al. specifically reviewed the effect of empagliflozin on some cardiometabolic risk factors [75]. In accordance with our review, they showed that empagliflozin could significantly reduce SUA level, HbA1c, and FPG. However, there are some differences: the mean change of HbA1c and FPG, unlike SUA, was higher in their study. The differences may be due to the mean treatment period, the number of patients, and different analysis tools.

4.1. Limitations and Strengths. Our study has some limitations. First, due to the paucity of available studies, we could not perform a meta-analysis for ertugliflozin and sotagliflozin. Second, some studies did not report the standard deviation or related data to calculate it. Third, trials with CKD patients, whose plasma UA level may be increased because of disease deterioration, could interfere with the results. Fourth, some studies had some dropouts, but they reported...
baseline data of all patients. Fifth, the baseline SUA level and follow-up period were different across the studies. Sixth, some of the administered doses of SGLT2i were not within the approved dose range for the T2DM treatment. Finally, the heterogeneity of SUA data was moderate or high except for canagliflozin (300 mg) and tofogliflozin. The comparison with active control groups and paucity of available studies were the other limitations of previous meta-analyses.

4.2. Conclusion. All SGLT2i analyzed in the meta-analysis can reduce SUA in patients with T2DM (MD = −34.076; CI [-37.006, -31.146]). The ability to reduce SUA is one of the advantages of SGLT2is over other antidiabetic medications, particularly in patients with T2DM and comorbid hyperuricemia. Moreover, the urate-lowering properties exerted by SGLT2i may partly explain their well-established renoprotective and cardioprotective actions. More placebo-controlled studies are warranted for luseogliflozin, licogliflozin, sotagliflozin, and ertugliflozin to clarify their effects on SUA.

Data Availability

There is no raw data associated with this article.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Supplementary Materials

Table S1: search strategy. Figure S1: meta-analysis of all canagliflozin studies to determine the drug efficacy in serum uric acid reduction. Figure S2: meta-analysis of all dapagliflozin studies to determine the drug efficacy in serum uric acid reduction. Figure S3: meta-analysis of all empagliflozin studies to determine the drug efficacy in serum uric acid reduction. Figure S4: scatterplots of metaregression on canagliflozin variables (weeks of treatment, drug dosage, and duration of diabetes). Figure S5: scatterplots of metaregression on dapagliflozin variables (weeks of treatment, drug dosage, and duration of diabetes). Figure S6: scatterplots of metaregression on empagliflozin variables (weeks of treatment, drug dosage, and duration of diabetes). Figure S7: meta-analysis of all canagliflozin studies to determine the drug effects on HbA1c. Figure S8: meta-analysis of all dapagliflozin studies to determine the drug effects on HbA1c. Figure S9: meta-analysis of all empagliflozin studies to determine the drug effects on HbA1c. Figure S10: meta-analysis of all canagliflozin studies to determine the drug effects on FPG. Figure S11: meta-analysis of all dapagliflozin studies to determine the drug effects on FPG. Figure S12: meta-analysis of all empagliflozin studies to determine the drug effects on FPG. Figure S13: meta-analysis of all canagliflozin studies to determine the drug effects on body weight. Figure S14: meta-analysis of all dapagliflozin studies to determine the drug effects on body weight. Figure S15: meta-analysis of all empagliflozin studies to determine the drug effects on body weight. (Supplementary Materials)

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