Effect of sodium-glucose cotransporter-2 (SGLT2) inhibitors on serum urate levels in patients with and without diabetes: a systematic review and meta-regression of 43 randomized controlled trials

Alicia Swee Yan Yip*, Shariel Leong*, Yao Hao Teo, Yao Neng Teo, Nicholas L. X. Syn, Ray Meng See, Caitlin Fern Wee, Elliot Yeung Chong, Chi-Hang Lee, Mark Y. Chan, Tiong-Cheng Yeo, Raymond C. C. Wong, Ping Chai and Ching-Hui Sia

Abstract

Objectives: Sodium-glucose cotransporter-2 (SGLT2) inhibitors have been found to reduce serum urate in patients with type 2 diabetes mellitus. To evaluate if this effect applies to both patients with and without diabetes, we conducted a systematic review and meta-analysis of SGLT2 inhibitors on serum urate levels in this population.

Methods: Four electronic databases (PubMed, Embase, Cochrane and SCOPUS) were searched on 25 September 2021 for articles published from 1 January 2000 up to 25 September 2021, for studies that examined the effect of SGLT2 inhibitors on serum urate in study subjects. Random-effects meta-analysis was performed, with subgroup analyses on the type of SGLT2 inhibitor agent administered, presence of type 2 diabetes mellitus, presence of chronic kidney disease and drug dose.

Results: A total of 43 randomized controlled trials, with a combined cohort of 31,921 patients, were included. Both patients with $[-31.48 \mu mol/L; 95\% \text{ confidence interval (CI): } -37.35 \text{ to } -25.60]$ and without diabetes $(-91.38 \mu mol/L; 95\% \text{ CI: } -126.53 \text{ to } -56.24)$ on SGLT2 inhibitors had significantly lower urate levels when compared with placebo. This treatment effect was similarly observed across different types of SGLT2 inhibitors. However, in type 2 diabetes mellitus (T2DM) patients with chronic kidney disease, the reduction in serum urate with SGLT2 inhibitors became insignificant (95% CI: $-22.17 \text{ to } 5.94$, $p < 0.01$).

Conclusion: This study demonstrated that SGLT2 inhibitors are beneficial in reducing serum urate in patients with and without diabetes. SGLT2 inhibitors could therefore contribute to the general treatment of hyperuricaemia.

Keywords: diabetes mellitus, nondiabetics, serum urate, serum uric acid, sodium-glucose cotransporter-2 (SGLT2) inhibitors, type 2 diabetes mellitus

Received: 8 November 2021; revised manuscript accepted: 8 February 2022.

Introduction

Sodium-glucose cotransporter-2 (SGLT2) inhibitors are an emerging class of glucose-lowering medications that decrease plasma glucose levels in an insulin-independent manner. By blocking SGLT2 receptors located in the early proximal renal tubule, the renal reabsorption of glucose is limited to approximately 80 g/day, thus lowering the glucose burden.

Beyond glycaemic control, SGLT2 inhibitors have also been found to have beneficial effects on
blood pressure, body weight, cardiometabolic markers, cardiovascular outcomes and renal function. Several mechanisms of how SGLT2 inhibitors exert their cardiorenal-protective effects have been proposed, one of them being a reduction in the levels of serum urate.

An elevated level of urate is an independent predictor of diabetes and often precedes the development of diabetes. High levels of urate have been found to inhibit post-receptor insulin signaling pathways, thus inducing insulin resistance. Raised serum urate levels have also been implicated in gout and are also associated with other common comorbidities such as hypertension, metabolic syndrome, nonalcoholic fatty liver disease, and chronic kidney disease. Previous studies on urate-lowering therapy demonstrated benefits such as an improvement in kidney function, prophylaxis of gout flares and a reduction in the risk of major adverse cardiovascular events and all-cause mortality. Given the increasing amount of evidence implicating the contributory causal role of urate in the pathogenesis of cardiovascular and renal diseases, it is thus crucial to study the impact of SGLT2 inhibitors in reducing serum urate levels.

In previous meta-analyses, SGLT2 inhibitors demonstrated an effect in reducing serum urate levels in patients with type 2 diabetes mellitus (T2DM). To the best of our knowledge, there has not been any meta-analysis examining whether this effect applies to patients without diabetes as well. We hypothesized that SGLT2 inhibitors would reduce serum urate levels in both patients with and without diabetes. Therefore, we conducted a systematic review and meta-analysis of SGLT2 inhibitors on serum urate levels in this population.

Methods

Search strategy
This meta-analysis was performed according to the 2020 Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Ethical approval was not required for this study as this study utilized publicly available data that were already previously published. Four electronic databases (PubMed, Embase, Cochrane and SCOPUS) were searched on 25 September 2021 for articles published from 1 January 2000 up to 25 September 2021, for studies that examined the effect of SGLT2 inhibitors on serum urate in study subjects. A combination of the following terms was used for the literature search: (‘empagliflozin’ OR ‘canagliflozin’ OR ‘dapagliflozin’ OR ‘ertugliflozin’ OR ‘luseogliflozin’ OR ‘ipragliflozin’ OR ‘remogliflozin’). The detailed search strategy is shown in Supplemental Table 1. A manual search of ClinicalTrials.gov, the retrieved references, relevant meta-analyses and reviews was carried out to identify additional trials.

Study selection
All randomized controlled trials comparing the effects of SGLT2 inhibitors against placebo on serum urate were included, according to the Population, Intervention, Comparison, Outcome, and Study (PICOS) framework (Table 1). We excluded all studies that were not randomized controlled trials.

Data extraction and quality assessment
Four independent reviewers evaluated the literature and extracted study data including participant baseline characteristics, study design, date of publication and sample size. Discrepancies were resolved by mutual consensus. Based on the title and abstract sieve, studies that were not randomized controlled trials or did not involve the use of SGLT2 inhibitors were first excluded. A full-text review was subsequently performed to assess for inclusion and exclusion criteria in detail.

Full-text articles and their respective supplementary materials from included publications were then retrieved for data extraction. The following baseline information of patients from eligible trials was collected: age, sex, body weight, body mass index (BMI), systolic blood pressure, diastolic blood pressure, haemoglobin A1c (HbA1c) and low-density lipoprotein cholesterol (LDL-C). Data of the SGLT2 inhibitor regimens were collected, namely drug name, drug dosage, drug frequency, control group, length of intervention and mean duration of follow-up and outcome (change in serum urate levels from baseline). For serum urate levels, a conversion factor of 1 mg/dl to $59.48 \mu mol/L$ was adopted. All repeated observations for participants were extracted. The quality of the included studies was evaluated using the Cochrane Risk of Bias tool, which comprises...
seven domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome, incomplete outcome data, selective reporting and other sources of bias, as shown in Supplemental Figure 1. The quality of pooled evidence was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system, which considered statistical heterogeneity, publication bias, risk of bias, indirectness and statistical imprecision, as shown in Supplemental Table 2. Consensus was reached among the four independent reviewers when assessing for risk of bias. The 2020 PRISMA checklist and Meta-analyses Of Observational Studies in Epidemiology (MOOSE) checklist are attached in Supplemental Figures 3 and 4, respectively.

Statistical analysis
In studies without standard deviations, p-values and confidence intervals, the square root of weighted mean variance of all other studies was used to estimate the standard deviation. The heterogeneity between studies was examined using $I^2$ and $\tau^2$ statistics. Heterogeneity was considered as significant for $I^2 > 50%$. Random-effects meta-regression analysis with the inverse-variance method was performed within each SGLT2 inhibitor to assess the association between drug dosage and the reduction of serum urate. Additional subgroup analyses were carried out to explore the association between effect size and baseline characteristics, namely: the SGLT2 inhibitor agent administered, presence of T2DM, presence of chronic kidney disease and drug dose. Two-tailed $p$-values $<0.05$ were considered statistically significant. All results were analysed using Review Manager (RevMan) Version 5.4 and Stata 16.0 (StataCorp, TX, USA).

Results

Study selection and characteristics
The PRISMA flowchart is illustrated in Figure 1. A systematic literature search identified 8648 articles. Four additional articles were identified from hand search. A total of 3062 duplicate articles were excluded. Title and abstract screening further excluded 5029 nonrelevant articles which did not assess serum urate as an outcome. Full-text screening excluded 536 articles. In total, 43 randomized controlled trials (published from 2010 to 2021) were included for the meta-analysis. The sample size of the studies ranged from 20 to 7034, giving a total of 31,921 participants.

The baseline characteristics of participants are compiled in Table 2. Out of the 43 randomized controlled trials, 39 trials included patients with T2DM, and none of the trials included patients with type 1 diabetes mellitus. Among the remaining four trials, healthy subjects were recruited in Chino et al. and Zanchi et al., while subjects

Table 1. PICOS, inclusion criteria and exclusion criteria applied to database search.

| PICOS | Inclusion criteria | Exclusion criteria |
|-------|-------------------|-------------------|
| Population | Patients with or without type 1 and 2 diabetes mellitus | Exclusion criteria applied to database search. |
| Intervention | SGLT2 inhibitors inclusive of Empagliflozin, Canagliflozin, Dapagliflozin, Ertugliflozin, Luseogliflozin, Ipragliflozin, Remogliflozin | Exclusion criteria applied to database search. |
| Comparison | Placebo | Exclusion criteria applied to database search. |
| Outcome | Serum urate | Exclusion criteria applied to database search. |
| Study design | Articles in English or translated to English | Articles in English or translated to English |
| | Randomized controlled trials | Randomized controlled trials |
| | Grey literature, conference abstracts, electronic and print information not controlled by commercial publishing of randomized clinical trials | Grey literature, conference abstracts, electronic and print information not controlled by commercial publishing of randomized clinical trials |
| | Databases: PubMed, Embase, Cochrane, SCOPUS | Databases: PubMed, Embase, Cochrane, SCOPUS |
| | Search period: Initiation–21 November 2020 | Search period: Initiation–21 November 2020 |

PICOS: Population, Intervention, Comparison, Outcome, and Study design; SGLT2, sodium-glucose cotransporter.
with prediabetes were recruited in Lee et al.\textsuperscript{32} and Ramírez-Rodríguez et al.\textsuperscript{33}

The SGLT2 inhibitor drug name, dose, frequency, length of intervention and length of follow-up are summarized in Supplemental Table 3. Empagliflozin, Dapagliflozin, Canagliflozin, Luseogliflozin and Ipragliflozin were administered in 14, 13, 7, 3 and 2 trials, respectively. All trials had a once-daily dosing regimen except Rosenstock et al.,\textsuperscript{36} Qiu et al.\textsuperscript{47} and Schumm-Draeger et al.,\textsuperscript{49} which have a twice-daily regimen. The length of follow-up ranged from 1 week to 3.1 years.

**Pooled outcome analyses**

The pooled urate outcomes are presented in Figure 2. Overall, SGLT2 inhibitors reduced serum urate by 33.03 μmol/L (95% CI: −37.38 to −28.69, \( p < 0.001 \)).

**Subgroup analyses**

Subgroup analyses were carried out to explore the association between effect size and baseline characteristics, focusing on the type of SGLT2 inhibitor administered, presence of T2DM, presence of chronic kidney disease and the drug dose.

**SGLT2 inhibitor administered.** Significant reduction of urate level was associated with each of the five SGLT2 inhibitors administered (canagliflozin, dapagliflozin, empagliflozin, ipragliflozin and luseogliflozin). The random effects model demonstrated that luseogliflozin had the greatest mean reduction in urate of 47.73 μmol/L (95% CI:
Table 2. Baseline characteristics of subjects.

| Study                | Mean length of follow-up | Study population | Concomitant medications | Sample size | Sample size (T2DM) | Duration of DM (in years) | Age (mean) | Males | Hypertension | Body mass index (kg/m²) | HbA1c (%) | LDL-C [mmol/L] | Location                |
|----------------------|--------------------------|------------------|--------------------------|-------------|--------------------|--------------------------|------------|-------|-------------|-----------------------|-----------|----------------|--------------------------|
| Ferrannini et al.    | 24 weeks                 | T2DM patients    | –                        | 558         | 558                | 0.487                    | 52         | 276   | NR          | 32.6                  | 8.29      | NR             | USA, Canada, Mexico, Russia |
| Strojek et al.       | 24 weeks                 | T2DM patients    | Glimepiride 4 mg/day     | 592         | 592                | 7.43                     | 59.8       | 285   | 437         | NR                    | 8.11      | NR             | Europe, Asia-Pacific     |
| Rosenstock et al.    | 12 weeks                 | T2DM patients    | Metformin >1500 mg/day   | 386         | 386                | 6                        | 53.1       | 198   | NR          | 31.5                  | 7.77      | NR             | 12 countries            |
| Bailey et al.        | 16 weeks                 | T2DM patients    | Metformin >1500 mg/day   | 564         | 564                | 6.07                     | 53.9       | 292   | NR          | 31.5                  | 8.05      | 2.65 NR         | 17 countries            |
| Bode et al.          | 102 weeks                | T2DM patients    | Metformin plus sulphonylurea | 714        | 714                | 11.7                     | 63.6       | 396   | 561         | 31.6                  | 7.7       | 2.37 NR         | Argentina, Brazil, Canada, Mexico, USA |
| Häring et al.        | 78 weeks                 | T2DM patients    | Metformin plus sulphonylurea | 666        | 666                | NR                       | 57.1       | 339   | NR          | 28.2                  | 8.1       | NR             | 17 countries            |
| Roden et al.         | 24 weeks                 | T2DM patients    | –                        | 676         | 676                | NR                       | 54.9       | 410   | NR          | 28.4                  | 7.88      | 2.83 NR         | 17 countries            |
| Stenlöf et al.       | 25 weeks                 | T2DM patients    | Metformin plus sulphonylurea | 584        | 584                | 4.3                      | 55.4       | 258   | NR          | 31.6                  | 8         | NR             | 12 countries            |
| Wilding et al.       | 52 weeks                 | T2DM patients    | Metformin plus sulphonylurea | 469        | 469                | 9.6                      | 56.8       | 239   | NR          | 33.1                  | 8.1       | NR             | 17 countries            |
| Wilding et al.       | 52 weeks                 | T2DM patients    | Metformin >1500 mg/day   | 342         | 342                | 5.9                      | 57.4       | 175   | NR          | 31.7                  | 7.78      | NR             | 11 countries            |
| Barnett et al.       | 52 weeks                 | T2DM patients    | Metformin plus sulphonylurea | 738        | 738                | NR                       | 63.9       | 181   | NR          | 30.7                  | 8         | 2.25 NR         | 15 countries            |
| Chino et al.         | 1 week                   | Healthy subjects | –                        | 24          | 0                  | 0                        | 28.9       | 24    | NR          | NR                    | 5.1       | NR             | Japan                    |
| Kadawaki et al.      | 12 weeks                 | T2DM patients    | –                        | 547         | 547                | NR                       | 57.5       | 410   | NR          | 25.5                  | 7.95      | NR             | Japan                    |
| Kashiwagi et al.     | 12 weeks                 | T2DM patients    | –                        | 360         | 360                | 6.7                      | 55.9       | 233   | NR          | 25.7                  | 8.33      | NR             | Japan                    |
| Qiu et al.           | 22 weeks                 | T2DM patients    | Metformin >1500 mg/day   | 279         | 279                | 7.0                      | 57.4       | 130   | NR          | 32.5                  | 7.6       | NR             | USA, Canada, Czech Republic, Mexico, Romania, Russia, Slovakia |
| Seino et al.         | 12 weeks                 | T2DM patients    | –                        | 239         | 239                | 6                        | 57         | 160   | NR          | 25                   | 8.07      | NR             | Japan                    |
| Schumm-Dräger et al. | 16 weeks                 | T2DM patients    | Metformin >1500 mg/day   | 399         | 399                | 5.2                      | 57.7       | 179   | NR          | 32.6                  | 7.8       | NR             | Europe and South Africa |
| Yale et al.          | 52 weeks                 | T2DM patients    | Metformin plus sulphonylurea or Metformin plus sulphonylurea | 269        | 269                | 16.3                     | 68.5       | 163   | NR          | 33                   | 8         | 19 countries    | China, Malaysia, Vietnam |
| Ji et al.            | 18 weeks                 | T2DM patients    | Metformin plus sulphonylurea | 676        | 676                | 6.7                      | 56.2       | 362   | NR          | 25.7                  | 7.967     | NR             | Japan                    |
| Nishimura et al.     | 29 days                  | T2DM patients    | –                        | 60          | 60                 | NR                       | 62.7       | 47    | NR          | 24.3                  | 7.91      | NR             | Japan                    |
| Study            | Mean length of follow-up | Study population | Concomitant medications                                                                 | Sample size | Sample size (T2DM) | Duration of DM (in years) | Age (mean) | Males | Hypertension | Body mass index (kg/m²) | HbA1c (%) | LDL-C (mmol/L) | Location                  |
|------------------|--------------------------|------------------|------------------------------------------------------------------------------------------|-------------|-------------------|--------------------------|------------|-------|--------------|--------------------------|-----------|----------------|----------------------------|
| Ross et al.      | 17 weeks T2DM patients on metformin | Metformin >1500 mg/day | 983 983 NR 58.2 520 NR 31.8 7.77 NR NR |             |                   |                           |            |       |              |                          |           |                |                           |
| Tikkanen et al.  | 12 weeks T2DM patients with hypertension | Up to two antihypertensive medications | 823 823 NR 60.2 495 823 32.6 7.9 NR NR |             |                   |                           |            |       |              |                          |           |                |                           |
| Weber et al.     | 13 weeks T2DM patients with hypertension | Antihyperglycaemic agents, plus a renin–angiotensin system blocker and an additional antihypertensive drug | 449 449 7.5 NR 247 449 NR 8.05 NR 16 countries |             |                   |                           |            |       |              |                          |           |                |                           |
| Yang et al.      | 24 weeks T2DM patients | Metformin >1500 mg/day | 444 444 4.93 53.7 241 NR 26.1 8.13 NR China and other Asian countries |             |                   |                           |            |       |              |                          |           |                |                           |
| Zinman et al.    | 3.1 years (median) T2DM patients | Antihyperglycaemic agent(s) | 7034 7034 NR 63.1 5026 NR 30.6 8.1 2.2 North America, Australia, NZ, Latin America, Europe, Africa, Asia |             |                   |                           |            |       |              |                          |           |                |                           |
| Weber et al.     | 13 weeks T2DM patients with hypertension | Antihyperglycaemic agent(s), ACEi or ARB | 613 613 7.9 55.9 350 613 NR 8.05 NR 16 countries |             |                   |                           |            |       |              |                          |           |                |                           |
| Eriksson et al.  | 12 weeks T2DM patients with nonalcoholic fatty liver disease | Metformin or sulphonylurea | 42 42 6.6 65.3 33 NR 30.4 NR NR Sweden |             |                   |                           |            |       |              |                          |           |                |                           |
| Fioretto et al.  | 27 weeks T2DM patients with CKD | Antihyperglycaemic agent(s) | 261 261 14.4 65.8 182 NR 32.1 8.12 NR USa, Canada, Bulgaria, the Czech Republic, Italy, Poland, Spain and Sweden |             |                   |                           |            |       |              |                          |           |                |                           |
| Seino et al.     | 16 weeks T2DM patients on insulin therapy | Insulin monotherapy at a fixed daily dose ranging from 8 to 40 U | 233 233 11.8 57.3 163 NR 25.3 8.74 NR Japan |             |                   |                           |            |       |              |                          |           |                |                           |
| Yang et al.      | 24 weeks T2DM patients on insulin therapy | Insulin at a stable dose >10U with or without other antihyperglycaemic agents | 272 272 12.45 57.5 130 NR 26.5 8.5 2.35 China, South Korea, Singapore |             |                   |                           |            |       |              |                          |           |                |                           |
| Kario et al.     | 12 weeks T2DM patients with uncontrolled nocturnal hypertension | Antihyperglycaemic agents, plus antihypertensive drugs including ARB | 131 131 10.1 70.1 69 131 26.1 6.6 2.77 Japan |             |                   |                           |            |       |              |                          |           |                |                           |
| Pollock et al.   | 24 weeks T2DM patients with CKD | Antihyperglycaemic agents and antihypertensive treatment including ACEi or ARB | 293 293 17.6 64.7 207 NR 45.4 8.5 2.35 Australia, Canada, Japan, South Korea, Mexico, South Africa, Spain, Taiwan, USA |             |                   |                           |            |       |              |                          |           |                |                           |
| Study                  | Mean length of follow-up | Study population                                                                 | Concomitant medications                                      | Sample size (T2DM) | Sample size (insulin therapy) | Duration of DM (in years) | Age (mean) | Males | Hypertension | Body mass index (kg/m²) | HbA1c (%) | LDL-C (mmol/L) | Location          |
|-----------------------|--------------------------|----------------------------------------------------------------------------------|----------------------------------------------------------------|-------------------|-----------------------------|----------------------------|-------------|-------|--------------|------------------------|-----------|----------------|----------------------|
| Zanchi et al.         | 4 weeks                  | Healthy subjects                                                                 | –                                                              | 45                | 0                          | 0                          | 33.2        | 27    | 0            | 28.2                   | 5.4       | NR             | Switzerland        |
| Griffin et al.        | 2 weeks                  | T2DM patients with chronic stable heart failure                                 | With or without loop diuretics                                   | 20                | 20                         | NR                        | 60          | 15    | 19           | 37                     | 7.1       | NR             | USA                 |
| Lee et al.            | 40 weeks                 | T2DM patients or pre-diabetic patients with heart failure and reduced ejection fraction | With or without other antihyperglycaemic agents                | 105               | 82                         | 9.7                       | NR          | NR    | NR           | NR                     | 7.2       | NR             | Scotland            |
| Lee et al.            | 12 weeks                 | T2DM patients on insulin therapy                                                  | Insulin, with or without metformin or sulphonylurea           | 84                | 84                         | 15.1                      | 58.67       | 35    | 54           | 26.94                  | 8.27      | 2.22           | South Korea         |
| Ramirez-Rodriguez et al. | 12 weeks              | Prediabetic patients                                                              | –                                                              | 24                | 0                          | 0                          | 49.1        | 7     | 0            | 31.7                   | 5.8       | 4              | Mexico              |
| Shimizu et al.        | 24 weeks                 | T2DM patients with history of AMI                                                | Conventional therapy including beta-blockers, ACEI, ARB, statins, diuretics, metformin, DPP-4 inhibitor | 96                | 96                         | 2.9                       | 64.3        | 77    | 77           | 25.2                   | 6.9       | 2.27           | Japan               |
| Packer et al.         | 16 months                | Patients with heart failure and reduced ejection fraction                        | Therapy for heart failure, including diuretics, ACEI, ARB, nephrilysin, beta-blockers, mineralocorticoid receptor antagonists, and when indicated, cardiac devices | 3730              | 1856                       | NR                        | 66.8        | 2837 | 2698         | 27.9                   | NR        | NR             | Multicenter         |
| Ferreira et al.       | 2.6 years                | T2DM patients                                                                     | –                                                              | 7020              | 7020                       | 7.93                      | 63.1        | 5016 | 6419         | 30.6                   | 8.1       | NR             | United States       |
| Hao et al.            | 3 months                 | T2DM patients with hypertension                                                   | Antihypertensive drugs                                         | 486               | 486                        | 3.5                       | 42.1        | 323   | 486          | 24.6                   | 7.0       | NR             | China               |
| Okada et al.          | 12 weeks                 | T2DM patients with hypertension                                                  | Antihyperglycaemic and antihypertensive agents                | 131               | 131                        | 10.9                      | 70.1        | 66    | 131          | 26                     | 6.6       | 107.3          | Japan               |
| Stack et al.          | 1 week                   | Non-DM patients with asymptomatic hyperuricaemia, on concomitant serum urate-lowering therapy | Oral verinurad 9 mg plus febuxostat 80mg                      | 36                | 36                         | NR                        | 42.3        | 35    | NR           | 27.9                   | NR        | NR             | United States       |

ACEI, angiotensin-converting enzyme inhibitors; AMI, acute myocardial infarction; ARB, angiotensin II receptor blocker; CAD, coronary artery disease; CKD, chronic kidney disease; DM, diabetes mellitus; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; HbA1c, haemoglobin A1c; LDL-C, low-density lipoprotein cholesterol; NR, not reported; T2DM, type 2 diabetes mellitus.

Combination therapy of antihyperglycaemic agents include metformin, sulphonylurea, DPP-4 inhibitor, α-glucosidase inhibitor, GLP-1 agonist, insulin and pioglitazone.
Figure 2. Forest plot of mean change in serum urate in μmol/L.
−79.50 to −15.96, \( p=0.003 \) (Figure 3(a)). This was followed by canagliflozin, which had a mean reduction in urate of 36.62 μmol/L (95% CI: −42.67 to −30.56, \( p<0.001 \)) (Figure 3(b)). Empagliflozin led to a mean reduction in urate of 35.19 μmol/L (95% CI: −42.61 to −27.78, \( p<0.001 \)) (Figure 3(c)), while dapagliflozin had a mean reduction in urate of 30.32 μmol/L (95% CI: −36.20 to −24.43, \( p<0.001 \)) (Figure 3(d)), and ipragliflozin had a mean reduction in urate of 26.50 μmol/L (95% CI: −32.71 to −20.29, \( p<0.001 \)) (Figure 3(e)).

Figure 3. (Continued)
20.37 μmol/L (95% CI: -29.17 to -11.56, \( p < 0.001 \)) (Figure 3(e)).

Presence of T2DM. The results demonstrated that patients without T2DM receiving SGLT2 inhibitors had a mean reduction in urate of 91.38 μmol/L (95% CI: -126.53 to -56.24, \( p < 0.001 \)) (Figure 4(a)). Patients with T2DM receiving SGLT2 inhibitors had a smaller mean reduction in urate of 31.48 μmol/L (95% CI: -37.35 to -25.60, \( p < 0.001 \)) (Figure 4(b)).

Presence of chronic kidney disease with T2DM. Barnett et al.,44 Fioretto et al.,59 Pollock et al.,63 and Yale et al.50 included patients with diabetes with an estimated glomerular filtration rate (eGFR) ranging from 15 to 90 ml/min/1.73 m², 40 to 65 ml/min/1.73 m², 25 to 75 ml/min/1.73 m² and 30 to 50 ml/min/1.73 m², respectively. No significant reduction in serum urate was shown in these patients (95% CI: -22.17 to 5.94, \( p < 0.01 \)) (Supplemental Figure 2).

Meta-regression: drug dose of dapagliflozin, canagliflozin and empagliflozin. Random-effects meta-regression was performed to evaluate whether reduction in serum urate levels was dependent on the dosage of any specific SGLT2 inhibitor (data not shown). There was no significant association between drug dosage and serum urate-lowering capacity of dapagliflozin (beta coefficient = -0.476, 95% CI: -3.04 to 2.09, \( p = 0.704 \)), canagliflozin (beta coefficient = -0.0073, 95% CI: -0.064 to 0.050, \( p = 0.79 \)) and empagliflozin (beta coefficient = 0.267, 95% CI: -0.654 to 1.19, \( p = 0.559 \)). We could not perform a meta-regression analysis for ipragliflozin and luseogliflozin in view of the limited number of studies.
Figure 4. Subgroup analysis of reduction in serum urate (in μmol/L) in (a) patients without diabetes and (b) patients with diabetes.
Risk of bias of included studies
The risk of bias is summarized in Supplemental Table 4. All included studies were randomized controlled trials. Majority of the studies had a low risk of reporting bias. Three trials were assessed to have a high risk of other bias, due to the small sample size. Chino et al., Griffin et al., Ramirez-Rodriguez et al. and Stack et al. had a sample size of 24, 20, 24 and 36, respectively. One trial had a high selection bias due to allocation concealment.

Discussion
This updated, pair-wise meta-analysis of 43 randomized controlled trials demonstrated that SGLT2 inhibitors had a beneficial effect on serum urate levels. This effect remained significant when stratified across the SGLT2 inhibitor agent administered, and the presence of T2DM. In patients without diabetes mellitus, there was a larger reduction in serum urate. No dose-dependent relationship was observed for dapagliflozin, canagliflozin and empagliflozin.

These findings largely concur with previous meta-analyses which quantify the serum urate-lowering properties of SGLT2 inhibitors in patients with T2DM. In the study by Hu et al., luseogliflozin was also found to have the greatest effect on reduction of serum urate levels in patients with T2DM, where a dose of 10 mg was shown to be the most efficacious when compared with lower doses. This is in contrast to our study, as well as Xin et al. and Chino et al., which did not find any significant dose-dependent difference in the urate-lowering effects of SGLT2 inhibitors. In addition, while there might be differences in the urate-lowering effect between different agents, this may not be clinically significant.

SGLT2 inhibitors lower serum urate by increasing the renal elimination of urate. Urate is freely filtered by the kidney and most of it is reabsorbed in the S1 segment of the proximal convoluted tubule (PCT). As such, the mechanism for the uricosuric properties of SGLT2 inhibitors has been attributed to the suppression of GLUT9 isoform 2 activity. GLUT9 isoform 2 is a facilitative hexose/urate transporter (SLC2A9b) found on the apical membrane of epithelial cells in the S1 segment of the PCT, involved in the excretion of urate. Therefore, when SGLT2 is inhibited, the increased concentration of glucose within the lumen of the PCT competes with urate for GLUT9 isoform 2. In addition to being found in the PCT, GLUT9 isoform 2 is also found in the collecting ducts, where it mediates urate reabsorption. It has been found that an increased concentration of glucose in the lumen by SGLT2 inhibition also inhibits urate reabsorption mediated by GLUT9 isoform 2 found in the collecting ducts. This uricosuric effect is also seen with phloridzin, a non-selective SGLT inhibitor, which induces uricosuria in healthy subjects.

It was previously reported that urate reduction by SGLT2 inhibitors declined or became absent in patients with chronic kidney disease, where the reduction in both urate and glucose filtration might mask the contribution of decreased urate reabsorption as a result of SGLT2 inhibition. In our analysis, comparing the effect of SGLT2 inhibitors against placebo, we demonstrated a larger mean reduction in serum urate levels in the subgroup of patients without diabetes, compared with the subgroup of patients with diabetes. An analysis of a subgroup of patients with both chronic kidney disease and T2DM also revealed an attenuated effect of SGLT2 inhibitors in terms of reducing serum urate levels. As such, it seems that the urate-lowering effect of SGLT2 inhibitors is dependent on renal function. Given that the progression of T2DM in patients with diabetes affects renal filtration function, this could contribute to the decreased effect of SGLT2 inhibitors on urate reduction in patients with diabetes. Even then, the reduction in serum urate levels in the diabetic population was still significant.

However, it is also important to note that at this current time, urate-lowering therapy is not indicated for asymptomatic hyperuricaemia in patients with chronic kidney disease and for the prevention of gouty arthritis. While lowering serum urate levels may have benefits, this effect has been difficult to characterize. Nevertheless, lowering serum urate has not been shown to be harmful. Given the strong association between urate levels and many other comorbidities, the urate-lowering properties of SGLT2 inhibitors should be viewed as an additional benefit in the management of the overall morbidity in patients with diabetes.
Strengths and limitations
To the best of our knowledge, this is the first and largest meta-analysis investigating the effects of SGLT2 inhibitors on serum urate in patients with and without diabetes. However, our study should be interpreted in light of its limitations. First, serum urate level was reported as the primary endpoint in only two of the included studies,22,30 of which Chino 2014 was a small study with a 1-week study period. Otherwise, there was no clear inclusion or exclusion criteria specific for baseline serum urate levels and no specified methodology for the urate assay as well. We also recognize the lack of information on the presence of other urate-modifying therapies. Should there be unreported concomitant use of urate-lowering therapies, the true effect of SGLT2 inhibitors on uric acid could be overestimated. Second, due to limited studies available, we were unable to comment on the urate-lowering effect of individual SGLT2 inhibitors in the nondiabetic population. It is also to be noted that these are small studies, thus these results should be re-evaluated in clinical trials on a larger scale. Third, heterogeneity of the studies present was likely attributed to the difference in baseline characteristics of the study population.

Conclusion
Our study demonstrated that SGLT2 inhibitors significantly reduced serum urate levels in patients with and without diabetes, compared with placebo. With the clinical importance of hyperuricaemia and associated comorbidities such as gout and chronic kidney disease, SGLT2 inhibitors might prove to be beneficial in the treatment of patients with diabetes with concomitant hyperuricaemia. Adequately powered randomized controlled trials are also required to formally interrogate the use of SGLT2 inhibitors in patients without diabetes. Future studies should also consider SGLT2 inhibitors in patients with gout, who have an absolute indication for urate-lowering therapy.

Author contributions
Alicia Swee Yan Yip: Data curation; Formal analysis; Investigation; Project administration; Writing – original draft; Writing – review & editing.
Shariel Leong: Data curation; Formal analysis; Investigation; Project administration; Writing – original draft; Writing – review & editing.

Yao Hao Teo: Conceptualization; Data curation; Formal analysis; Methodology.
Yao Neng Teo: Data curation; Formal analysis; Methodology; Project administration.
Nicholas L. X. Syn: Conceptualization; Validation.
Ray Meng See: Data curation; Methodology.
Caitlin Fern Wee: Data curation.
Elliot Yeung Chong: Data curation; Validation.
Chi-Hang Lee: Supervision.
Mark Y. Chan: Supervision.
Tiong-Cheng Yeo: Supervision.
Raymond C. C. Wong: Supervision.
Ping Chai: Supervision.
Ching-Hui Sia: Conceptualization; Methodology; Supervision; Validation; Writing – review & editing.

Funding
The authors disclosed receipt of the following financial support for the research, authorship and/or publication of this article: This work was supported by the National University of Singapore Yong Loo Lin School of Medicine’s Junior Academic Faculty Scheme.

Conflict of interest statement
The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

ORCID iD
Shariel Leong https://orcid.org/0000-0002-2812-1424

Supplemental material
Supplemental material for this article is available online.

References
1. Seufert J. SGLT2 inhibitors – an insulin-independent therapeutic approach for treatment of type 2 diabetes: focus on canagliflozin. Diabetes Metab Syndr Obes 2015; 8: 543–554.
2. Wanner C and Marx N. SGLT2 inhibitors: the future for treatment of type 2 diabetes mellitus and other chronic diseases. Diabetologia 2018; 61: 2134–2139.
3. Bonora BM, Avogaro A and Fadini GP. Extragnecemic effects of SGLT2 inhibitors: a review of the evidence. Diabetes Metab Syndr Obes 2020; 13: 161–174.
4. Chilton R, Tikkanen I, Helnke U, et al. Impact of empagliflozin on blood pressure in dipper and non-dipper patients with type 2 diabetes mellitus and hypertension. *Diabetes Obes Metab* 2017; 19: 1620–1624.

5. Leiter LA, Cefalu WT, de Bruin TW, et al. Long-term maintenance of efficacy of dapagliflozin in patients with type 2 diabetes mellitus and cardiovascular disease. *Diabetes Obes Metab* 2016; 18: 766–774.

6. Zaccardi F, Webb DR, Htike ZZ, et al. Efficacy and safety of sodium-glucose co-transporter-2 inhibitors in type 2 diabetes mellitus: systematic review and network meta-analysis. *Diabetes Obes Metab* 2016; 18: 783–794.

7. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015; 373: 2117–2128.

8. Xu L, Li Y, Lang J, et al. Effects of sodium-glucose co-transporter 2 (SGLT2) inhibition on renal function and albuminuria in patients with type 2 diabetes: a systematic review and meta-analysis. *PeerJ* 2017; 5: e3405.

9. Bailey CJ. Uric acid and the cardio-renal effects of SGLT2 inhibitors. *Diabetes Obes Metab* 2019; 21: 1291–1298.

10. Johnson RJ, Nakagawa T, Sanchez-Lozada LG, et al. Sugar, uric acid, and the etiology of diabetes and obesity. *Diabetes* 2013; 62: 3307–3315.

11. Krishnan E, Pandya BJ, Chung L, et al. Hyperuricemia in young adults and risk of insulin resistance, prediabetes, and diabetes: a 15-year follow-up study. *Am J Epidemiol* 2012; 176: 108–116.

12. Yoo TW, Sung KC, Shin HS, et al. Relationship between serum uric acid concentration and insulin resistance and metabolic syndrome. *Circ J* 2005; 69: 928–933.

13. Zhu Y, Hu Y, Huang T, et al. High uric acid directly inhibits insulin signalling and induces insulin resistance. *Biochem Biophys Res Commun* 2014; 447: 707–714.

14. Kanbay M, Jensen T, Solak Y, et al. Uric acid in metabolic syndrome: from an innocent bystander to a central player. *Eur J Intern Med* 2016; 29: 3–8.

15. Sharma G, Dubey A, Nolkha N, et al. Hyperuricemia, urate-lowering therapy, and kidney outcomes: a systematic review and meta-analysis. *Ther Adv Musculoskel Dis* 2021; 13: 1–21.

16. Levy G, Shi JM, Cheetham TC, et al. Urate-lowering therapy in moderate to severe chronic kidney disease. *Perm J* 2018; 22: 17–142.

17. Seth R, Kydd ASR, Falzon L, et al. Preventing attacks of acute gout when introducing urate-lowering therapy: a systematic literature review. *J Rheumatol Suppl* 2014; 92: 42–47.

18. Wortmann RL, Macdonald PA, Hunt B, et al. Effect of prophylaxis on gout flares after the initiation of urate-lowering therapy: analysis of data from three phase III trials. *Clin Ther* 2010; 32: 2386–2397.

19. Chen Q, Wang Z, Zhou J, et al. Effect of urate-lowering therapy on cardiovascular and kidney outcomes: a systematic review and meta-analysis. *Clin J Am Soc Nephrol* 2020; 15: 1576–1586.

20. Filipooulos V, Hadjiyannakos D and Vlassopoulos D. New insights into uric acid effects on the progression and prognosis of chronic kidney disease. *Ren Fail* 2012; 34: 510–520.

21. Xin Y, Guo Y, Li Y, et al. Effects of sodium glucose cotransporter-2 inhibitors on serum uric acid in type 2 diabetes mellitus: a systematic review with an indirect comparison meta-analysis. *Saudi J Biol Sci* 2019; 26: 421–426.

22. Zhao Y, Xu L, Tian D, et al. Effects of sodium-glucose co-transporter 2 (SGLT2) inhibitors on serum uric acid level: a meta-analysis of randomized controlled trials. *Diabetes Obes Metab* 2018; 20: 458–462.

23. Hu X, Yang Y, Hu X, et al. Effects of sodium-glucose cotransporter 2 inhibitors on serum uric acid in patients with type 2 diabetes mellitus: a systematic review and network meta-analysis. *Diabetes Obes Metab* 2022; 24: 228–238.

24. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021; 372: n71.

25. Holger Schünemann JB, Guyatt G and Oxman A. Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach, 2013, https://www.rama.mahidol.ac.th/ceb/sites/default/files/public/pdf/journal_club/2017/GRADE%20handbook.pdf

26. Higgins JP and Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002; 21: 1539–1558.

27. van Houwelingen HC, Arends LR and Stijnen T. Advanced methods in meta-analysis: multivariate approach and meta-regression. *Stat Med* 2002; 21: 589–624.
28. Review manager (RevMan). 5.4 ed. London: The Cochrane Collaboration, 2020.

29. Stata statistical software: Release 16. College Station, TX: StataCorp, 2019.

30. Chino Y, Samukawa Y, Sakai S, et al. SGLT2 inhibitor lowers serum uric acid through alteration of uric acid transport activity in renal tubule by increased glycosuria. Biopharm Drug Dispos 2014; 35: 391–404.

31. Zanchi A, Burnier M, Muller ME, et al. Acute and chronic effects of SGLT2 inhibitor empagliflozin on renal oxygenation and blood pressure control in nondiabetic normotensive subjects: a randomized, placebo & controlled trial. J Am Heart Assoc 2020; 9: e016173.

32. Lee MMY, Brooksbank KJM, Wetherall K, et al. Effect of empagliflozin on left ventricular volumes in patients with type 2 diabetes, or prediabetes, and heart failure with reduced ejection fraction (SUGAR-DM-HF). Circulation 2021; 143: 516–525.

33. Ramírez-Rodríguez AM, González-Ortiz M and Martínez-Abundis E. Effect of dapagliflozin on insulin secretion and insulin sensitivity in patients with prediabetes. Exp Clin Endocrinol Diabetes 2020; 128: 506–511.

34. Ferrannini E, Ramos SJ, Salsali A, et al. Dapagliflozin monotherapy in type 2 diabetic patients with inadequate glycemic control by diet and exercise: a randomized, double-blind, placebo-controlled, phase 3 trial. Diabetes Care 2010; 33: 2217–2224.

35. Strojek K, Yoon KH, Hrubá V, et al. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycemic control with glimepiride: a randomized, 24-week, double-blind, placebo-controlled trial. Diabetes Obes Metab 2011; 13: 928–938.

36. Rosenstock J, Aggarwal N, Polidori D, et al. Dose-ranging effects of canagliflozin, a sodium-glucose cotransporter 2 inhibitor, as add-on to metformin in subjects with type 2 diabetes. Diabetes Care 2012; 35: 1232–1238.

37. Bailey CJ, Gross JL, Hennicken D, et al. Dapagliflozin add-on to metformin in type 2 diabetes inadequately controlled with metformin: a randomized, double-blind, placebo-controlled 102-week trial. BMC Med 2013; 11: 43.

38. Bode B, Stenlöf K, Sullivan D, et al. Efficacy and safety of canagliflozin treatment in older subjects with type 2 diabetes mellitus: a randomized trial. Hosp Pract (1995) 2013; 41: 72–84.

39. Häring HU, Merker L, Seewaldt-Becker E, et al. Empagliflozin as add-on to metformin plus sulfonylurea in patients with type 2 diabetes: a 24-week, randomized, double-blind, placebo-controlled trial. Diabetes Care 2013; 36: 3396–3404.

40. Roden M, Weng J, Eilbracht J, et al. Empagliflozin monotherapy with sitagliptin as an active comparator in patients with type 2 diabetes: a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Diabetes Endocrinol 2013; 1: 208–219.

41. Stenlöf K, Cefalu WT, Kim KA, et al. Efficacy and safety of canagliflozin monotherapy in subjects with type 2 diabetes mellitus inadequately controlled with diet and exercise. Diabetes Obes Metab 2013; 15: 372–382.

42. Wilding JP, Charpentier G, Hollander P, et al. Efficacy and safety of canagliflozin in patients with type 2 diabetes mellitus inadequately controlled with metformin and sulphonylurea: a randomised trial. Int J Clin Pract 2013; 67: 1267–1282.

43. Wilding JP, Ferrannini E, Fonseca VA, et al. Efficacy and safety of ipragliflozin in patients with type 2 diabetes inadequately controlled on metformin: a dose-finding study. Diabetes Obes Metab 2013; 15: 403–409.

44. Barnett AH, Mithal A, Manassie J, et al. Efficacy and safety of empagliflozin added to existing antidiabetes treatment in patients with type 2 diabetes and chronic kidney disease: a randomised, double-blind, placebo-controlled trial. Lancet Diabetes Endocrinol 2014; 2: 369–384.

45. Kadowaki T, Haneda M, Inagaki N, et al. Empagliflozin monotherapy in Japanese patients with type 2 diabetes mellitus: a randomized, 12-week, double-blind, placebo-controlled trial. Metab Dispos 2014; 1: 54–60.

46. Kashiwagi A, Kazuta K, Yoshida S, et al. Acute and chronic effects of SGLT2 inhibitor ipragliflozin in renal tubule by increased glycosuria. Alteration of uric acid transport activity in renal. J Diabetes Investig 2014; 5: 382–391.

47. Qiu R, Capuano G and Meininger G. Randomized, placebo-controlled, double-blind glycemic control trial of novel sodium-dependent glucose cotransporter 2 inhibitor ipragliflozin in Japanese patients with type 2 diabetes mellitus. J Diabetes Invest 2014; 5: 382–391.

48. Seino Y, Sasaki T, Fukatsu A, et al. Efficacy and safety of luseogliflozin monotherapy in Japanese patients with type 2 diabetes mellitus inadequately controlled on metformin plus sulfonylurea: a randomized trial. Diabetes Care 2013; 36: 3396–3404.

49. Häring HU, Merker L, Seewaldt-Becker E, et al. Empagliflozin as add-on to metformin plus sulfonylurea in patients with type 2 diabetes: a 24-week, randomized, double-blind, placebo-controlled trial. Diabetes Care 2013; 36: 3396–3404.
patients with type 2 diabetes mellitus: a 12-week, randomized, placebo-controlled, phase II study. *Curr Med Res Opin* 2014; 30: 1219–1230.

49. Schumm-Draeger P-M, Burgess L, Korányi L, et al. Twice-daily dapagliflozin co-administered with metformin in type 2 diabetes: a 16-week randomized, placebo-controlled clinical trial. *Diabetes Obes Metab* 2015; 17: 42–51.

50. Yale JF, Bakris G, Cariou B, et al. Efficacy and safety of canagliflozin over 52 weeks in patients with type 2 diabetes mellitus and chronic kidney disease. *Diabetes Obes Metab* 2014; 16: 1016–1027.

51. Ji L, Han P, Liu Y, et al. Canagliflozin in Asian patients with type 2 diabetes on metformin alone or metformin in combination with sulphonylurea. *Diabetes Obes Metab* 2015; 17: 23–31.

52. Nishimura R, Tanaka Y, Koiwai K, et al. Effect of empagliflozin monotherapy on postprandial glucose and 24-hour glucose variability in Japanese patients with type 2 diabetes mellitus: a randomized, double-blind, placebo-controlled, 4-week study. *Cardiovasc Diabetol* 2015; 14: 11.

53. Ross S, Thamer C, Cescutti J, et al. Efficacy and safety of empagliflozin twice daily versus once daily in patients with type 2 diabetes inadequately controlled on metformin: a 16-week, randomized, placebo-controlled trial. *Diabetes Obes Metab* 2015; 17: 699–702.

54. Tikkanen I, Narko K, Zeller C, et al. Empagliflozin reduces blood pressure in patients with type 2 diabetes and hypertension. *Diabetes Care* 2015; 38: 420–428.

55. Weber MA, Mansfield TA, Cain VA, et al. Blood pressure and glycaemic effects of dapagliflozin versus placebo in patients with type 2 diabetes on combination antihypertensive therapy: a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Diabetes Endocrinol* 2016; 4: 211–220.

56. Yang W, Han P, Min KW, et al. Efficacy and safety of dapagliflozin in Asian patients with type 2 diabetes after metformin failure: a randomized controlled trial. *J Diabetes* 2016; 8: 796–808.

57. Weber MA, Mansfield TA, Alessi F, et al. Effects of dapagliflozin on blood pressure in hypertensive diabetic patients on renin-angiotensin system blockade. *Blood Press* 2016; 25: 93–103.

58. Eriksson JW, Lundkvist P, Jansson PA, et al. Effects of dapagliflozin and n-3 carboxylic acids on non-alcoholic fatty liver disease in people with type 2 diabetes: a double-blind randomised placebo-controlled study. *Diabetologia* 2018; 61: 1923–1934.

59. Fioretto P, Del Prato S, Buse JB, et al. Efficacy and safety of dapagliflozin in patients with type 2 diabetes and moderate renal impairment (chronic kidney disease stage 3A): the DERIVE study. *Diabetes Obes Metab* 2018; 20: 2532–2540.

60. Seino Y, Sasaki T, Fukatsu A, et al. Efficacy and safety of luseogliflozin added to insulin therapy in Japanese patients with type 2 diabetes: a multicenter, 52-week, clinical study with a 16-week, double-blind period and a 36-week, open-label period. *Curr Med Res Opin* 2018; 34: 981–994.

61. Yang W, Ma J, Li Y, et al. Dapagliflozin as add-on therapy in Asian patients with type 2 diabetes inadequately controlled on insulin with or without oral antihyperglycemic drugs: a randomized controlled trial. *J Diabetes* 2018; 10: 589–599.

62. Kario K, Okada K, Kato M, et al. 24-Hour blood pressure-lowering effect of an SGLT-2 inhibitor in patients with diabetes and uncontrolled nocturnal hypertension: results from the randomized, placebo-controlled SACRA study. *Circulation* 2018; 139: 2089–2097.

63. Pollock C, Stefansson B, Reyner D, et al. Albuminuria-lowering effect of dapagliflozin alone and in combination with saxagliptin and effect of dapagliflozin and saxagliptin on glycaemic control in patients with type 2 diabetes and chronic kidney disease (DELIGHT): a randomised, double-blind, placebo-controlled trial. *Lancet Diabetes Endocrinol* 2019; 7: 429–441.

64. Griffin M, Rao VS, Ivey-Miranda J, et al. Empagliflozin in heart failure: diuretic and cardiorenal effects. *Circulation* 2020; 142: 1028–1039.

65. Lee SH, Min KW, Lee BW, et al. Effect of dapagliflozin as an add-on therapy to insulin on the glycemic variability in subjects with type 2 diabetes mellitus (DIVE): a multicenter, placebo-controlled, double-blind, randomized study. *Diabetes Metab J* 2020; 45: 339–348.

66. Shimizu W, Kubota Y, Hoshika Y, et al. Effects of empagliflozin versus placebo on cardiac sympathetic activity in acute myocardial infarction patients with type 2 diabetes mellitus: the EMBODY trial. *Cardiovasc Diabetol* 2020; 19: 148.

67. Packer M, Anker SD, Butler J, et al. Effect of empagliflozin on the clinical stability of patients with heart failure and a reduced ejection fraction:
the EMPEROR-reduced trial. *Circulation* 2021; 143: 326–336.

68. Ferreira JP, Inzucchi SE, Mattheus M, *et al.* Empagliflozin and uric acid metabolism in diabetes: a post-hoc analysis of the EMPA-REG outcome trial. *Diabetes Obes Metab* 2022; 24: 135–141.

69. Hao Z, Sun Y, Wen Y, *et al.* Effects and mechanisms of dapagliflozin treatment on ambulatory blood pressure in diabetic patients with hypertension. *Med Sci Monit* 2020; 26: e925987.

70. Okada K, Hoshide S, Kato M, *et al.* Safety and efficacy of empagliflozin in elderly Japanese patients with type 2 diabetes mellitus: a post hoc analysis of data from the SACRA study. *J Clin Hypertens* 2021; 23: 860–869.

71. Stack AG, Han D, Goldwater R, *et al.* Dapagliflozin added to verinurad plus febuxostat further reduces serum uric acid in hyperuricemia: the QUARTZ study. *J Clin Endocrinol Metab* 2021; 106: e2347–e2356.

72. Lytvyn Y, Škrtić M, Yang GK, *et al.* Glycosuria-mediated urinary uric acid excretion in patients with uncomplicated type 1 diabetes mellitus. *Am J Physiol Renal Physiol* 2015; 308: F77–F83.

73. So A and Thorens B. Uric acid transport and disease. *J Clin Invest* 2010; 120: 1791–1799.

74. Lytvyn Y, Perkins BA and Cherney DZ. Uric acid as a biomarker and a therapeutic target in diabetes. *Can J Diabetes* 2015; 39: 239–246.

75. Kimura T, Takahashi M, Yan K, *et al.* Expression of SLC2A9 isoforms in the kidney and their localization in polarized epithelial cells. *PLoS ONE* 2014; 9: e84996.

76. Skeith MD, Healey LA and Cutler RE. Effect of phloridzin on uric acid excretion in man. *Am J Physiol* 1970; 219: 1080–1082.

77. Dabla PK. Renal function in diabetic nephropathy. *World J Diabetes* 2010; 1: 48–56.

78. Eckardt KU, Bansal N, Coresh J et al. Improving the prognosis of patients with severely decreased glomerular filtration rate (CKD G4+): conclusions from a kidney disease: improving global outcomes (KDIGO) controversies conference. *Kidney Int* 2018; 93: 1281–1292.

79. FitzGerald JD, Dalbeth N, Mikuls T, *et al.* 2020 American College of Rheumatology guideline for the management of gout. *Arthritis Care Res (Hoboken)* 2020; 72: 744–760.

80. Vinik O, Wechalekar MD, Falzon L, *et al.* Treatment of asymptomatic hyperuricemia for the prevention of gouty arthritis, renal disease, and cardiovascular events: a systematic literature review. *J Rheumatol Suppl* 2014; 92: 70–74.