# 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

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# 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. Randomeffects 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% confidence interval (CI): -37.35 to -25.60] and without diabetes (-91.38  $\mu$ mol/L; 95% CI: -126.53 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 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

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# 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.<sup>1</sup> By blocking SGLT2 receptors located in the early proximal renal tubule, the renal reabsorption of glucose is limited to approximately 80 g/day,<sup>2</sup> thus lowering the glucose burden.

Beyond glycaemic control,<sup>3</sup> SGLT2 inhibitors have also been found to have beneficial effects on

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blood pressure,<sup>4</sup> body weight,<sup>5</sup> cardiometabolic markers,<sup>6</sup> cardiovascular outcomes<sup>7</sup> and renal function.<sup>8</sup> 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.<sup>9</sup>

An elevated level of urate is an independent predictor of diabetes and often precedes the development of diabetes.<sup>10,11</sup> High levels of urate have been found to inhibit post-receptor insulin signalling pathways, thus inducing insulin resistance.12,13 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.14 Previous studies on urate-lowering therapy demonstrated benefits such as an improvement in kidney function,<sup>15,16</sup> prophylaxis of gout flares<sup>17,18</sup> and a reduction in the risk of major adverse cardiovascular events and all-cause mortality.<sup>19</sup> Given the increasing amount of evidence implicating the contributory causal role of urate in the pathogenesis of cardiovascular and renal diseases,<sup>20</sup> 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).<sup>21–23</sup> 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.<sup>24</sup> 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 fulltext 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 umol/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

	Inclusion criteria	Exclusion criteria
Population	Patients with or without type 1 and 2 diabetes mellitus	
Intervention	SGLT2 inhibitors inclusive of Empagliflozin, Canagliflozin, Dapagliflozin, Ertugliflozin, Luseogliflozin, Ipragliflozin, Remogliflozin	
Comparison	Placebo	
Outcome	Serum urate	
Study design	<ul> <li>Articles in English or translated to English</li> <li>Randomized controlled trials</li> <li>Grey literature, conference abstracts, electronic and print information not controlled by commercial publishing of randomized clinical trials</li> <li>Databases: PubMed, Embase, Cochrane, SCOPUS</li> <li>Search period: Initiation-21 November 2020</li> </ul>	<ul> <li>Mixed methods research, meta- analyses, systematic reviews, cohort studies, case-control studies, cross- sectional studies and descriptive papers</li> <li>Case reports and series, ideas, editorials and perspectives</li> </ul>

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

PICOS: Population, Intervention, Comparison, Outcome, and Study design; SGLT2, sodium-glucose cotransporter.

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,<sup>25</sup> 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  $I^2 >50\%$ .<sup>26</sup> 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.<sup>27</sup> 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).<sup>28,29</sup>

### 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.*<sup>30</sup> and Zanchi *et al.*<sup>31</sup> while subjects



Figure 1. PRISMA flowchart.

with prediabetes were recruited in Lee *et al.*<sup>32</sup> and Ramírez-Rodríguez *et al.*<sup>33</sup>

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.*,<sup>36</sup> Qiu *et al.*<sup>47</sup> and Schumm-Draeger *et al.*,<sup>49</sup> 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  $\mu$ mol/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:

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 (%)	(mmol/L) LDL-C	Location
Ferrannini <i>et al.</i> <sup>34</sup>	24 weeks	T2DM patients	I	558	558	0.487	52	276	NR	32.6	8.29	NR	USA, Canada, Mexico, Russia
Strojek <i>et al.</i> <sup>35</sup>	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. <sup>36</sup>	12 weeks	T2DM patients	Metformin ≥1500 mg/day	386	386	9	53.1	198	NR	31.5	7.77	NR	12 countries
Bailey <i>et al.</i> <sup>37</sup>	16 weeks	T2DM patients	M etformin ≥1500 mg/day	546	546	6.07	53.9	292	NR	31.5	8.05	2.65	NR
Bode <i>et al.</i> <sup>38</sup>	102 weeks	T2DM patients	Monotherapy or combination therapy of antihyperglycaemic agents	714	714	11.7	63.6	396	561	31.6	7.7	2.37	Argentina, Brazil, Canada, Mexico, USA
Häring <i>et al.</i> <sup>39</sup>	78 weeks	T2DM patients	Metformin plus sulphonylurea	999	666	NR	57.1	339	NR	28.2	8.1	NR	17 countries
Roden <i>et al.</i> 40	24 weeks	T2DM patients	ı	676	676	NR	54.9	410	NR	28.4	7.88	2.83	9 countries
Stenlöf <i>et al.</i> <sup>41</sup>	25 weeks	T2DM patients	Metformin plus sulphonylurea	584	584	4.3	55.4	258	NR	31.6	80	NR	12 countries
Wilding et al. <sup>42</sup>	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. <sup>43</sup>	52 weeks	T2DM patients	Metformin ≥1500 mg/day	342	342	5.9	57.4	175	NR	31.7	7.78	NR	11 countries
Barnett <i>et al.</i> <sup>44</sup>	52 weeks	T2DM patients with CKD	Antihyperglycaemic and antihypertensive agents	738	738	NR	63.9	181	NR	30.7	œ	2.25	15 countries
Chino <i>et al.</i> <sup>30</sup>	1 week	Healthy subjects	1	24	0	0	28.9	24	NR	NR	5.1	NR	Japan
Kadowaki <i>et al.</i> <sup>45</sup>	12 weeks	T2DM patients	1	547	547	NR	57.5	410	NR	25.5	7.95	NR	Japan
Kashiwagi <i>et al.</i> <sup>46</sup>	12 weeks	T2DM patients	1	360	360	6.7	55.9	233	NR	25.7	8.33	NR	Japan
Qiu <i>et al.<sup>47</sup></i>	22 weeks	T2DM patients	Metformin ≥1500 mg/day	279	279	7.0	57.4	130	NR	32.5	7.6	N	USA, Canada, Czech Republic, Mexico, Romania, Russia, Slovakia
Seino <i>et al.</i> <sup>48</sup>	12 weeks	T2DM patients	1	239	239	9	57	160	NR	25	8.07	NR	Japan
Schumm-Draeger et al. <sup>49</sup>	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 <i>et al.</i> <sup>50</sup>	52 weeks	T2DM patients with CKD	Monotherapy or combination therapy of antihyperglycaemic agents	269	269	16.3	68.5	163	NR	33	00	NR	19 countries
Ji et al. <sup>51</sup>	18 weeks	T2DM patients	Metformin monotherapy or metformin plus sulphonylurea	676	676	6.7	56.2	362	NR	25.7	7.967	NR	China, Malaysia, Vietnam
Nishimura <i>et al.</i> <sup>52</sup>	29 days	T2DM patients	1	90	60	NR	62.7	47	NR	24.3	7.91	NR	Japan
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Therapeutic	Advances	in	Chronic	Disease	13

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 (%)	(mmol/L) LDL-C	Location
Ross <i>et al.</i> <sup>53</sup>	17 weeks	T2DM patients on metformin	Metformin ≥1500 mg/day	983	983	NR	58.2	520	NR	31.8	7.77	NR	NR
Tikkanen <i>et al.</i> <sup>54</sup>	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 <i>et al.</i> <sup>55</sup>	13 weeks	T2DM patients with hypertension	Antihyperglycaemic agents, plus a renin-angiotensin system blocker and an additional antihypertensive drug	677	449	7.5	R	247	449	R	8.05	NR	16 countries
Yang <i>et al.</i> <sup>56</sup>	24 weeks	T2DM patients	Metformin ≥1500 mg/day	777	444	4.93	53.7	241	NR	26.1	8.13	NR	China and other Asian countries
Zinman <i>et al.</i> 7	3.1 years (median)	T2DM patients	Antihyperglycaemic agent(s)	7034	7034	R	63.1	5026	NR	30.6	8.1	2.2	North America, Australia, NZ, Latin America, Europe, Africa, Asia
Weber <i>et al.</i> <sup>57</sup>	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 <i>et al.</i> <sup>58</sup>	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 <i>et al.</i> 59	27 weeks	T2DM patients with CKD	Antihyperglycaemic agent(s)	261	261	14.4	65.8	182	NR	32.1	8.12	N	USA, Canada, Bulgaria, the Czech Republic, Italy, Poland, Spain and Sweden.
Seino <i>et al.<sup>60</sup></i>	16 weeks	T2DM patients on insulin therapy	Insulin monotherapy at a fixed daily dose ranging from 8 to 40U	233	233	11.8	57.3	163	NR	25.3	8.74	NR	Japan
Yang <i>et al.</i> <sup>61</sup>	24 weeks	T2DM patients on insulin therapy	Insulin at a stable dose >20U with or without other antihyperglycaemic agents	272	272	12.45	57.5	130	NR	26.5	8.55	R	China, South Korea, Singapore
Kario <i>et al.</i> <sup>62</sup>	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 <i>et al.</i> <sup>63</sup>	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
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Study Me of I	ean length	Study population	Concomitant medications	Sample	Sample size	Duration	Age	Males	Hvpertension	Body mass	HbA1c	LDL-C	Location
	follow-up			size	(T2DM)	of DM (in years)	(mean)			index (kg/m²)	(%)	(mmol/L)	
Zanchi <i>et al.</i> <sup>31</sup>	veeks	Healthy subjects	I	45	0	0	33.2	27	0	28.2	5.4	NR	Switzerland
Griffin <i>et al.<sup>64</sup></i> 2w	veeks	T2DM patients with chronic stable heart failure	With or without loop diuretics	20	20	R	60	13	19	37	7.1	NR	USA
Lee <i>et al.</i> <sup>22</sup> 40	weeks	T2DM patients or prediabetic patients with heart failure and reduced ejection fraction	With or without other antihyperglycaemic agents	105	82	6.7	х Х	и Z	ж	х	7.2	л	Scotland
Lee <i>et al.</i> <sup>65</sup> 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
Ramírez- Rodríguez <i>et al.</i> <sup>33</sup>	weeks	Predia betic patients	1	24	0	0	49.1	7	0	31.7	5.8	4	Mexico
Shimizu <i>et al.</i> <sup>66</sup> 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 <i>et al.<sup>67</sup></i> 16	months	Patients with heart failure and reduced ejection fraction	Therapy for heart failure, including diuretics, ACEI, ARB, neprilysin, beta- blockers, mineralocorticoid receptor antagonists, and when indicated, cardiac devices.	3730	1856	R	66.8	2837	2698	27.9	Х Х	N	Multicenter
Ferreira <i>et al.</i> <sup>68</sup> 2.6	Śyears	T2DM patients	1	7020	7020	7.93	63.1	5016	6419	30.6	8.1	NR	United States
Hao et al. <sup>69</sup> 3n	nonths	T2DM patients with hypertension	Antihypertensive drugs	486	486	3.5	42.1	323	486	24.6	7.0	NR	China
Okada <i>et al.</i> <sup>70</sup> 12	weeks	T2DM patients with hypertension	Antihyperglycaemic and antihypertensive agents	131	131	10.9	70.1	99	131	26	6.6	107.3	Japan
Stack <i>et al.</i> " 1 v	×ee k	Non-DM patients with asymptomatic hyperuricaemia, on concomitant serum urate- lowering therapy	Oral verinurad 9 mg plus febuxostat 80 mg	36	36	ЖZ	42.3	35	х	27.9	к Z	ж Z	United States

				Mean Difference	Mean Difference
Study or Subgroup	Mean Difference	SE	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Bailey 2013 (10mgDapa)	-51.12	84.0968	0.1%	-51.12 [-215.95, 113.71]	
Bailey 2013 (2.5mgDapa)	-54.12	73.9064	0.1%	-54.12 [-198.97, 90.73]	
Balley 2013 (5mgDapa)	-44.62	84.0968	0.1%	-44.62 [-209.45, 120.21]	
Barnett 2014 (TurngEmpa Stage2CKD)	-31	9.0914	1.2%	-31.00 [-48.82, -13.18]	
Barnett 2014 (25mgEmpa Stage2CKD)	-30	8 9947	1.1%	-50.00[-52.09,-7.91]	
Barnett 2014 (25mgEmpa Stage4CKD)	51	23 6735	0.6%	51 00 [4 60 97 40]	
Bode 2013 (100mgCana)	-41.4863	5.4158	1.4%	-41.49[-52.10, -30.87]	-
Bode 2013 (300mgCana)	-45 1188	5 5621	1.4%	-45 12 [-56 02 -34 22]	-
Chino 2014 (10mgLuseo)	-126.06786	17.21946	0.8%	-126.07 [-159.82, -92.32]	<u> </u>
Chino 2014 (5mgLuseo)	-117.074484	17.522808	0.8%	-117.07 [-151.42, -82.73]	<u> </u>
Eriksson 2018 (10mgDapa)	-74	14.4278	0.9%	-74.00 [-102.28, -45.72]	<u> </u>
Ferrannini 2010 (10mgDapa)	-39.8	8.0623	1.3%	-39.80 [-55.60, -24.00]	
Ferrannini 2010 (2.5mgDapa)	-27.4	8.2073	1.3%	-27.40 [-43.49, -11.31]	-
Ferrannini 2010 (5mgDapa)	-38.7	8.2807	1.3%	-38.70 [-54.93, -22.47]	
Ferreira 2021 (10mgEmpa Week108)	-19.63	2.2783	1.5%	-19.63 [-24.10, -15.16]	-
Ferreira 2021 (10mgEmpa Week206)	-27.9579	5.9187	1.4%	-27.96 [-39.56, -16.36]	-
Ferreira 2021 (10mgEmpa Week52)	-22.6042	1.9749	1.5%	-22.60 [-26.47, -18.73]	•
Ferreira 2021 (25mgEmpa Week108)	-21.4145	2.1236	1.5%	-21.41 [-25.58, -17.25]	-
Ferreira 2021 (25mgEmpa Week206)	-22.6042	5.9187	1.4%	-22.60 [-34.20, -11.00]	
Ferreira 2021 (25mgEmpa Week52)	-20.8197	1.9749	1.5%	-20.82 [-24.69, -16.95]	-
Fioretto 2018 (10mgDapa)	-24.9	8.0614	1.3%	-24.90 [-40.70, -9.10]	
Griffin 2020 (10mgEmpa)	0.6	0.9879	1.6%	0.60 [-1.34, 2.54]	f
Hao 2020 (5mgDapa)	-23	2.8753	1.5%	-23.00 [-28.64, -17.36]	~
Haring 2013 (10mgEmpa)	-39	118.8697	0.0%	-39.00 [-271.98, 193.98]	
Haring 2013 (25mgEmpa)	-37	114.5513	0.0%	-37.00 [-261.52, 187.52]	
JI 2015 (100mgCana)	-29.7948	6.4139	1.4%	-29.79 [-42.37, -17.22]	-
JI 2015 (300mgCana)	-34.8723	6.1083	1.4%	-34.87 [-46.84, -22.90]	
Kadowaki 2014 (10mgEmpa)	-51	10.8455	1.1%	-51.00 [-72.26, -29.74]	
Kaαowaki 2014 (25mgEmpa)	-62	9.9674	1.2%	-62.00 [-81.54, -42.46]	<u> </u>
Kaαowaki 2014 (50mgEmpa)	-45	10.2996	1.2%	-45.00 [-65.19, -24.81]	
Kadowaki 2014 (5mgEmpa)	-57	10.2996	1.2%	-57.00 [-77.19, -36.81]	
Kario 2019 (10mgEmpa)	-32.714	9.671448	1.2%	-32.71 [-51.67, -13.76]	
Kasniwagi 2014 (100mgipra)	-7.7324	5.3274	1.4%	-7.73 [-18.17, 2.71]	T
Kashiwagi 2014 (12.5mgipra)	-2.974	4.3858	1.5%	-2.97 [-11.57, 5.62]	1
Kashiwagi 2014 (25mgipra)	-23.1972	5.0475	1.4%	-23.20 [-33.09, -13.30]	-
Kashiwagi 2014 (50mglpra)	-17.844	6.0985	1.4%	-17.84 [-29.80, -5.89]	-
Lee 2020 (10mgEmpa)	-66.2	13.1125	1.0%	-66.20 [-91.90, -40.50]	
Lee SH 2020 (10mgDapa)	-13.6804	10.635024	1.1%	-13.68 [-34.52, 7.16]	
Nishimura 2015 (10mgEmpa)	-17	16.9262	0.8%	-17.00[-50.17, 16.17]	
Nishimura 2015 (25mgEmpa) Skada 2824 (48mgEmpa, 25 years ald and above)	-58	18.798	0.7%	-58.00 [-94.84, -21.16]	
Okada 2021 (10mgEmpa, 75 years old and above)	-17.2506	3.5215	1.5%	-17.25 [-24.15, -10.35]	-
Okada 2021 (10mgEmpa, less than 75 years old)	-35.0901	1.48/1	1.0%	-35.10 [-38.01, -32.18]	
Packer 2021 (10mgEmpa)	-52.2/1024	5.983688	1.4%	-52.27 [-64.00, -40.54]	- <u> </u>
Pollock 2019 (TorngDapa) Oliv 2014 (150mmCone)	-5.3	8.9287	1.2%	-5.30 [-22.80, 12.20]	
Qiu 2014 (150mgCana) Qiu 2014 (50mgCana)	-30.02	7 0000	1.170	-30.02 [-09.12, -12.12]	
Giu zuria (surriguaria) Deminar Dedvizuer 2020 (40mm/Dene)	-39./454	7.9983	1.3%	-39.75[-55.42,-24.07]	
Ramirez-Rounguez 2020 (TomgDapa) Rodon 3013 (19maEmpo)	-02	21.3100	0.0%	-02.00[-103.70,-20.22]	
Roden 2013 (TomgEmpa)	-00	J.34J2	1.470	-30.00 [-00.40, -47.32]	_
Rouen 2015 (2011gEmpa)	-02	0.0407	1.470	-02.00 [-72.07, -01.10]	<u> </u>
Rosenstock 2012 (100mgquCana)	-53.2300	0.522	1.2.%	-53.20 [-50.74, -21.77]	<u> </u>
Rosenstock 2012 (200mg/dCana)	-39.0672	8 452108	1.2%	-38 07 [-54 63 -21 50]	<u></u>
Rosenstock 2012 (300mgaluCana)	-36.699	8 462108	1.3%	-36.69 [-59.05, -21.30]	
Rosenstock 2012 (50mggdCana)	-28 5504	9 403788	1.2%	-28 55 [-46 98 -10 12]	
Ross 2015 (10mggdEmpa)	-51	113 719	0.0%	-51 00 1-273 89, 171 891	
Ross 2015 (12 5mgbidEmpa)	-65	112 8938	0.0%	-65 00 F-286 27 156 271	·
Ross 2015 (25mggdEmpa)	-56	110 4355	0.0%	-56 00 [-272 45 160 45]	
Ross 2015 (SmobidEmpa)	-65	106.4002	0.0%	-65.00 [-273.54, 143.54]	
Schumm-Draeger 2014 (10mggdDapa)	-48.18	6.16	1.4%	-48.18 [-60.2536.11]	-
Schumm-Draeger 2014 (2.5mgbidDapa)	-38.07	5.63	1.4%	-38.07 [-49.10, -27.04]	-
Schumm-Draeger 2014 (SmgbidDapa)	-39.26	6.33	1.4%	-39.26 [-51.6726.85]	-
Seino 2014 (0.5mgLuseo)	-15.4648	8.487796	1.3%	-15.46 [-32.10, 1.17]	
Seino 2014 (2.5mgLuseo)	-27.3608	8.487796	1.3%	-27.36 [-44.00, -10.73]	
Seino 2014 (5mgLuseo)	-23.792	9.659552	1.2%	-23.79 [-42.72, -4.86]	
Seino 2018 (2.5mgLuseo)	2.974	5.97774	1.4%	2.97 [-8.74, 14.69]	+
Shimizu 2020 (10mgEmpa)	-59.48	11.134656	1.1%	-59.48 [-81.30, -37.66]	
Stack 2021 (10mgDapa)	-62.3	10.4594	1.2%	-62.30 [-82.80, -41.80]	
Stenlöf 2013 (100mgCana)	-48.8365	5.6445	1.4%	-48.84 [-59.90, -37.77]	-
Stenlöf 2013 (300mgCana)	-52.6363	5.6195	1.4%	-52.64 [-63.65, -41.62]	-
Strojek 2011 (10mgDapa)	-27.36	6.8383	1.4%	-27.36 [-40.76, -13.96]	-
Strojek 2011 (2.5mgDapa)	-22.6	6.4154	1.4%	-22.60 [-35.17, -10.03]	
Strojek 2011 (5mgDapa)	-27.36	7.1826	1.3%	-27.36 [-41.44, -13.28]	-
Tikkanen 2015 (10mgEmpa)	-33.04	4.4076	1.5%	-33.04 [-41.68, -24.40]	-
Fikkanen 2015 (25mgEmpa)	-30.29	4.4095	1.5%	-30.29 [-38.93, -21.65]	-
Neber 2015 (10mgDapa)	-23.67	5.1174	1.4%	-23.67 [-33.70, -13.64]	-
Neber 2016 (10mgDapa)	-17.844	6.06696	1.4%	-17.84 [-29.74, -5.95]	-
//ilding 2013a (100mgCana)	-30.6927	9.5308	1.2%	-30.69 [-49.37, -12.01]	
/viiding 2013a (300mgCana)	-34.2997	9.1273	1.2%	-34.30 [-52.19, -16.41]	
/vitaing 2013b (12.5mgipra)	-37.8	8.7009	1.3%	-37.80 [-54.85, -20.75]	
winding 2013b (150mglpra)	-29.2	10.3624	1.2%	-29.20 [-49.51, -8.89]	
/vitaing 2013b (300mgipra)	-30.8	9.633	1.2%	-30.80 [-49.68, -11.92]	
/viruing ∠0130 (50mgipra)	-27.1	8.6754	1.3%	-27.10[-44.10, -10.10]	
raie ∠014 (100mgCana)	13.0044	15.9708	0.9%	13.00 [-18.30, 44.31]	<u>+-</u>
rale 2014 (300mgCana)	11.7458	14.1163	1.0%	11.75 [-15.92, 39.41]	+
rang 2015 (10mgDapa)	-18.4	45.49747413	0.2%	-18.40 [-107.57, 70.77]	
(ang 2015 (5mgDapa)	-19	45.8853539	0.2%	-19.00 [-108.93, 70.93]	
rang 2018 (10mgDapa)	-9.5168	6.370308	1.4%	-9.52 [-22.00, 2.97]	
Zanchi 2019 (10mgEmpa)	-97	11.3842	1.1%	-97.00 [-119.31, -74.69]	
Zinman 2015 (10mgEmpa)	-18.3516	41.1540138	U.2%	-18.35 [-99.01, 62.31]	
Zinman 2015 (25mgEmpa)	-20.5642	40.06509016	U.3%	-20.56 [-99.09, 57.96]	
Total (95% CI)			100.0%	33 03 1 37 30 30 601	<u>،</u>
Hotorogonoity Touis- 214 05: 05:2 - 4407 70 - 16 - 00	VB = 0.000043-17	0.204	100.0%	-33.03 [-37.38, -28.69]	
Test for overall effect: Z = 14.89 (P < 0.00001)	r (r ≤ 0.00001), i*=	J∠70			-200 -100 0 100 200 Favours ISGLT2il Favours (Placebol
					r avours [OGETZI] i avours [Flace00]

Figure 2. Forest plot of mean change in serum urate in  $\mu$ mol/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  $36.62 \,\mu mol/L$  (95% CI: -42.67 to -30.56, p < 0.001) (Figure 3(b)). Empagliflozin led to a mean reduction in urate

of 35.19µmol/L (95% CI: -42.61 to -27.78, p < 0.001) (Figure 3(c)), while dapagliflozin had a mean reduction in urate of  $30.32\,\mu mol/L$  (95% CI: -36.20 to -24.43, p < 0.001) (Figure 3(d)), and ipragliflozin had a mean reduction in urate of

Study or Subgroup Mean D	ifference S	E Weiaht	Mean Di IV. Rai	nerence ndom, 95% Cl	Mean Diffe IV. Random.	rence 95% Cl
Chino 2014 (10mgLuseo) -1	26.06786 17.2194	6 15.1% -1	26.07 [-15	59.82, -92.321		
Chino 2014 (5mgLuseo) -11	7.074484 17.52280	8 15.1% -1	17.07 [-19	51.42, -82.73]	<b>—</b>	
Seino 2014 (0.5mgLuseo)	-15.4648 8.48779	6 17.4%	-15.46	[-32.10, 1.17]		
Seino 2014 (2.5mgLuseo)	-27.3608 8.48779	6 17.4%	-27.36 [-4	44.00, -10.73]		
Seino 2014 (5mgLuseo)	-23.792 9.65955	2 17.2%	-23.79 [	-42.72, -4.86]		
Seino 2018 (2.5mgLuseo)	2.974 5.9777	4 17.8%	2.97	[-8.74, 14.69]	+	
Total (95% CI)		100.0%	-47.73 [-7	79.50, -15.96]	-	
Heterogeneity: $Tau^2 = 1438.01$ ; $Chi^2 = Test for overall effect: 7 = 2.94 (P = 0.0$	84.43, df = 5 (P < 0.0	0001); I² = 94%	6	-200	-100 0	100 2
					Favours [SGLT2i] Fa	avours [Placebo]
h)						
Study or Subgroup	Mean Difference	SE Weigh	Mean nt IV.F	n Difference Random, 95% Cl	Mean Diffe	erence 95% Cl
Bode 2013 (100mgCana)	-41 4863	5 4158 7 99	6 -41 49	1-52 10 -30 871		,0070
Bode 2013 (300mgCana)	-45 1188	5.5621 7.89	% -4512	[-56.02]-34.22]		
Ji 2015 (100mgCana)	-29.7948	6.4139 7.29	6 -29.79	[-42.3717.22]		
Ji 2015 (300mgCana)	-34.8723	6.1083 7.49	6 -34.87	[-46.84, -22.90]		
Qiu 2014 (150mgCana)	-35.62 1	1.9906 4.09	% -35.62	[-59.12, -12.12]		
Qiu 2014 (50mgCana)	-39.7454	7.9983 6.19	6 -39.75	[-55.42, -24.07]		
Rosenstock 2012 (100mgqdCana)	-39.2568	8.922 5.69	% -39.26	[-56.74, -21.77]	— <b>—</b>	
Rosenstock 2012 (200mgqdCana)	-54.1268 9.8	97472 5.09	6 -54.13	[-73.53, -34.73] =		
Rosenstock 2012 (300mgbidCana)	-38.0672 8.4	52108 5.89	% -38.07	[-54.63, -21.50]		
Rosenstock 2012 (300mgqdCana)	-35.688 8.4	52108 5.89	% -35.69	[-52.25, -19.12]		
Rosenstock 2012 (50mgqdCana)	-28.5504 9.4	03788 5.39	% -28.55	[-46.98, -10.12]		
Steniot 2013 (100mgCana)	-48.8365	5.6445 7.79	% -48.84 K 50.04	[-59.90, -37.77]		
Stenior 2013 (300mgCana)	-52.0303	5.6195 7.73	% -52.64 K - 20.60	[-03.05,-41.02]		
Wilding 2013a (100mgCana) Wilding 2013a (200mgCana)	-30.0927	9.5308 5.2% 04373 640	No -30.09 K - 34.30	[-49.37,-1Z.01] [[60.10] 16.41]		
Vale 2014 (100maCana)	-34.2997	9.1273 J.47 5.0709 2.90	∧ง -34.30 K. 1ว∩เ	0.619.20.44.21		
Yale 2014 (100mgCana)	11 7458 1	4.1163 3.39	% 11.7	5 [-15 92 39 41]		
raio zor r (ocorrigo ana)				0 [ 10:02, 00:11]		
Total (95% CI)		100.09	6 -36.62	[-42.67, -30.56]	•	
Heterogeneity: Tau <sup>2</sup> = 92 07: Chi <sup>2</sup> = 41 2	22 df = 16 /P = 0.0006					
Test for overall effect: Z = 11.85 (P < 0.0	0001)	);  * = 61%			-50 -25 Ó Favours (SGLT2i) F	2'5 5'0 avours [Placebo]
Test for overall effect: Z = 11.85 (P < 0.0 C)	0001)	); I*= 61%	- Weight	Mean Difference	-50 -25 0 Favours (SGLT2i) F Mean (	25 50 "avours [Placebo] Difference
Test for overall effect: Z = 11.85 (P < 0.0 C) Study or Subgroup Barnett 2014 (10moEmna Stane 20KD)	0001) Mean Differen	); i*= 61 %6	E Weight	Mean Difference IV, Random, 95% C -31 00 L48 82 - 13 18	-50 -25 0 Favours [SGLT2i] F Mean I IV, Rand	25 50 Favours [Placebo] Difference om, 95% Cl
Test for overall effect: Z = 11.85 (P < 0.0 C) Study or Subgroup Barnett 2014 (10mgEmpa Stage2CKD) Barnett 2014 (25mgEmpa Stage2CKD)	0001) Mean Differen	);  r = 61 % ce <u>Si</u> 31 9.091/ 30 11.270	E <u>Weight</u> 4 3.4% 3 3.1%	Mean Difference IV, Random, 95% C -31.00 [+8.82, -13.18] -30.00 [+52.09 - 7.8]	-50 -25 0 Favours [SGLT2i] F Mean I IV, Rand	25 50 avours [Placebo] Difference om, 95% Cl
Test for overall effect: Z = 11.85 (P < 0.0 C) Study or Subgroup Barnett 2014 (10mgEmpa Stage2CKD) Barnett 2014 (25mgEmpa Stage2CKD) Barnett 2014 (25mgEmpa Stage2CKD)	0001) Mean Differen	ce SI 31 9.0914 30 11.2703 -5 8.9943	E Weight 4 3.4% 3 3.1% 7 3.4%	Mean Difference IV, Random, 95% C -31.00 (+48.82, -13.18 -30.00 (-52.09, -7.91) -5.00 (-22.63, 12.63)	-50 -25 0 Favours [SGLT21] F Mean 1 I IV, Rand	25 50 avours [Placebo] om, 95% Cl
Test for overall effect: Z = 11.85 (P < 0.0 C) Study or Subgroup Barnett 2014 (10mgEmpa Stage2CKD) Barnett 2014 (25mgEmpa Stage2CKD) Barnett 2014 (25mgEmpa Stage2CKD) Barnett 2014 (25mgEmpa Stage4CKD)	0001) Mean Differen	ce SI 31 9.091 30 11.270 -5 8.994 51 23.673	E Weight 4 3.4% 3 3.1% 7 3.4% 5 1.6%	Mean Difference IV, Random, 95% C -31.00 (+48.82, -13.18 -30.00 (-52.09, -7.91 -5.00 (-22.63, 12.63 51.00 (4.60, 97.40)	-50 -25 Ó Favours (SGLT21) F Mean t I IV, Rand	25 50 avours [Placebo] Difference om, 95% Cl
Test for overall effect: Z = 11.85 (P < 0.0 C) Study or Subgroup Barnett 2014 (10mgEmpa Stage2CKD) Barnett 2014 (25mgEmpa Stage3CKD) Barnett 2014 (25mgEmpa Stage4CKD) Ferreira 2021 (10mgEmpa Week108)	0001) Mean Differen 	ce SI 31 9.091- 30 11.2703 51 23.6733 63 2.278	E Weight 4 3.4% 3 3.1% 5 1.6% 3 4.2%	Mean Difference IV, Random, 95% C 31.00 [48.82, -13.18 -30.00 [-52.09, -7.91 -5.00 [-22.63, 12.63 51.00 [4.60, 97.40 -19.63 [-24.10, -15.16	-50 -25 0 Favours (SGLT2I) F Mean ( IV, Rand	25 50 iavours [Placebo] Mifference om, 95% Cl
Test for overall effect: Z = 11.85 (P < 0.0 Study or Subgroup Barnett 2014 (10mgEmpa Stage2CKD) Barnett 2014 (25mgEmpa Stage2CKD) Barnett 2014 (25mgEmpa Stage3CKD) Barnett 2014 (25mgEmpa Stage4CKD) Ferreira 2021 (10mgEmpa WeeK108) Ferreira 2021 (10mgEmpa WeeK108) Ferreira 2021 (10mgEmpa WeeK108)	Mean Differen 	ce SI 31 9.091 30 11.270 -5 8.994 51 23.673 63 2.278 79 5.918 42 12	E Weight 4 3.4% 3 3.1% 5 1.6% 3 4.2% 7 3.9%	Mean Difference IV, Random, 95% C -31.00 [48.82, -13.18 -30.00 [52.09, -7.91 -5.00 [22.63, 12.63 -19.63 [24.10, -15.16 -27.96 [39.56] -16.35 -20.01 (24.19.27)	-50 -25 0 Favours [SGLT2i] F Mean ( IV, Rand	25 50 (avours (Placebo) )ifference om, 95% Cl
Test for overall effect: Z = 11.85 (P < 0.0 Study or Subgroup Barnett 2014 (10mgEmpa Stage2CKD) Barnett 2014 (25mgEmpa Stage2CKD) Barnett 2014 (25mgEmpa Stage3CKD) Barnett 2014 (25mgEmpa Stage3CKD) Ferreira 2021 (10mgEmpa Week108) Ferreira 2021 (10mgEmpa Week208) Ferreira 2021 (10mgEmpa Week208) Ferreira 2021 (10mgEmpa Week208) Ferreira 2021 (10mgEmpa Week208)		); I*= 81 % <u>ce</u> SI 31 9.091 -5 8.994 51 23.673 79 5.918 42 1.974 45 2.1274	E Weight 4 3.4% 3 3.1% 5 1.6% 3 4.2% 9 4.2% 9 4.2% 6 4.2%	Mean Difference IV. Random, 95% C -31.00 [+48.82, -13.16 -30.00 [+52.03, -7.43] -5.00 [-2.63, 12.63 -5.100 [46.0] 97.40 -19.63 [-24.10, -15.16 -27.86 [-39.56, -16.36 -22.60 [-26.47, -18.73] -21.41 [+25.58, -17.25]	-50 -25 0 Favours [SGLT2i] F Mean f IV, Rand	25 50 (avours [Placebo] (m, 95% Cl
Test for overall effect: Z = 11.85 (P < 0.0 Study or Subgroup Barnett 2014 (10mgEmpa Stage2CKD) Barnett 2014 (25mgEmpa Stage2CKD) Barnett 2014 (25mgEmpa Stage4CKD) Barnett 2014 (25mgEmpa Stage4CKD) Ferreira 2021 (10mgEmpa Week108) Ferreira 2021 (10mgEmpa Week52) Ferreira 2021 (10mgEmpa Week52) Ferreira 2021 (25mgEmpa Week108) Ferreira 2021 (25mgEmpa Week108) Ferreira 2021 (25mgEmpa Week206)		ce SI 31 9.091 -5 8.994 51 23.673 53 2.278 79 5.918 42 1.974 45 2.123	E Weight 4 3.4% 7 3.4% 5 1.6% 3 4.2% 7 3.9% 9 4.2% 7 3.9%	Mean Difference IV, Random, 95% C -31.00 [+48.82, -13.18 -30.00 [+52.09, -731] -500 [-22.63, 12.63 -51.00 [4.60, 97.40 -19.63 [-24.10, -15.16] -27.96 [-39.65, -16.36 -22.60 [-26.47, -18.73] -21.41 [-25.59, -17.25 -22.60 [-34.20, -11.00]	-50 -25 0 Favours [SGLT2i] F Mean t IV, Rand	25 50 (avours [Placebo] )ifference on, 95% Cl
Test for overall effect: Z = 11.85 (P < 0.0 Study or Subgroup Barnett 2014 (10mgEmpa Stage2CkD) Barnett 2014 (25mgEmpa Stage3CkD) Barnett 2014 (25mgEmpa Stage3CkD) Barnett 2014 (25mgEmpa Stage4CkD) Ferreira 2021 (10mgEmpa Week108) Ferreira 2021 (10mgEmpa Week52) Ferreira 2021 (25mgEmpa Week108) Ferreira 2021 (25mgEmpa Week108) Ferreira 2021 (25mgEmpa Week1206) Ferreira 2021 (25mgEmpa Week52)	Mean Differen 19. - 27.85 - 22.60 - 21.41 - 22.60 - 20.81	); I*= 81 % 20 21 23 23 23 23 23 23 23 23 23 23	E Weight 4 3.4% 3 3.1% 7 3.4% 5 1.6% 3 4.2% 6 4.2% 6 4.2% 9 4.2% 9 4.2%	Mean Difference IV, Random, 95% C 31.00 [48.82, -13.18 -30.00 [-52.09, -74] -5.00 [-22.63, 12.63 51.00 [4.60, 97.40 -27.96 [-39.56, -16.36 -22.60 [-26.47, -18.73 -21.41 [-25.58, -17.26] -22.60 [-24.07, -11.00 -20.82 [-24.69, -16.95]	-50 -25 0 Favours [SGLT2i] F Mean I IV, Rand	25 50 [avours [Placebo] )ifference om, 95% Cl
Test for overall effect: Z = 11.85 (P < 0.0 Study or Subgroup Barnett 2014 (10mgEmpa Stage2CkD) Barnett 2014 (25mgEmpa Stage2CkD) Barnett 2014 (25mgEmpa Stage2CkD) Barnett 2014 (25mgEmpa Stage4CkD) Ferreira 2021 (10mgEmpa Week108) Ferreira 2021 (10mgEmpa Week108) Ferreira 2021 (25mgEmpa Week208) Ferreira 2021 (25mgEmpa Week108) Ferreira 2021 (25mgEmpa Week108) Ferreira 2021 (25mgEmpa Week208) Ferreira 2021 (25mgEmpa Week52) Griffin 2020 (10mgEmpa)	Mean Differen 	Cce         SI           31         9.091           30         1.1.270           36         2.273           57         8.994           51         2.3.673           79         5.918           42         1.974           45         2.123           42         5.918           37         1.974           36         0.987	E Weight 4 3.4% 3 3.1% 7 3.6% 3 4.2% 7 3.9% 9 4.2% 9 4.2% 9 4.2% 9 4.2% 9 4.2% 9 4.2%	Mean Difference IV, Random, 95% C -31.00 [48.82, -13.18 -30.00 [52.09, -7.91 -5.00 [22.63, 12.63 -19.63 [24.10, -15.16 -27.96 [39.56, -16.35 -22.60 [26.47, 18.73 -21.41 [25.58, -17.25 -20.60 [34.20, -11.05 -0.02 [24.69, -16.95 -0.06 [-1.34, 25.46 -0.01 [24.04, -0.05]	-50 -25 0 Favours [SGLT2i] F Mean ( IV, Rand	25 50 (avours (Placebo) )ifference om, 95% Cl
Test for overall effect: Z = 11.85 (P < 0.0 Study or Subgroup Barnett 2014 (10mgEmpa Stage2CKD) Barnett 2014 (25mgEmpa Stage2CKD) Barnett 2014 (25mgEmpa Stage3CKD) Barnett 2014 (25mgEmpa Stage4CKD) Ferreira 2021 (10mgEmpa Week108) Ferreira 2021 (10mgEmpa Week206) Ferreira 2021 (25mgEmpa Week206) Haring 2013 (25mgEmpa) Haring 2013 (25mgEmpa)	Mean Differen 	Ce         SI           31         9.091           30         11.270           58.994         56           59.591         51           59         5.918           42         1.974           45         1.23673           97         1.974           45         0.987           39         118.869           37         114.651	E Weight 4 3.4% 3 3.1% 5 1.6% 3 4.2% 7 3.9% 9 4.2% 6 4.2% 9 4.2% 9 4.2% 9 4.2% 9 4.2% 9 1.0% 3 0.1%	Mean Difference IV, Random, 95% C -31.00 [+8.82, -13.18 -30.00 [+52.08, -7.48] -5.00 [-26.83, 12.63 -5.00 [-26.83, 12.63 -19.63 [-24.10, -15.16 -22.60 [-26.47, -18.73 -21.41 [-25.56, -17.25 -22.60 [-34.20, -11.00 -20.82 [-24.69, -16.36 0.60 [+1.34, 2.54 -39.00 [-271.98, 193.86	-50 -25 0 Favours [SGLT2i] F Mean ( IV, Rand	25 50 (avours [Placebo] )ifference om, 95% Cl
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Test for overall effect: Z = 11.85 (P < 0.0 Study or Subgroup Barnett 2014 (10mgEmpa Stage2CKD) Barnett 2014 (25mgEmpa Stage2CKD) Barnett 2014 (25mgEmpa Stage3CKD) Barnett 2014 (25mgEmpa Stage3CKD) Barnett 2014 (25mgEmpa Stage4CKD) Ferreira 2021 (10mgEmpa Week108) Ferreira 2021 (25mgEmpa Week206) Ferreira 2021 (25mgEmpa Week52) Griffin 2020 (10mgEmpa) Haring 2013 (25mgEmpa) Kadowaki 2014 (10mgEmpa) Kadowaki 2014 (10mgEmpa) Kadowaki 2014 (65mgEmpa) Kadowaki 2014 (65mgEmpa)	-19, -27,95 -22,60 -20,81 -21,41 -22,60 -20,81 -21,41 -22,60 -20,81 -21,41 -22,60 -20,81 -21,41 -22,60 -20,81 -21,41 -22,60 -20,81 -21,41 -22,60 -20,81 -21,41 -22,60 -20,81 -21,41 -22,60 -20,81 -21,41 -22,60 -20,81 -21,41 -21,	ce         Si           31         9.091           30         11.270           30         11.270           58.994         53           573         5.918           42         1.974           45         1.213           45         1.974           45         9.987           39         118.869           51         10.845           52         9.967           54         10.299           57         10.299           57         10.299	E Weight 4 3.4% 3 3.1% 7 3.4% 5 1.6% 3 4.2% 6 4.2% 6 4.2% 9 4.2% 9 4.2% 9 4.2% 9 4.2% 9 3.2% 6 3.2% 6 3.2% 6 3.2%	Mean Difference IV, Random, 95% C -31.00 [+48.82, -13.16 -30.00 [+52.09, -7.91 +5.00 [-22.83, 12.63 51.00 [46.0] 97.40 -19.63 [-24.10, -15.16 -27.96 [-39.56, -16.36 -22.60 [-34.24, -14.73 -21.41 [-25.58, -17.25 -22.60 [-34.24, -14.93 -21.41 [-25.58, -17.25 -22.60 [-34.24, -14.93 -37.00 [-271.98, 193.98 -37.00 [-271.98, 193.98 -37.00 [-271.98, 193.98 -37.00 [-271.98, 193.98 -45.00 [61.54, -42.46 -45.00 [61.54, -42.46 -45.00 [61.54, -42.46 -45.00 [67.19, -24.81]	-50 -25 0 Favours [SGLT2i] F Mean ( IV, Rand	25 50 [avours [Placebo] )ifference 0,95% C1
Test for overall effect: Z = 11.85 (P < 0.0 Study or Subgroup Barnett 2014 (10mgEmpa Stage2CkD) Barnett 2014 (25mgEmpa Stage2CkD) Barnett 2014 (25mgEmpa Stage3CkD) Barnett 2014 (25mgEmpa Stage3CkD) Barnett 2014 (25mgEmpa Stage4CkD) Ferreira 2021 (10mgEmpa Week108) Ferreira 2021 (10mgEmpa Week208) Ferreira 2021 (25mgEmpa Week208) Kadowaki 2014 (25mgEmpa) Kadowaki 20	Mean Differen 	Ce         SI           31         9.091           331         9.091           30         11.270           51         23.673           53         2.781           42         1.974           45         2.123           37         1.974           45         2.123           37         1.874           10         0.987           39         118.869           37         114.551           51         10.299           57         10.299           14         9.67144           39         13.442	E         Weight           4         3.4%           3         3.1%           7         3.4%           5         1.6%           3         4.2%           7         3.4%           9         4.2%           7         0.1%           5         3.2%           6         3.2%           6         3.2%           6         3.2%           8         3.3%	Mean Difference IV, Random, 95% C 31.00 [48.82, 13.18 -30.00 [52.09, 7.31 5 00 [22.63, 12.83 5 1.00 [4 60, 97.40 -19.63 [24.10, 15.16] -27.38 [39.56, 16.36 -22.60 [26.47, 18.73 -21.41 [25.58, 17.25 -22.60 [24.20, 11.00 -20.82 [24.99, 16.85 0 60 [1.34, 254 -39.00 [271.98, 193.88 -37.00 [261.52, 187.52 -51.00 [72.20, 29.74 -52.00 [81.54, 424.64 -45.00 [65.19, -24.81 -37.71 [51.67, -13.76]	-50 -25 0 Favours [SGLT2i] F Mean I IV, Rand	25 50 (avours (Placebo) )ifference om, 95% Cl
Test for overall effect: Z = 11.85 (P < 0.0 Study or Subgroup Barnett 2014 (10mgEmpa Stage2CkD) Barnett 2014 (25mgEmpa Stage2CkD) Barnett 2014 (25mgEmpa Stage3CkD) Barnett 2014 (25mgEmpa Stage3CkD) Barnett 2014 (25mgEmpa Stage4CkD) Ferreira 2021 (10mgEmpa Week108) Ferreira 2021 (10mgEmpa Week108) Ferreira 2021 (25mgEmpa Week108) Ferreira 2021 (25mgEmpa Week20) Ferreira 2021 (25mgEmpa Week52) Griffin 2020 (10mgEmpa) Haring 2013 (25mgEmpa) Kadowaki 2014 (25mgEmpa) Kadowaki 2014 (25mgEmpa) Kadowaki 2014 (25mgEmpa) Kadowaki 2014 (10mgEmpa) Kadowaki 2014 (50mgEmpa) Kadowaki 2014 (50mgEmpa) Kado	Mean Differen 	ce         SI           31         9.091.           30         9.094.           50         8.994.           51         23.673.           79         5.918.           42         5.918.           45         2.123.           45         2.123.           45         2.123.           45         1.974.           56         9.987.           37         114.551.           51         10.299.           57         10.299.           57         10.299.           57         10.291.           57         10.291.           57         10.291.           57         10.211.           14         9.671.44.           12         13.112.           13.112.         13.112.	E         Weight           4         3.4%           3         3.1%           5         1.6%           3         4.2%           6         4.2%           7         3.9%           9         4.2%           6         3.2%           8         3.2%           6         3.2%           6         3.2%           8         3.3%           5         2.2%	Mean Difference IV, Random, 95% C -31.00 [48.82, -13.18 -30.00 [52.09, -7.91 -5.00 [22.63, 12.63 51.00 [46.09, -7.04 -19.63 [24.10, -15.16 -27.86 [39.56, -16.35 -22.60 [26.47, 18.73 -21.41 [25.58, -17.25 -20.80 [24.89, -16.95 0.80 [-13.4, 22.46 -39.00 [-27.198, 91.63 57.00 [72.18, 93.88 -37.00 [73.15, 18.73 -51.00 [72.26, -29.74 -62.00 [81.54, 42.46 -45.00 [65.19, -24.81 -57.00 [77.19, -36.81 -32.71 [51.67, -13.76 -66.20 [91.90, -40.55	-50 -25 0 Favours [SGLT2i] F Mean I IV, Rand	25 50 (avours (Placebo) )ifference om, 95% Cl
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Test for overall effect: Z = 11.85 (P < 0.0 Study or Subgroup Barnett 2014 (10mgEmpa Stage2CKD) Barnett 2014 (25mgEmpa Stage2CKD) Barnett 2014 (25mgEmpa Stage2CKD) Barnett 2014 (25mgEmpa Stage2CKD) Barnett 2014 (25mgEmpa Stage4CKD) Ferreira 2021 (10mgEmpa Week108) Ferreira 2021 (10mgEmpa Week206) Ferreira 2021 (25mgEmpa Week206) Kadowaki 2014 (25mgEmpa) Kadowaki 2014 (25mgEmpa) Kadowaki 2014 (25mgEmpa) Kadowaki 2014 (10mgEmpa) Kadowaki 2014 (50mgEmpa) Nishimura 2015 (10mgEmpa) Nishimura 2015 (10mgEmpa) Nishimura 2015 (10mgEmpa)	Mean Differen 	ce         Si           31         9.091-           30         11.270           58         23.673           63         2.278           79         5.918           42         1.974           45         1.273           37         1.974           45         9.987           37         114.561           51         10.845           52         9.96714           9.67144         9.07144           42         1.3112           17         16.265           58         18.796           58         18.796           58         18.796	E Weight 4 3.4% 3 3.1% 5 1.6% 3 4.2% 7 3.9% 9 4.2% 9 4.2% 9 4.2% 9 4.2% 9 4.2% 6 3.2% 6 3.2% 6 3.2% 8 3.3% 6 3.2% 8 3.3% 5 2.8% 5 4.1%	Mean Difference IV, Random, 95% C -31.00 [+8.82, -13.18 -30.00 [+52.08, -7.81 +5.00 [-22.63, 12.63 51.00 [46.0, 97.40 -19.63 [-24.10, -15.16 -22.60 [-26.47, -18.73 -21.41 [-25.68, -17.25 -22.60 [-34.24, -14.63 -22.60 [-34.24, -14.63 -22.60 [-34.24, -14.63 -20.62 [-24.89, -16.63 -20.62 [-24.89, -16.63 -37.00 [-271.98, 193.98 -37.00 [-21.94, -134, -254 -51.00 [-77.19, -3681] -32.71 [-51.67, -13.76 -65.20 [-61.9, -44.84 -57.00 [-77.19, -3684] -32.71 [-51.67, -13.76 -65.20 [-61.9, -44.84, -21.16 -17.25 [-24.15, -10.35	-50 -25 0 Favours [SGLT2i] F IV, Rand	25 50 iavours (Placebo) om, 95% Cl
Test for overall effect: Z = 11.85 (P < 0.0 Study or Subgroup Barnett 2014 (10mgEmpa Stage2CkD) Barnett 2014 (25mgEmpa Stage2CkD) Barnett 2014 (25mgEmpa Stage3CkD) Barnett 2014 (25mgEmpa Stage4CkD) Ferreira 2021 (10mgEmpa Week108) Ferreira 2021 (10mgEmpa Week206) Ferreira 2021 (25mgEmpa Week108) Ferreira 2021 (25mgEmpa Week52) Griffin 2013 (25mgEmpa) Haring 2013 (10mgEmpa) Kadowaki 2014 (25mgEmpa) Kadowaki 2014 (25mgEmpa) Kadowaki 2014 (25mgEmpa) Kadowaki 2014 (10mgEmpa) Kadowaki 2014 (10mgEmpa) Kadowaki 2015 (10mgEmpa) Nshimura 2015 (25mgEmpa) Nshimura 2015 (25mgEmpa) Nshimura 2015 (10mgEmpa) Nshimura 2015 (25mgEmpa) Nshimura 2015 (10mgEmpa) Nshimura 2015 (25mgEmpa) Nshimura 2015 (10mgEmpa) Nshimura 2015 (25mgEmpa) Nshimura 2015 (25mgEmpa) Nshimura 2015 (10mgEmpa) Stada 2021 (10mgEmpa, 55 years old and a Okada 2021 (10mgEmpa, 55 years old and a	Mean Differen 	ce         SI           31         9.091           31         9.091           30         11.270           5         8.994           51         23.673           83         2.278           79         5.918           42         1.974           45         2.123           42         5.918           37         114.6513           51         10.8467           37         114.5513           51         10.299           71         16.9267           52         9.967           45         10.299           71         16.926           58         18.791           58         18.791           59         13.122           71         16.926           58         18.791           59         1.497	E         Weightt           4         3.4%           3.1%         3.1%           7         3.4%           5         1.6%           3         4.2%           6         4.2%           9         4.2%           9         4.2%           6         3.2%           6         3.2%           8         3.3%           2         2.3%           8         2.1%           5         4.1%           6         3.2%           8         2.1%           5         4.1%           6         3.2%           6         3.2%           6         3.2%           7         3.1%           8         2.1%           5         4.1%           6         4.2%	Mean Difference IV, Random, 95% C -31.00 [48.82, -13.18 -30.00 [52.09, -7.91 -500 [22.63, 12.63 51.00 [46.09, 74.01 -19.63 [24.10, 15.16 -27.86 [39.56, -16.35 -22.60 [26.47, -18.73 -21.41 [25.59, -17.25 -20.60 [24.20, -11.00 -20.82 [24.89, -16.85 -0.60 [-1.34, 2.54 -37.00 [26.15, 21.87.52 -51.00 [72.26, -29.74 -50.00 [57.19, -24.81 -37.00 [56.19, -24.81 -37.00 [56.19, -24.81 -37.00 [56.19, -24.81 -37.00 [56.19, -34.81 -37.00 [56.19, -34.81 -32.71 [51.67, -13.76 -66.20 [91.30, -40.50 -17.72 [52.41, 51.03 -35.10 [38.01], -32.18 -35.10 [38.01], -32.18	-50 -25 0 Favours [SGLT2i] F IV, Rand	25 50 (avours (Placebo) )ifference om, 95% Cl
Test for overall effect: Z = 11.85 (P < 0.0 Study or Subgroup Barnett 2014 (10mgEmpa Stage2CkD) Barnett 2014 (25mgEmpa Stage2CkD) Barnett 2014 (25mgEmpa Stage3CkD) Barnett 2014 (25mgEmpa Stage4CkD) Ferreira 2021 (10mgEmpa Week108) Ferreira 2021 (10mgEmpa Week108) Ferreira 2021 (25mgEmpa Week108) Ferreira 2021 (25mgEmpa Week20) Ferreira 2021 (25mgEmpa Week20) Haring 2013 (26mgEmpa) Kadowaki 2014 (10mgEmpa) Kadowaki 2014 (	Mean Differen 	ce         SI           31         9.091.           331         9.091.           301         1.270.           302         23.673.           303         2.273.           304         23.673.           305         2.123.           42         5.918.           37         1.974.           16         0.997.           39         114.551.           51         10.249.           57         10.299.           57         10.299.           57         10.299.           57         10.299.           57         10.399.           58         8.771.44.           50         10.399.           57         10.399.           57         10.399.           58         10.299.           58         10.399.           58         10.399.           58         10.399.           58         10.399.           58         10.399.           59.856.         3.521.           51         1.487.           51         1.497.           58         5.298.568.     <	E         Weightt           4         3.4%           3         3.1%           5         1.6%           3         4.2%           6         4.2%           7         3.9%           9         4.2%           6         3.2%           9         4.2%           6         3.2%           8         3.3%           5         2.8%           2         2.8%           2         2.8%           2         2.1%           5         4.1%           1         4.2%           6         3.2%           8         2.1%           5         4.1%	Mean Difference IV, Random, 95% C -31 00 [-48.82, -13.18 -30.00 [-52.08, -7.8] -5.00 [-22.63, 12.63 51.00 [4.60, 97.40 -19.63 [-24.10, -15.16 -27.96 [-39.56, -16.36 -22.60 [-26.47, -18.73 -21.41 [-25.58, -17.25 -22.60 [-34.20, -11.00 -20.82 [-24.69, -16.35 -0.60 [-1.34, 2.54 -39.00 [-271.98, -16.35 -0.60 [-1.34, 2.54 -39.00 [-271.98, -16.35 -37.00 [-271.52, 12.75 -51.00 [-72.26, -29.74 -52.00 [-77.19, -36.61 -52.00 [-77.19, -36.61 -32.27 [-51.00 [-77.19, -36.51 -17.00 [-50.17, 16.77 -56.00 [-94.84, -21.16 -17.25 [-24.15, -10.35 -51.01 [-38.01, -32.18 -52.27 [-54.00, -40.45 -53.00 [-94.84, -27.55]	-50 -25 0 Favours [SGLT2i] F Mean ( IV, Rand	25 50 (avours [Placebo] )ifference om, 95% Cl
Test for overall effect: Z = 11.85 (P < 0.0 Study or Subgroup Barnett 2014 (10mgEmpa Stage2CKD) Barnett 2014 (25mgEmpa Stage3CKD) Barnett 2014 (25mgEmpa Stage3CKD) Barnett 2014 (25mgEmpa Stage4CKD) Barnett 2014 (25mgEmpa Stage4CKD) Ferreira 2021 (10mgEmpa Week108) Ferreira 2021 (10mgEmpa Week206) Ferreira 2021 (25mgEmpa Week206) Ferreira 2021 (25mgEmpa Week206) Ferreira 2021 (25mgEmpa Week52) Griffin 2020 (10mgEmpa) Haring 2013 (25mgEmpa Week52) Griffin 2020 (10mgEmpa) Haring 2013 (25mgEmpa) Kadowaki 2014 (25mgEmpa) Kadowaki 2014 (25mgEmpa) Kadowaki 2014 (10mgEmpa) Kadowaki 2014 (10mgEmpa) Kadowaki 2014 (10mgEmpa) Kadowaki 2016 (10mgEmpa) Kadowaki 2016 (10mgEmpa) Nishimura 2015 (10mgEmpa) Okada 2021 (10mgEmpa) Okada 2021 (10mgEmpa) Roden 2013 (25mgEmpa) Roden 2013 (25mgEmpa)	Mean Differen 	ce         SI           31         9.091;           30         11.270;           30         11.270;           51         23.673;           63         2.278;           79         5.918;           42         1.974;           45         1.23.673;           46         2.123;           45         9.967;           1.974;         1.0.987;           39         118.869;           51         10.845;           52         9.967;           51         10.299;           57         10.299;           57         10.299;           58         18.79;           106         3.521;           11         9.67144;           12         1.3112;           17         16.926;           58         18.79;           58         5.345;           59.368;         5.345;           52         5.545;	E         Weight           4         3.4%           3         3.1%           7         3.4%           5         1.6%           3         4.2%           6         4.2%           9         4.2%           9         4.2%           9         4.2%           9         4.2%           9         4.2%           9         4.2%           9         4.2%           9         4.2%           9         4.2%           9         4.2%           9         4.2%           9         4.2%           9         4.2%           9         4.2%           8         3.3%           6         3.2%           8         3.3%           5         2.8%           2         2.3%           8         2.1%           8         3.8%           7         3.9%           7         3.9%	Mean Difference IV, Random, 95% C 31.00 [+48.82, -13.18 -30.00 [+52.08, -7.81 -5.00 [-26.83, 12.63 51.00 [46.09, 74.04 -19.63 [-24.10, -15.16 -22.60 [-26.47, -18.73 -21.41 [-25.68, -17.25 -22.60 [-24.47, -18.73 -21.41 [-25.68, -17.25 -22.60 [-24.47, -18.73 -22.60 [-24.42, -14.42, -44.42, -45.04 -06.52, 12.74 -51.00 [-72.18, -13.26 -51.00 [-72.28, -29.74 -62.00 [-71.94, -42.44 -55.00 [-71.94, -42.44 -55.00 [-71.79, -26.81 -17.26 [-24.15, -13.26 -52.27 [-64.00, -40.54 -52.27 [-64.00, -40.54 -52.20 [-7.27, -51.13]	-50 -25 0 Favours [SGLT2i] F Mean ( IV, Rand	25 50 [avours [Placebo] Difference om, 95% C1
Test for overall effect: Z = 11.85 (P < 0.0 Study or Subgroup Barnett 2014 (10mgEmpa Stage2CkD) Barnett 2014 (25mgEmpa Stage2CkD) Barnett 2014 (25mgEmpa Stage2CkD) Barnett 2014 (25mgEmpa Stage2CkD) Barnett 2014 (25mgEmpa Stage3CkD) Ferreira 2021 (10mgEmpa Week108) Ferreira 2021 (10mgEmpa Week208) Ferreira 2021 (25mgEmpa Week208) Ferreira 2021 (25mgEmpa) Kadowaki 2014 (25mgEmpa) Kadowaki 2014 (25mgEmpa) Kadowaki 2014 (25mgEmpa) Kadowaki 2014 (10mgEmpa) Kadowaki 2014 (10mgEmpa) Kadowaki 2015 (10mgEmpa) Nishimura 2015 (25mgEmpa) Nishimura 2015 (25mgEmpa) Nishimura 2015 (25mgEmpa) Nishimura 2015 (25mgEmpa) Rodan 2021 (10mgEmpa) Rodan 2021 (10mgEmpa) Roden 2013 (10mgEmpa) Roden 2013 (10mgEmpa)	Mean Differen - 19. - 27.95 - 27.95 - 27.95 - 27.95 - 22.60 - 21.41 - 22.60 - 21.41 - 22.60 - 21.41 - 22.60 - 21.41 - 22.60 - 23.07 - 66 - 5.2710 -	ce         SI           31         9.091           331         9.094           54         8.994           51         23.673           53         2.278           79         5.918           42         1.974           45         2.123           42         5.918           42         1.974           16         0.987           37         114.5615           52         9.967           45         10.299           71         16.926           55         10.299           71         1.6.926           58         5.245           59.8389         5.245           52         5.545           52         5.545           53         5.345           54         51           54         51	E         Weighti           4         3.4%           3         3.1%           7         3.4%           5         1.6%           3         4.2%           7         3.9%           6         4.2%           7         3.9%           9         4.2%           7         0.1%           6         3.2%           6         3.2%           6         3.2%           8         2.1%           5         2.8%           2         2.3%           2         3.9%           9         0.1%           8         3.8%           2         3.9%           9         0.1%	Mean Difference IV, Random, 95% C -31.00 [48.82, -13.18 -30.00 [52.09, -7.91 -5.00 [22.63, 12.63 f1.00 [46.09, 7.40 -19.63 [24.10, 15.16 -27.66 [34.66, -16.43 -22.66 [24.64, -18.73 -22.66 [24.64, -18.73 -22.66 [24.69, -16.95 -0.60 [-1.34, 2.54 -30.00 [27.18, 91.19.88 -37.00 [52.18, -12.28 -51.00 [72.26, -29.74 -45.00 [65.19, -24.81 -32.71 [51.67, -13.76 -66.20 [91.90, -40.50 -17.02 [54.17, -13.63 -35.00 [94.44, -21.16, -17. -58.00 [94.84, -47.52 -35.00 [72.77, -51.13] -35.00 [72.76, -11.75] -35.00 [72.77, -51.13]	-50 -25 0 Favours [SGLT2i] F Mean I IV, Rand	25 50 (avours (Placebo) )ifference om, 95% Cl
Test for overall effect: Z = 11.85 (P < 0.0 Study or Subgroup Barnett 2014 (10mgEmpa Stage2CkD) Barnett 2014 (25mgEmpa Stage2CkD) Barnett 2014 (25mgEmpa Stage3CkD) Barnett 2014 (25mgEmpa Stage3CkD) Barnett 2014 (25mgEmpa Stage4CkD) Ferreira 2021 (10mgEmpa Week108) Ferreira 2021 (10mgEmpa Week208) Ferreira 2021 (25mgEmpa Week208) Haring 2013 (25mgEmpa Week208) Kadowaki 2014 (10mgEmpa) Kadowaki 2014 (25mgEmpa) Kadowaki 2014 (25mgEmpa) Kadowaki 2014 (25mgEmpa) Kadowaki 2014 (50mgEmpa) Kadowaki 2014 (10mgEmpa) Kadowaki 2014 (10mgEmpa) Roden 2013 (10mgEmpa) Roden 2014 (10mgEmpa) Roden 2014 (	Mean Differen 	ce         SI           31         9.091           331         9.094           301         11.2703           58         8.994           51         23.6733           79         5.918           42         1.974           45         2.1231           42         5.918           37         1.14.551           51         10.2991           57         10.2991           57         10.2991           57         10.2991           57         10.2991           57         10.2991           57         10.2991           57         10.2991           57         10.2911           58         3.5211           54         9.67144           55         10.5265           56         15.98368           58         5.3455           54         5.5455           55         112.2833	E         Weight           4         3.4%           3         3.1%           5         1.6%           3         4.2%           6         4.2%           7         3.9%           9         4.2%           6         3.2%           8         3.3%           6         3.2%           8         3.3%           5         2.8%           2         2.8%           2         3.8%           7         3.9%           8         3.3%           5         2.1%           5         4.1%           1         4.2%           6         3.2%           8         3.3%           5         2.8%           2         3.9%           8         3.3%           9         0.1%           8         0.1%	Mean Difference IV, Random, 95% C -31.00 [-48.82, -13.18 -30.00 [-52.09, -7.91 -5.00 [-22.63, 12.63 51.00 [46.09, -7.04 -19.63 [-24.10, -15.16 -27.86 [-39.56, -17.25 -22.60 [-26.47, -18.73 -22.60 [-26.47, -18.73 -21.41 [-25.65, -17.25 -20.80 [-24.89, -16.95 -0.80 [-24.24, -18.75 -0.80 [-24.89, -16.95 -0.80 [-27.98, -16.95 -0.80 [-27.98, -16.95 -51.00 [-72.26, -29.74 -51.00 [-72.26, -29.74 -51.00 [-72.36, -29.74] -55.00 [-54.84, -42.46 -45.00 [-55.18, -24.81 -57.00 [-50.17, -11.76 -66.20 [-91.90, -40.55 -51.10 [-38.10, -32.18 -52.27 [-54.00, -40.45 -55.00 [-24.84, -47.55 -55.00 [-24.84, -47.55 -55.00 [-27.89, -17.18] -55.00 [-27.89, -17.18]	-50 -25 0 Favours [SGLT2i] F Mean I IV, Rand	25 50 [avours [Placebo] )ifference om, 95% C1 
Test for overall effect: Z = 11.85 (P < 0.0 Study or Subgroup Barnett 2014 (10mgEmpa Stage2CKD) Barnett 2014 (25mgEmpa Stage3CKD) Barnett 2014 (25mgEmpa Stage3CKD) Barnett 2014 (25mgEmpa Stage3CKD) Barnett 2014 (25mgEmpa Stage4CKD) Ferreira 2021 (10mgEmpa Week108) Ferreira 2021 (10mgEmpa Week206) Ferreira 2021 (25mgEmpa Week206) Ferreira 2021 (25mgEmpa Week206) Ferreira 2021 (25mgEmpa Week52) Griffin 2020 (10mgEmpa) Haring 2013 (10mgEmpa) Haring 2013 (10mgEmpa) Kadowaki 2014 (25mgEmpa Week52) Griffin 2020 (10mgEmpa) Kadowaki 2014 (10mgEmpa) Kadowaki 2014 (10mgEmpa) Kadowaki 2014 (10mgEmpa) Kadowaki 2014 (10mgEmpa) Kadowaki 2015 (10mgEmpa) Kadowaki 2016 (10mgEmpa) Nishimura 2015 (10mgEmpa) Okada 2021 (10mgEmpa) Roden 2013 (25mgEmpa) Roden 2013 (25mgEmpa) Roden 2013 (25mgEmpa) Ross 2015 (10mgAEmpa) Ross 2015 (125mgbidEmpa) Ross 2015 (125mgbidEmpa)	Mean Differen -19, -19, -27.95 -22.60 -22.60 -22.60 -22.61 -22.60 -20.81 -22.60 -20.81 -22.60 -20.81 -22.60 -20.81 -22.60 -20.81 -22.60 -20.81 -22.60 -20.81 -22.60 -20.81 -22.60 -20.81 -22.60 -20.81 -22.60 -20.81 -22.60 -20.81 -22.60 -20.81 -22.60 -20.81 -22.60 -20.81 -22.60 -20.81 -22.60 -20.81 -20.81 -20.80 -20.81 -20.80 -20.81 -20.80 -20.81 -20.80 -20.81 -20.80 -20.81 -20.80 -20.80 -20.81 -20.80 -20.81 -20.80 -20.81 -20.80 -20	ce         SI           31         9.091           30         11.270           30         11.270           58         2.278           79         5.918           42         1.974           45         2.1231           45         9.947           1.6         0.987           39         118.869           31         10.451           51         10.299           57         10.299           57         10.299           56         18.791           56         5.945           58         8.5945           58         5.3455           54         5.98368           55         5.5455           51         112.8933           56         113.7112           56         113.712	E         Weightt           4         3.4%           3         3.1%           7         3.4%           5         1.6%           3         4.2%           6         4.2%           9         4.2%           9         4.2%           9         4.2%           9         4.2%           9         4.2%           9         4.2%           9         4.2%           9         4.2%           9         3.2%           8         3.3%           6         3.2%           8         3.3%           5         2.8%           2         3.8%           5         4.1%           8         3.8%           9         0.1%           8         0.1%           8         0.1%           9         0.1%	Mean Difference IV, Random, 95% C 31.00 [48.82, -13.18 -30.00 [52.09, 7.31] -5.00 [-26.31, 263 -19.83 [24.10, -15.16 -27.96 [39.56, -16.36 -22.60 [-26.47, -18.73 -21.41 [25.58, -17.25 -22.60 [-34.20, -11.00 -20.82 [24.69, -16.95 0.60 [-1.34, 2.54 -39.00 [-27.19, -16.95 0.60 [-1.34, 2.54 -51.00 [-72.26, -29.44] -57.00 [-77.19, -36.81 -45.00 [-65.19, -24.81] -57.00 [-77.19, -36.81 -17.70 [-50.71, 16, -13.76 -66.20 [-91.90, -44.50] -17.70 [-50.71, 16, -13.76 -56.20 [-91.90, -44.54] -57.00 [-64.84, -47.55] -51.00 [-72.87, -51.13] -51.00 [-72.87, -51.13] -51.00 [-72.87, -51.13] -51.00 [-72.88, 7, -51.13] -51.00 [-72.88, 7] [-50.75] -50.00 [-72.45, 160.45]	-50 -25 0 Favours [SGLT2i] F Mean I IV, Rand	25 50 [avours [Placebo] Difference om, 95% C1 
Test for overall effect: Z = 11.85 (P < 0.0 Study or Subgroup Barnett 2014 (10mgEmpa Stage2CkD) Barnett 2014 (25mgEmpa Stage2CkD) Barnett 2014 (25mgEmpa Stage2CkD) Barnett 2014 (25mgEmpa Stage2CkD) Barnett 2014 (25mgEmpa Stage4CkD) Ferreira 2021 (10mgEmpa Week108) Ferreira 2021 (10mgEmpa Week206) Ferreira 2021 (25mgEmpa Week206) Ferreira 2021 (25mgEmpa Week206) Ferreira 2021 (25mgEmpa Week206) Ferreira 2021 (25mgEmpa Week207) Ferreira 2021 (25mgEmpa Week207) Ferreira 2021 (25mgEmpa Week207) Ferreira 2021 (25mgEmpa Week52) Griffin 2020 (10mgEmpa) Haring 2013 (25mgEmpa) Kadowaki 2014 (25mgEmpa) Kadowaki 2014 (25mgEmpa) Kadowaki 2014 (25mgEmpa) Kadowaki 2014 (10mgEmpa) Kadowaki 2014 (10mgEmpa) Kadowaki 2014 (10mgEmpa) Kadowaki 2015 (10mgEmpa) Nishimura 2015 (10mgEmpa) Roden 2013 (10mgEmpa) Roden 2013 (10mgEmpa) Roden 2013 (10mgEmpa) Roden 2013 (10mgEmpa) Rodes 2015 (10mgadEmpa) Ross 2015 (12.5mgbidEmpa) Ross 2015 (GmgbidEmpa) Ross 2015 (GmgbidEmpa) Ross 2015 (GmgbidEmpa) Ross 2015 (GmgbidEmpa) Ross 2015 (GmgbidEmpa)	Mean Differen - 19. - 27.95 - 27.95 - 22.60 - 21.41 - 21.61 - 21.61	ce         SI           31         9.091           31         9.091           31         9.094           51         23.673           53         2.278           79         5.918           42         1.974           45         2.123           42         1.974           16         0.987           37         114.561           51         10.299           14         9.67144           12         13.112           13         11.487           14         9.6714           15         1.0.299           14         9.67144           12         13.112           13         11.487           15         1.0.299           14         9.67144           12         5.99368           58         5.345           52         5.545           54         112.893           56         10.435           56         10.435           56         10.495           56         10.495	E         Weight!           4         3.4%           3         3.1%           7         3.4%           5         1.6%           3         4.2%           7         3.9%           9         4.2%           9         4.2%           9         4.2%           9         4.2%           9         4.2%           9         4.2%           9         4.2%           9         4.2%           8         3.2%           6         3.2%           8         2.1%           5         2.8%           2         2.3%           8         3.8%           9         0.1%           8         3.8%           9         0.1%           8         0.1%           8         0.1%	Mean Difference IV, Random, 95% C -31.00 [+48.82, -13.16 -30.00 [+52.08, -7.81 -50.0 [-22.81, 12.63 -51.00 [46.0, 97.40 -19.63 [-24.10, -15.16 -27.96 [-39.56, -16.36 -22.80 [-28.47, -18.73 -21.41 [-25.58, -17.25 -22.60 [-34.24, -14.63 -0.60 [-34, -24.45 -0.60 [-1.34, -25.4 -39.00 [-271.98, 193.98 -37.00 [-271.98, 193.98 -37.00 [-271.98, 193.98 -37.00 [-71.97, -13.76 -66.20 [-91.90, -40.50 -17.00 [-70.17, 13.76 -66.20 [-91.90, -40.50 -17.00 [-70.17, 16.71, -13.76 -52.27 [-64.00, -40.54 -52.27 [-64.00, -40.54 -52.27 [-64.00, -40.54 -52.27 [-64.00, -40.54 -52.27 [-64.00, -40.54 -55.00 [-72.87, -51.13 -51.00 [-72.88, -171.89 -55.00 [-28.27, 156.27] -55.00 [-27.38, 171.89 -55.00 [-27.38, 171.89	-50 -25 0 Favours [SGLT2i] F Mean I IV, Rand	25 50 (avours (Placebo) )ifference om, 95% Cl
Test for overall effect: Z = 11.85 (P < 0.0 Study or Subgroup Barnett 2014 (10mgEmpa Stage2CkD) Barnett 2014 (25mgEmpa Stage2CkD) Barnett 2014 (25mgEmpa Stage3CkD) Barnett 2014 (25mgEmpa Stage3CkD) Barnett 2014 (25mgEmpa Stage4CkD) Ferreira 2021 (10mgEmpa Week108) Ferreira 2021 (10mgEmpa Week206) Ferreira 2021 (25mgEmpa Week52) Griffin 2020 (10mgEmpa Week52) Griffin 2020 (10mgEmpa Week52) Griffin 2020 (10mgEmpa) Haring 2013 (25mgEmpa) Haring 2013 (25mgEmpa) Haring 2013 (10mgEmpa) Kadowaki 2014 (10mgEmpa) Kadowaki 2014 (10mgEmpa) Kadowaki 2014 (10mgEmpa) Kadowaki 2014 (10mgEmpa) Kadowaki 2015 (10mgEmpa) Kadowaki 2015 (10mgEmpa) Kadowaki 2015 (10mgEmpa) Kadowaki 2015 (10mgEmpa) Roden 2013 (10mgEmpa) Roden 2015 (10mgEmpa) Roden 2015 (10mgEmpa) Rod	Mean Differen - 19, - 27.85 - 22.80 - 27.41 - 22.80 - 21.41 - 22.60 - 21.41 - 22.60 - 21.41 - 2.2.60 - 21.41 - 2.2.60 - 21.41 - 2.2.60 - 21.41 - 2.60 - 20.81 - 2.3 - 2.3 - 2.5 - 2.5	Cce         SI           31         9.091.           331         9.091.           30         11.2703.           5         8.994.           51         23.673.           79         5.918.           42         1.974.           45         2.123.           42         5.918.           37         1.14.551.           51         10.897.           39         118.869.           53         2.123.           42         5.918.           37         1.14.551.           51         10.299.           57         10.299.           57         10.299.           56         10.571.44.           58         5.983.68.           58         5.993.68.           58         5.346.           56         11.0.437.           56         11.2.893.           56         11.3.41.3465.           55         56           56         10.6.400.           48         1.1.3465.	E         Weightt           4         3.1%           3         3.1%           5         1.6%           3         4.2%           7         3.9%           9         4.2%           7         3.9%           9         4.2%           7         3.9%           9         4.2%           3         0.1%           3         3.2%           6         3.2%           8         3.3%           5         2.1%           5         3.2%           8         3.3%           6         3.2%           8         2.1%           5         4.1%           8         3.3%           9         0.1%           8         0.1%           8         0.1%           9         0.1%           9         0.1%           9         0.1%           9         0.1%	Mean Difference IV, Random, 95% C -31.00 [48.82, -13.18 -30.00 [52.09, -7.91 -5.00 [22.63, 12.63 51.00 [46.00, 97.40 -19.63 [24.10, -15.16 -27.86 [39.56, -16.35 -22.60 [26.47, 18.73 -21.41 [25.58, -17.25 -20.80 [24.09, -16.95 -0.80 [24.94, -16.95 -0.80 [24.94, -16.95 -0.80 [24.94, -16.95 -0.80 [24.94, -16.95 -0.80 [24.94, -16.95 -0.80 [24.94, -42.46 -45.00 [65.19, -24.81] -57.00 [-70.19, -36.81 -37.01 [-51.67, -13.76 -68.20 [-91.90, -40.84, -42.46 -50.00 [-54.84, -42.46 -50.00 [-54.84, -42.46 -50.00 [-54.84, -42.46 -55.00 [-72.84, -42.46 -55.00 [-72.84, -42.46 -55.00 [-72.84, -42.46 -55.00 [-72.84, -42.45] -55.00 [-72.84, -42.45] -50.00 [-72.84,	-60 -25 0 Favours [SGLT2i] F Mean ( IV, Rand	25 50 [avours [Placebo] )ifference om, 95% C1
Test for overall effect: Z = 11.85 (P < 0.0 Study or Subgroup Barnett 2014 (10mgEmpa Stage2CkD) Barnett 2014 (25mgEmpa Stage2CkD) Barnett 2014 (25mgEmpa Stage3CkD) Barnett 2014 (25mgEmpa Stage3CkD) Barnett 2014 (25mgEmpa Stage4CkD) Ferreira 2011 (10mgEmpa Week108) Ferreira 2021 (10mgEmpa Week208) Ferreira 2021 (25mgEmpa Week208) Griffin 2020 (10mgEmpa) Kadowaki 2014 (10mgEmpa) Kadowaki 2014 (25mgEmpa) Kadowaki 2014 (25mgEmpa) Kadowaki 2014 (10mgEmpa) Kadowaki 2014 (10mgEmpa) Kadowaki 2015 (10mgEmpa) Kadowaki 2015 (10mgEmpa) Nishimura 2015 (10mgEmpa) Nishimura 2015 (10mgEmpa) Roden 2013 (10mgEmpa) Roden 2013 (25mgEmpa) Roden 2013 (25mgEmpa) Roden 2013 (25mgEmpa) Roden 2013 (25mgEmpa) Ross 2015 (10mgEmpa) Ross 2015 (10mgEmpa) Ross 2015 (25mgdEmpa) Ross 2015 (	Mean Differen 	ce         SI           31         9.091.           331         9.091.           30         11.270.           31         23.673.           51         23.673.           79         5.918.           42         1.974.           45         2.123.           445         2.123.           45         9.087.           39         118.869.           31         114.551.           51         10.249.           57         10.299.           57         10.299.           56         11.272.           58         8.791.44.           59.856.         5.3452.           52         5.5452.           51         112.893.           56         110.435.           56         110.435.           56         110.435.           565         106.400.           565         106.400.           565         106.400.           565         106.400.           565         104.44.407.           57         113.711.34651.	E         Weightt           4         3.4%           3         3.1%           5         1.6%           3         4.2%           6         4.2%           7         3.9%           9         4.2%           6         3.2%           8         3.3%           6         3.2%           8         3.3%           5         2.8%           2         2.8%           2         3.9%           7         3.9%           6         3.2%           8         3.3%           6         3.2%           8         3.3%           5         2.8%           2         3.9%           7         3.9%           9         0.1%           8         3.8%           9         0.1%           5         0.1%           5         0.1%           6         3.1%           6         3.1%	Mean Difference IV, Random, 95% C 31.00 [+8.82, -13.18 -30.00 [+52.08, -7.81 5.00 [-26.31, 12.83 51.00 [4.60, 97.40 19.83 [-24.10, -15.16 -27.96 [-39.56, -16.36 -22.60 [-26.47, -18.73 -21.41 [-25.58, 17.25 -22.60 [-34.20, -11.00 -20.82 [-24.80, -16.96 0.60 [-1.34, 2.54 -39.00 [-27.18, -16.96 0.60 [-1.34, 2.54 -39.00 [-27.26, -29.74 -45.00 [+65.19, -24.81 -57.00 [+7.71, 9, -36.81 -57.00 [+7.71, 9, -36.81 -57.00 [+7.71, 9, -36.81 -57.00 [+7.71, 9, -36.81 -57.00 [+7.17, 16, -13.76 -56.20 [+91.90, -40.54 -55.00 [+24.24, -11.61 -17.25 [-24.15, -10.35 -51.00 [-27.28, -15.13] -55.00 [+27.28, -15.13] -55.00 [+27.28, -15.13] -55.00 [+27.24, -16.45 -59.48 [+1.30, -37.66 -33.04 [+41.88, -24.40] -30.04 [+41.88, -24.40]	-60 -25 0 Favours [SGLT2i] F Mean I IV, Rand	25 50 [avours [Placebo] Difference om, 95% Cl 
Test for overall effect: Z = 11.85 (P < 0.0 Study or Subgroup Barnett 2014 (10mgEmpa Stage 2CkD) Barnett 2014 (25mgEmpa Stage 2CkD) Barnett 2014 (25mgEmpa Stage 2CkD) Barnett 2014 (25mgEmpa Stage 2CkD) Barnett 2014 (25mgEmpa Stage 4CkD) Ferreira 2021 (10mgEmpa Week108) Ferreira 2021 (10mgEmpa Week206) Ferreira 2021 (25mgEmpa Week207) Griffin 2020 (10mgEmpa) Haring 2013 (25mgEmpa) Kadowaki 2014 (25mgEmpa) Kadowaki 2014 (10mgEmpa) Kadowaki 2014 (25mgEmpa) Kadowaki 2014 (10mgEmpa) Kadowaki 2014 (10mgEmpa) Kadowaki 2014 (10mgEmpa) Kadowaki 2014 (10mgEmpa) Nishimura 2015 (10mgEmpa) Nishimura 2015 (10mgEmpa) Roden 2013 (10mgEmpa) Roden 2013 (10mgEmpa) Roden 2013 (10mgEmpa) Roden 2013 (10mgEmpa) Roden 2013 (25mgEmpa) Rodes 2015 (10mgdEmpa) Roses 2015 (10mgEmpa) Roses 2015 (10mgdEmpa) Roses 2015 (10mgEmpa) Roses 2015 (10mgE	Mean Differen - 19, - 27.95 - 27.95 - 22.60 - 21.41 - 22.71 - 66 - 21.41 - 22.710 - 52.2710 - 52.2710 - 52.2710 - 52.2710 - 55.2710 - 55.273 - 55. - 55.	ce         Si           31         9.091;           331         9.091;           30         11.270;           58         2.278;           79         5.918;           42         1.974;           45         2.123;           46         2.123;           47         5.918;           37         114.551;           51         10.845;           52         9.667;           53         110.299;           57         10.299;           56         10.714;           58         18.79;           58         5.345;           56         113.71;           55         10.439;           56         110.355;           56         10.439;           56         10.4035;           56         10.440;           51         113.71;           55         10.430;           56         10.430;           56         10.440;           51         113.71;           55         10.440;           56         10.440;      57         113.446;      56<	E         Weightt           4         3.4%           3         3.1%           7         3.4%           5         1.6%           7         3.4%           7         3.9%           9         4.2%           9         4.2%           9         4.2%           9         4.2%           9         4.2%           9         4.2%           6         3.2%           6         3.2%           6         3.2%           5         2.1%           5         4.1%           9         0.1%           5         3.8%           6         3.2%           8         0.1%           5         0.1%           6         0.1%           8         0.1%           6         4.0%           6         4.0%           6         4.0%           6         4.0%           6         4.0%           6         4.0%	Mean Difference IV, Random, 95% C 31.00 [+8.82, -13.16 -30.00 [+52.09, -7.41] -5.00 [-22.83, 12.63 51.00 [46.09, 74.00 -19.63 [-24.10, -15.16 -22.60 [-26.47, -18.73 -21.41 [-25.68, -17.25 -22.60 [-24.47, -18.73 -21.41 [-25.68, -17.25 -22.60 [-24.42, -14.73 -20.60 [-21.48, -12.56 -0.60 [-1.34, -24.4 -39.00 [-27.19, -16.81 -0.60 [-1.34, -24.45 -51.00 [-72.26, -29.74 -62.00 [-61.54, -42.46 -45.00 [-61.49, -44.45 -51.00 [-71.9, -24.81] -57.00 [-74.19, -24.81] -57.00 [-74.48, -21.16 -17.25 [-24.15, -10.35 -62.00 [-72.48, -17.16 -52.27 [-64.00, -40.54 -53.00 [-28.48, -47.25 -62.00 [-72.45, 160.45 -55.00 [-28.47, 151.03 -55.00 [-28.45, 160.45 -55.00 [-27.45, 160.45	-50 -25 0 Favours [SGLT2i] F Mean I IV, Rand	25 50 (avours (Placebo) )ifference om, 95% Cl
Test for overall effect: Z = 11.85 (P < 0.0 Study or Subgroup Barnett 2014 (10mgEmpa Stage2CkD) Barnett 2014 (25mgEmpa Stage2CkD) Barnett 2014 (25mgEmpa Stage2CkD) Barnett 2014 (25mgEmpa Stage2CkD) Ferreira 2021 (10mgEmpa Week108) Ferreira 2021 (10mgEmpa Week208) Ferreira 2021 (25mgEmpa Week208) Ferreira 2021 (25mgEmpa Week208) Ferreira 2021 (25mgEmpa Week208) Ferreira 2021 (25mgEmpa Week52) Griffin 2020 (10mgEmpa) Haring 2013 (25mgEmpa) Kadowaki 2014 (25mgEmpa) Kadowaki 2014 (25mgEmpa) Kadowaki 2014 (25mgEmpa) Kadowaki 2014 (25mgEmpa) Kadowaki 2014 (10mgEmpa) Kadowaki 2014 (10mgEmpa) Kadowaki 2014 (10mgEmpa) Kadowaki 2015 (10mgEmpa) Kadowaki 2015 (10mgEmpa) Nishimura 2015 (25mgEmpa) Nishimura 2015 (25mgEmpa) Roden 2013 (10mgEmpa) Roden 2013 (10mgEmpa) Roden 2013 (10mgEmpa) Ross 2015 (10mgdEmpa) Ross 2015 (12.5mgdEmpa) Ross 2015 (10mgEmpa) Ross 2015 (12.5mgdEmpa) Ross 2015 (12	Mean Differen - 19, - 27.85 - 22.80 - 27.41 - 22.60 - 21.41 - 25.79 - 5.90 - 3.3 - 30. - 30	$\begin{array}{c cc} & SI\\ \hline \\ \hline$	E         Weightt           4         3.4%           3.1%         3.1%           7         3.4%           5         1.6%           7         3.9%           6         4.2%           7         0.1%           3         0.1%           5         3.2%           6         3.2%           6         3.2%           8         2.1%           5         2.3%           8         2.1%           5         2.3%           8         2.1%           5         0.1%           6         3.2%           8         2.1%           5         2.3%           8         2.1%           5         0.1%           6         3.1%           6         4.0%           5         0.1%           6         1.1%           6         4.0%           6         4.0%           6         4.0%           6         3.1%           6         3.1%           6         3.1%           7         3.1% <td>Mean Difference IV, Random, 95% C 31.00 [48.82, -13.18 -30.00 [52.09, -7.91 -500 [22.63, 12.63 51.00 [46.09, -7.04 -19.63 [24.10, -15.16 -27.86 [39.56, -16.35 -22.60 [26.47, -18.73 -21.41 [25.59, -17.25 -20.60 [34.20, -11.00 -20.82 [24.89, -16.95 -0.60 [-1.34, 2.54 -39.00 [27.18, 91.8138 -37.00 [261.52, 187.52 -51.00 [72.26, -29.74 -45.00 [65.19, -24.81 -32.71 [51.67, -13.76 -66.20 [91.90, -46.05 -57.00 [77.19, -36.81 -32.71 [51.67, -13.76 -56.00 [94.84, -21.16 -55.00 [72.47, 51.13] -55.00 [54.84, -47.55 -55.00 [54.84, -47.55] -55.00 [24.84, -47.55] -55.00 [24.84, -47.55] -55.00 [24.84, -47.55] -55.00 [27.245, 160.45] -55.00 [27.245, 160.45] -55.00 [27.245, 160.45] -59.00 [54.86, -24.40] -30.29 [38.33], -71.66 -97.00 [119.31], -74.68] -11.74 [59.01, 62.31]</td> <td>-60 -25 0 Favours [SGLT2i] F Mean I IV, Rand</td> <td>25 50 [avours [Placebo] )ifference om, 95% C1</td>	Mean Difference IV, Random, 95% C 31.00 [48.82, -13.18 -30.00 [52.09, -7.91 -500 [22.63, 12.63 51.00 [46.09, -7.04 -19.63 [24.10, -15.16 -27.86 [39.56, -16.35 -22.60 [26.47, -18.73 -21.41 [25.59, -17.25 -20.60 [34.20, -11.00 -20.82 [24.89, -16.95 -0.60 [-1.34, 2.54 -39.00 [27.18, 91.8138 -37.00 [261.52, 187.52 -51.00 [72.26, -29.74 -45.00 [65.19, -24.81 -32.71 [51.67, -13.76 -66.20 [91.90, -46.05 -57.00 [77.19, -36.81 -32.71 [51.67, -13.76 -56.00 [94.84, -21.16 -55.00 [72.47, 51.13] -55.00 [54.84, -47.55 -55.00 [54.84, -47.55] -55.00 [24.84, -47.55] -55.00 [24.84, -47.55] -55.00 [24.84, -47.55] -55.00 [27.245, 160.45] -55.00 [27.245, 160.45] -55.00 [27.245, 160.45] -59.00 [54.86, -24.40] -30.29 [38.33], -71.66 -97.00 [119.31], -74.68] -11.74 [59.01, 62.31]	-60 -25 0 Favours [SGLT2i] F Mean I IV, Rand	25 50 [avours [Placebo] )ifference om, 95% C1
Test for overall effect: Z = 11.85 (P < 0.0 Study or Subgroup Barnett 2014 (10mgEmpa Stage2CkD) Barnett 2014 (25mgEmpa Stage2CkD) Barnett 2014 (25mgEmpa Stage3CkD) Barnett 2014 (25mgEmpa Stage3CkD) Barnett 2014 (25mgEmpa Stage4CkD) Ferreira 2021 (10mgEmpa Week108) Ferreira 2021 (10mgEmpa Week206) Ferreira 2021 (25mgEmpa Week206) Ferreira 2021 (25mgEmpa Week52) Griffin 2020 (10mgEmpa Week52) Griffin 2020 (10mgEmpa) Kadowaki 2014 (25mgEmpa) Kadowaki 2014 (25mgEmpa) Kadowaki 2014 (10mgEmpa) Kadowaki 2015 (10mgEmpa) Kadowaki 2015 (10mgEmpa) Kadowaki 2015 (10mgEmpa) Roden 2013 (10mgEmpa) Roden 2015 (25mgEmpa) Roden 2015 (25m	Mean Differen - 19, - 27,36 - 27,86 - 22,80 - 21,41 - 22,60 - 21,41 - 22,60 - 21,41 - 22,60 - 21,41 - 2,260 - 21,41 - 2,260 - 21,41 - 2,260 - 21,41 - 2,260 - 21,41 - 2,260 - 21,41 - 2,260 - 2,41 - 2,260 - 2,270 - 5,2770 - 5,2770	ce         SI           31         9.091           331         9.094           30         11.2703           5         8.994           51         23.673           79         5.918           42         1.974           45         2.123           42         5.918           71         14.551           51         10.8957           37         114.551           51         10.2999           57         10.2999           56         10.6926           58         10.714           59         13.112           51         1.2.933           56         10.497           56         10.437           56         11.342           56         5.455           56         5.455           56         10.6400           44         11.3467           54         11.3467           55         11.407           56         10.6400           41         11.3467           54         41.154013           41         40.0650901	E         Weightt           4         3.4%           3         3.1%           5         1.6%           3         4.2%           6         4.2%           7         3.9%           9         4.2%           6         3.2%           8         3.2%           6         3.2%           8         3.2%           8         2.1%           5         2.2%           8         3.3%           9         0.1%           8         3.8%           9         0.1%           8         0.1%           9         0.1%           9         0.1%           9         0.1%           9         0.1%           9         0.1%           6         3.1%           6         3.1%           6         0.1%           6         0.7%	Mean Difference IV, Random, 95% C 3100 [48.82, -13.18 -30.00 [52.09, -7.91 -5.00 [22.63, 12.63 51.00 [4.60, 97.40 -19.63 [24.10, -15.16 -27.86 [39.56, -16.35 -22.60 [26.47, 18.73 -21.41 [25.58, -17.25 -20.80 [24.89, -16.95 -0.80 [27.19, 91.38 -37.00 [27.19, 91.38 -37.00 [27.19, 91.38 -37.00 [27.19, 19.38 -37.00 [27.19, 19.38 -37.00 [27.19, 19.38 -42.00 [81.54, 42.46 -45.00 [85.19, -24.81 -57.00 [50.17, 11.376 -66.20 [91.90, 40.50 -17.00 [50.01, 71.13, 76 -65.20 [91.30, 11.32, 18 -55.00 [24.84, -21.16 -55.27, [54.01, -10.35 -55.10 [27.28, 19.13, 17.86 -55.00 [27.28, 14.32, 44] -55.00 [27.28, 14.33, 44] -55.00 [27.28, 14.33, 44] -59.00 [58.27, 156.27, -56.00] -37.34 [41.68, -24.40 -30.29 [38.33, -21.65 -37.00 [50.19, 27.38] -18.35 [99.00, 62.31] -20.56 [-99.00, 67.96]	-60 -25 0 Favours [SGLT2i] F Mean I IV, Rand	25 50 [avours [Placebo] )ifference om, 95% C1 
Test for overall effect: Z = 11.85 (P < 0.0 Study or Subgroup Barnett 2014 (10mgEmpa Stage2CkD) Barnett 2014 (25mgEmpa Stage2CkD) Barnett 2014 (25mgEmpa Stage3CkD) Barnett 2014 (25mgEmpa Stage3CkD) Barnett 2014 (25mgEmpa Stage4CkD) Ferreira 2021 (10mgEmpa Week108) Ferreira 2021 (10mgEmpa Week208) Ferreira 2021 (25mgEmpa Week208) Haring 2013 (25mgEmpa) Kadowaki 2014 (10mgEmpa) Kadowaki 2014 (10mgEmpa) Roden 2013 (10mgEmpa) Roden 2013 (10mgEmpa) Roden 2013 (10mgEmpa) Roden 2013 (10mgEmpa) Roden 2013 (10mgEmpa) Ross 2016 (10mgEmpa) Rikkanen 2015 (25mgUmpa) Rikkanen 2015 (25mgEmpa) Zinman 2015 (25mgEmpa) Total (95% CI)	Mean Differen 	ce         SI           31         9.091.           331         9.091.           301         1.270.           58.994.         51           51         23.673.           53         2.273.           53         2.273.           542         1.974.           45         2.123.           42         5.918.           37         1.974.           16         0.997.           39         118.869.           51         10.299.           57         10.299.           57         10.299.           57         10.299.           58         8.79.           58         10.299.           56         10.6490.           56         5.365.           56         1.13.711.           56         1.2.893.           56         1.10.435.           56         10.6400.           41.1.3465.           51.12.893.           56         10.6400.           41.1.3463.           42         4.06509011.	E         Weightt           4         3.4%           3         3.1%           5         1.6%           3         4.2%           6         4.2%           7         3.9%           9         4.2%           7         3.9%           9         4.2%           6         3.2%           8         3.3%           6         3.2%           8         3.3%           5         2.8%           2         3.9%           9         0.1%           8         3.3%           6         3.2%           8         3.3%           5         2.8%           9         0.1%           8         3.3%           9         0.1%           5         0.1%           6         4.0%           5         4.0%           6         4.0%           6         0.7%           6         0.7%	Mean Difference IV, Random, 95% C 31.00 [+28.82, -13.18 -30.00 [+2.08, 7.81 -5.00 [-22.63, 7.81 -5.00 [-22.63, 7.83 51.00 [4.60, 97.40 -9.83, [24.10, -15.16 -27.96 [-39.56, -16.36 -22.60 [-26.47, -18.73 -21.41 [-25.58, -17.25 -22.60 [-34.20, -11.00 -20.82 [-24.89, -16.35 -0.60 [-1.34, 2.54 -0.60 [-1.34, 2.54 -0.60 [-1.34, 2.54 -0.60 [-1.34, 2.54 -57.00 [-72.18, -13.76 -66.20 [-91.90, -40.55 -51.10 [-73.76] -55.10 [-73.76] -55.00 [-24.7, -15.13 -51.00 [-27.36, 11.32, -15.25 -51.00 [-27.24, 150.45 -55.00 [-27.24, 150.45 -59.48 [-1.30, -37.66 -30.24 [-1.43, 2.41 -30.25 [-39.33, -21.65 -37.00 [-11.93, 17.48] -13.55 [-99.00, 57.86 -35.19 [-42.61, -27.78]	-60 -25 0 Favours [SGLT2i] F Mean I IV, Rand	25 50 [avours [Placebo] )Ifference om, 95% Cl 

Figure 3. (Continued)

					Mean Difference		Mean Difference
Study or Subgroup	Mean Difference	e	SE	Weight	IV, Random, 95	% CI	IV, Random, 95% Cl
3ailey 2013 (10mgDapa)	-51.1	2 8	84.0968	0.1%	-51.12 [-215.95, 113	3.71] ——	
3ailey 2013 (2.5mgDapa)	-54.1	2 7	73.9064	0.2%	-54.12 [-198.97, 90	0.73] —	
Salley 2013 (SmgDapa)	-44.8	i2 8	34.0968	0.1%	-44.62 [-209.45, 120		
riksson 2018 (10mgDapa)	-7	4 1	14.4278	2.8%	-74.00 [-102.28, -45	5.72]	
errannini 2010 (10mgDapa)	-39	.8	8.0623	5.1%	-39.80 [-55.60, -24	1.00]	
errannini 2010 (2.5mgDapa)	-27	.4	8.2073	5.0%	-27.40 [-43.49, -11	.31]	
errannini 2010 (5mgDapa)	-38	.(	8.2807	5.0%	-38.70 [-54.93, -22	2.47]	
loretto 2018 (10mgDapa)	-24	.9	8.0614	5.1%	-24.90 [-40.70, -9	9.10J	
Hao 2020 (SmgDapa)		:3	2.8/53	1.5%	-23.00 [-28.64, -17	.36]	-
Lee SH 2020 (10mgDapa)	-13.68	4 10.	635024	4.0%	-13.68 [-34.52, 7	.16]	
Pollock 2019 (10mgDapa)	-5	.3	8.9287	4.7%	-5.30 [-22.80, 12	2.20]	
Ramirez-Rodriguez 2020 (10mgDa)	ра)	2 2	21.3186	1.6%	-62.00 [-103.78, -20	1.22]	
schumm-Draeger 2014 (10mgqdD)	apa) -48.1	8	6.16	6.0%	-48.18 [-60.25, -36	0.11]	
schumm-Draeger 2014 (2.5mgbldL	Japa) -38.0	17	5.63	6.3%	-38.07 [-49.10, -27	.04]	
Schumm-Draeger 2014 (SmgbidDa	(pa) -39.2	.6 	6.33	5.9%	-39.26 [-51.67, -26	6.85]	
stack 2021 (10mgDapa)	-62	.3 1	10.4594	4.1%	-62.30 [-82.80, -41	.80]	
strojek 2011 (10mgDapa)	-21.3	10	0.8383	5.7%	-27.36[-40.76,-13	5.96]	
strojek 2011 (2.5mgDapa)	-22	.6	6.4154	5.9%	-22.60 [-35.17, -10	1.03]	
strojek 2011 (SmgDapa)	-27.3	10	7.1826	5.5%	-27.36[-41.44,-13	5.28j	
veber 2015 (TurngDapa)	-23.6		5.1174	0.5%	-23.67 [-33.70,-13	5.64]	
/veber 2016 (10mgDapa)	-17.84	4 15 10	0.00090	6.1%	-17.84 [-29.74, -5	).95] \.771	
rang 2015 (TumgDapa)	-18	.4 45.49	/4/413	0.4%	-18.40 [-107.57,70	0.77]	
/ang 2015 (5mgDapa)	-1	9 45.8	853539	0.4%	-19.00[-108.93,70	J.93]	
rang zona (nomgDapa)	-9.516	0 0.	370308	0.9%	-9.52 [-22.00, 2		
Total (95% CI)				100.0%	-30.32 [-36.20, -24	.43]	♦
Jotorononoity: Tou≥ – 111 07: Chi≥ –							
recordgeneity, rad = 111.37, Off -	= 68.80, df = 23 (P < 0.00	001); I² =	67%			- 200	-100 0 100
Fest for overall effect: Z = 10.09 (P <	= 68.80, df = 23 (P < 0.00 : 0.00001)	001); I² =	67%			-200	-100 0 100 Favours [SGLT2i] Favours [Placebo]
Fest for overall effect: Z = 10.09 (P <	= 68.80, df = 23 (P < 0.00 : 0.00001)	001); I²=	67%			-200	-100 0 100 Favours [SGLT2i] Favours [Placebo]
e)	= 68.80, df = 23 (P < 0.00 < 0.00001)	001); I² =	67%	Mea	n Difference	-200	-100 0 100 Favours [SGLT2i] Favours [Placebo] Mean Difference
est for overall effect Z = 10.09 (P <	= 68.80, df = 23 (P < 0.00 : 0.00001) Mean Difference	001); I <sup>2</sup> = <b>S</b> E	67% Weight	Mea IV,	n Difference Random, 95% Cl	-200	-100 0 100 Favours [SGLT2i] Favours [Placebo] Mean Difference IV, Random, 95% Cl
est for overall effect: Z = 10.09 (P < e) Study or Subgroup (ashiwaqi 2014 (100mqlpra)	= 68.80, df = 23 (P < 0.00 : 0.00001) Mean Difference -7.7324	001); I <sup>2</sup> = <u>SE</u> 5.3274	67% Weight 14.6%	Mea IV, 1	n Difference Random, 95% Cl 73 (-18.17, 2.71)	-200	-100 0 100 Favours (SGLT2i) Favours (Placebo) Mean Difference IV, Random, 95% Cl
estion of the second se	= 68.80, df = 23 (P < 0.00 • 0.00001) <u>Mean Difference</u> -7.7324 -2.974	001); I <sup>2</sup> = SE 5.3274 4.3858	67% Weight 14.6% 15.7%	Mea IV, I -7. -2.	n Difference Random, 95% CI .73 [-18.17, 2.71] 97 [-11.57, 5.62]	-200	-100 100 Favours [SGLT2i] Favours [Placebo] Mean Difference IV, Random, 95% Cl
Festfor overall effect Z = 10.09 (P < e) <u> Study or Subgroup</u> (ashiwagi 2014 (100mglpra) (ashiwagi 2014 (25mglpra) (ashiwagi 2014 (25mglpra)	= 68.80, df = 23 (P < 0.00 • 0.00001) <u>Mean Difference</u> -7.7324 -2.974 -23.1972	001); I²= <u>SE</u> 5.3274 4.3858 5.0475	Weight 14.6% 15.7% 14.9%	Mea IV, 1 -7. -2. -23.20	n Difference Random, 95% Cl 73 [-18.17, 2.71] 97 [-11.57, 5.62] 9 [-33.09, -13.30]	-200	-100 0 100 Favours [SGLT2i] Favours [Placebo] Mean Difference IV, Random, 95% Cl
e) <u>Study or Subgroup</u> (ashiwagi 2014 (100mglpra) (ashiwagi 2014 (2.5mglpra) (ashiwagi 2014 (25mglpra) (ashiwagi 2014 (25mglpra)	= 68.80, df = 23 (P < 0.00 • 0.00001) <u>Mean Difference</u> -7.7324 -2.974 -23.1972 -17.844	SE 5.3274 4.3858 5.0475 6.0985	Weight 14.6% 15.7% 14.9% 13.7%	Mea IV, 1 -7. -2. -23.20 -17.8	n Difference Random, 95% Cl 73 [-18.17, 2.71] 97 [-11.57, 5.62] 0 [-33.09, -13.30] 34 [-29.80, -5.89]	-200	-100 0 100 Favours [SGLT2i] Favours [Placebo] Mean Difference IV, Random, 95% Cl
estioroverall effect: Z = 10.09 (P < estion overall effect: Z = 10.09 (P < estimation of the state of the s	= 68.80, df = 23 (P < 0.00 ○.000001) -7.7324 -2.974 -23.1972 -17.844 -37.8	SE 5.3274 4.3858 5.0475 6.0985 8.7009	Weight 14.6% 15.7% 14.9% 13.7% 10.9%	Mea IV, 1 -7. -2. -23.20 -17.8 -37.80	n Difference Random, 95% CI 73 [-18.17, 2.71] 97 [-11.57, 5.62] 9 [-33.09, -13.30] 94 [-29.80, -5.89] 15-54 85 - 20 75]	-200	-100 100 Favours [SGLT2i] Favours [Placebo] Mean Difference IV, Random, 95% Cl
estiogeneny rat = 111.97,011 = Festfor overall effect: Z = 10.09 (P < <u>Study or Subgroup</u> (ashiwagi 2014 (100mglpra) (ashiwagi 2014 (12.5mglpra) (ashiwagi 2014 (25mglpra) (Ashiwagi 2014 (50mglpra) Aliding 2013b (12.5mglpra) Aliding 2013b (12.5mglpra)	= 68.80, df = 23 (P < 0.00 0.00001) -7.7324 -7.7324 -2.974 -23.1972 -17.844 -37.8 -29.21	SE 5.3274 4.3858 5.0475 6.0985 8.7009 0.3624	Weight 14.6% 15.7% 14.9% 13.7% 10.9% 9.3%	Mea IV, 1 -7. -23.20 -17.8 -37.80 -29.2	n Difference Random, 95% Cl 73 [-18.17, 2.71] 97 [-11.57, 5.62] 97 [-3.09, -13.30] 94 [-29.80, -5.89] 9 [-54.85, -20.75] 9 [-54.85, -20.75]	-200	-100 0 100 Favours [SGLT2i] Favours [Placebo] Mean Difference IV, Random, 95% Cl
e) Study or Subgroup Xashiwagi 2014 (100mglpra) Xashiwagi 2014 (12.5mglpra) Xashiwagi 2014 (25mglpra) Xashiwagi 2014 (25mglpra) Milding 2013b (12.5mglpra) Milding 2013b (150mglpra)	= 68.80, df = 23 (P < 0.00 0.00001) - 7.7324 - 2.974 - 23.1972 - 17.844 - 37.8 - 29.2 1 - 20.9 2	SE 5.3274 4.3858 5.0475 6.0985 8.7009 0.3624 9.622	Weight 14.6% 15.7% 14.9% 13.7% 10.9% 9.3%	Mea IV, 1 -7. -23.20 -17.8 -37.80 -29.2	n Difference Random, 95% Cl 73 [-18.17, 2.71] 97 [-11.57, 5.62] 0 [-33.09, -13.30] 34 [-29.80, -5.89] 0 [-54.85, -20.75] 20 [-49.51, -8.89] 0 [-54.95, -1.82]	-200	-100 0 100 Favours [SGLT2i] Favours [Placebo] Mean Difference IV, Random, 95% Cl
estingeneny rat = 111.97,011 = restfor overall effect: Z = 10.09 (P < C) Study or Subgroup Kashiwagi 2014 (100mglpra) (ashiwagi 2014 (12.5mglpra) (Ashiwagi 2014 (25mglpra) (Alding 2013b (12.5mglpra) (Alding 2013b (150mglpra) (Alding 2013b (150mglpra) (Alding 2013b (50mglpra))	= 68.80, df = 23 (P < 0.00 ○.000001) -7.7324 -2.974 -23.1972 -17.844 -37.8 -29.2 1 -30.8 -29.2 1 -30.8	SE 5.3274 4.3858 5.0475 6.0985 8.7009 0.3624 9.635	Weight 14.6% 15.7% 14.9% 13.7% 10.9% 9.3% 10.0%	Mea IV, 1 -7. -23.20 -17.8 -37.80 -29.2 -30.80	n Difference Random, 95% CI 73 [-18.17, 2.71] 97 [-11.57, 5.62] 0 [-33.09, -13.30] 34 [-29.80, -5.89] 34 [-29.80, -5.89] 20 [-54.85, -20.75] 20 [-49.61, -8.89] 21 [-49.68, -11.92]	-200	-100 100 Favours [SGLT2i] Favours [Placebo] Mean Difference IV, Random, 95% Cl
estiogeneny fait = 111.97,011 = Festfor overall effect: Z = 10.09 (P < C) Study or Subgroup Kashiwagi 2014 (100mglpra) (ashiwagi 2014 (12.5mglpra) (ashiwagi 2014 (25mglpra) Milding 2013b (12.5mglpra) Milding 2013b (150mglpra) Milding 2013b (50mglpra)	■ 68.80, df = 23 (P < 0.00 © .000001) • .000001) • .7.7324 - 2.974 - 23.1972 - 17.844 - 37.8 - 29.2 1 - 30.8 - 27.1	SE 5.3274 4.3858 5.0475 6.0985 8.7009 0.3624 9.633 8.6754	Weight 14.6% 15.7% 14.9% 13.7% 10.9% 9.3% 10.0% 10.9%	Mea IV, -2. -23.20 -17.8 -37.80 -29.2 -30.80 -27.10	n Difference Random, 95% CI 73 [-18.17, 2.71] 97 [-11.57, 5.62] 0 [-33.09, -13.30] 24 [-29.80, -5.89] 0 [-54.85, -20.75] 20 [-49.61, -8.89] 0 [-49.68, -11.92] 0 [-44.10, -10.10]	-200	-100 0 100 Favours [SGLT2i] Favours [Placebo] Mean Difference IV, Random, 95% Cl
estingginany, rad = 111.37, Oli P < e) <u>Study or Subgroup</u> (ashiwagi 2014 (100mglpra) (ashiwagi 2014 (12.5mglpra) (ashiwagi 2014 (25mglpra) Ailding 2013b (12.5mglpra) Ailding 2013b (150mglpra) Ailding 2013b (50mglpra) Ailding 2013b (50mglpra) Total (95% CI)	= 68.80, df = 23 (P < 0.00 ○.000001) -7.7324 -2.974 -23.1972 -17.844 -37.8 -29.2 1 -30.8 -27.1	001); I <sup>≠</sup> = 5.3274 4.3858 5.0475 6.0985 8.7009 0.3624 9.633 8.6754	Weight 14.6% 15.7% 14.9% 13.7% 10.9% 9.3% 10.0% 10.9% <b>100.0%</b>	Mea IV, 1 -7. -23.20 -17.8 -37.80 -29.2 -30.80 -27.10 -20.37	n Difference Random, 95% CI 73 [-18.17, 2.71] 97 [-11.57, 5.62] 0 [-33.09, -13.30] 34 [-29.80, -5.89] 0 [-48.5, -20.75] 0 [-49.51, -8.89] 0 [-49.68, -11.92] 0 [-44.10, -10.10] 7 [-29.17, -11.56]	-200	-100 0 100 Favours [SGLT2i] Favours [Placebo] Mean Difference IV, Random, 95% Cl
Construction         Construction           Construction         Construction           Study or Subgroup         Construction           Cashiwagi 2014 (10.0mglpra)         Cashiwagi 2014 (12.5mglpra)           Cashiwagi 2014 (25mglpra)         Cashiwagi 2014 (25mglpra)           Kashiwagi 2014 (25mglpra)         Cashiwagi 2014 (50mglpra)           Milding 2013b (12.5mglpra)         Milding 2013b (150mglpra)           Milding 2013b (50mglpra)         Milding 2013b (50mglpra)           Fotal (95% CI)         Heterogenetity Tau <sup>2</sup> = 109.67° C	= 68.80, df = 23 (P < 0.00 0.00001) - 7.7324 - 2.974 - 23.1972 - 17.844 - 37.8 - 29.2 1 - 30.8 - 27.1 hi <sup>2</sup> = 25.22 df = 7 (P =	SE 5.3274 4.3858 5.0475 6.0985 8.7009 0.3624 9.633 8.6754 0.0007	Weight 14.6% 15.7% 14.9% 13.7% 10.9% 9.3% 10.9% 10.9% 100.0% 100.0%	Mea IV, 1 -7. -23.20 -17.8 -37.80 -29.2 -30.80 -27.10 -20.37 6	n Difference Random, 95% CI 73 (-18.17, 2.71) 97 (-11.57, 5.62) 97 (-11.57, 5.62) 97 (-11.57, 5.62) 97 (-29.80, -13.30) 94 (-29.80, -13.30) 94 (-29.80, -5.89) 94 (-29.80, -5.89) 94 (-29.51, -8.89) 94 (-29.17, -11.56) 94 (-29.17, -11.56) 94 (-29.17, -11.56)	-200	-100 0 100 Favours [SGLT2i] Favours [Placebo] Mean Difference IV, Random, 95% Cl

**Figure 3.** (a) Meta-analysis of mean difference and 95% CI for changes in serum urate in μmol/L with administration of (a) luseogliflozin, (b) canagliflozin, (c) empagliflozin, (d) dapagliflozin and (e) ipragliflozin.

20.37  $\mu$ mol/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  $\mu$ mol/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  $\mu$ mol/L (95% CI: -37.35 to -25.60, p < 0.001) (Figure 4(b)).

Presence of chronic kidney disease with T2DM. Barnett *et al.*,<sup>44</sup> Fioretto *et al.*,<sup>59</sup> Pollock *et al.*<sup>63</sup> and Yale *et al.*<sup>50</sup> included patients with diabetes with an estimated glomerular filtration rate (eGFR) ranging from 15 to 90 ml/min/1.73 m<sup>2</sup>, 40 to 65 ml/min/1.73 m<sup>2</sup>, 25 to 75 ml/min/1.73 m<sup>2</sup> and 30 to 50 ml/min/1.73 m<sup>2</sup>, 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 metaregression 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.

# (a)

(u)				Mean Difference	Mean Dif	ference
Study or Subgroup	Mean Difference	SE	Weight	IV, Random, 95% CI	IV, Randor	n, 95% Cl
Chino 2014 (10mgLuseo)	-126.06786	17.21946	24.7%	-126.07 [-159.82, -92.32]		
Chino 2014 (5mgLuseo)	-117.074484	17.522808	24.5%	-117.07 [-151.42, -82.73]		
Ramírez-Rodríguez 2020 (10mgDapa)	-62	21.3186	22.0%	-62.00 [-103.78, -20.22]		
Stack 2021 (10mgDapa)	-62.3	10.4594	28.8%	-62.30 [-82.80, -41.80]		
Total (95% CI)			100.0%	-91.38 [-126.53, -56.24]	•	
Heterogeneity: Tau <sup>2</sup> = 1006 05: Chi <sup>2</sup> = 14	190 df = 3 (P = 0 00	2): I <sup>2</sup> = 80%				

3 (P JO2); Test for overall effect: Z = 5.10 (P < 0.00001)

-200 -1	00 (	) 10	)0 2	00
Favours [	SGLT2i]	Favours	[Placeb	0]

tudy or Subgroup	Mean Difference	¢C	Weight	Mean Difference	Mean Difference
alloy 2013 (10mnDana)	-51 10	3E 94 0060	n 1 %	-51 12 L215 05 112 711	iv, ranuom, 95% Ci
ailey 2013 (15mgDapa)	-54.12	73 9064	0.1%	-54 12 [-198 97 90 73]	
ailey 2013 (5mgDapa)	-44.62	84.0968	0.1%	-44.62 [-209.45, 120.21]	
arnett 2014 (10mgEmpa Stage2CKD)	-31	9.0914	1.5%	-31.00 [-48.82, -13.18]	
arnett 2014 (25mgEmpa Stage2CKD)	-30	11.2703	1.4%	-30.00 [-52.09, -7.91]	
arnett 2014 (25mgEmpa Stage3CKD)	-5	8.9947	1.5%	-5.00 [-22.63, 12.63]	-+
arnett 2014 (25mgEmpa Stage4CKD)	51	23.6735	0.8%	51.00 [4.60, 97.40]	
ode 2013 (100mgCana)	-41.4863	5.4158	1.7%	-41.49 [-52.10, -30.87]	-
ode 2013 (300mgCana)	-45.1188	5.5621	1.7%	-45.12 [-56.02, -34.22]	-
riksson 2018 (10mgDapa)	-74	14.4278	1.3%	-74.00 [-102.28, -45.72]	
errannini 2010 (10mgDapa)	-39.8	8.0623	1.6%	-39.80 [-55.60, -24.00]	
errannini 2010 (2.5mgDapa)	-27.4	8.2073	1.6%	-27.40 [-43.49, -11.31]	
errannini 2010 (SmgDapa)	-38.7	8.2807	1.6%	-38.70 [-54.93, -22.47]	
riffin 2020 (10mgDapa)	-24.9	8.0014	1.0%	-24.90 [-40.70, -9.10]	
aring 2013 (10mgEmpa)	-39	119 9697	0.1%	-30 00 [-1.34, 2.34]	
aring 2013 (25mgEmpa)	-37	114 5513	0.1%	-37 00 [-261 52 187 52]	
2015 (100mgCana)	-29,7948	6,4139	1.7%	-29.79 [-42.3717.22]	
2015 (300mgCana)	-34.8723	6.1083	1.7%	-34.87 [-46.84, -22.90]	-
adowaki 2014 (10mgEmpa)	-51	10.8455	1.5%	-51.00 [-72.26, -29.74]	<u> </u>
adowaki 2014 (25mgEmpa)	-62	9.9674	1.5%	-62.00 [-81.54, -42.46]	
adowaki 2014 (50mgEmpa)	-45	10.2996	1.5%	-45.00 [-65.19, -24.81]	
adowaki 2014 (5mgEmpa)	-57	10.2996	1.5%	-57.00 [-77.19, -36.81]	
ario 2019 (10mgEmpa)	-32.714	9.671448	1.5%	-32.71 [-51.67, -13.76]	
ashiwagi 2014 (100mglpra)	-7.7324	5.3274	1.7%	-7.73 [-18.17, 2.71]	-
ashiwagi 2014 (12.5mglpra)	-2.974	4.3858	1.7%	-2.97 [-11.57, 5.62]	+
ashiwagi 2014 (25mglpra)	-23.1972	5.0475	1.7%	-23.20 [-33.09, -13.30]	-
ashiwagi 2014 (50mglpra)	-17.844	6.0985	1.7%	-17.84 [-29.80, -5.89]	
ee SH 2020 (10mgDapa)	-13.6804	10.635024	1.5%	-13.68 [-34.52, 7.16]	-+
ishimura 2015 (10mgEmpa)	-17	16.9262	1.1%	-17.00 [-50.17, 16.17]	+
ishimura 2015 (25mgEmpa)	-58	18.798	1.1%	-58.00 [-94.84, -21.16]	
ollock 2019 (10mgDapa)	-5.3	8.9287	1.5%	-5.30 [-22.80, 12.20]	
iu 2014 (150mgCana)	-35.62	11.9906	1.4%	-35.62 [-59.12, -12.12]	
iu 2014 (50mgCana)	-39.7454	7.9983	1.6%	-39.75 [-55.42, -24.07]	
oden 2013 (10mgEmpa)	-58	5.3452	1.7%	-58.00 [-68.48, -47.52]	
oden 2013 (25mgEmpa)	-02	5.5457	1.7%	-02.00 [-72.87, -01.13]	
osenstock 2012 (ToomgqdCana)	-39.2008	0.922	1.5%	-39.20 [-30.74, -21.77]	
osenstock 2012 (200mghidCana)	-04.1200	9.097472	1.0%	-04.15[-75.05,-54.75]	
osenstock 2012 (300mgadCana)	-35.688	8.452108	1.6%	-36.60 [-57.25 -10.12]	
osenstock 2012 (500mgquounu)	-28 5504	9.403788	1.5%	-28 55 [-46 98 -10 12]	
oss 2015 (10mggdEmna)	-20.3304	113 719	0.1%	-51 00 (-273 89 171 89)	
oss 2015 (12.5mgbidEmpa)	-65	112,8938	0.1%	-65.00 [-286.27, 156.27]	• • • • • • • • • • • • • • • • • • • •
oss 2015 (25mggdEmpa)	-56	110.4355	0.1%	-56.00 [-272.45, 160.45]	
oss 2015 (5mgbidEmpa)	-65	106.4002	0.1%	-65.00 [-273.54, 143.54]	
chumm-Draeger 2014 (10mgqdDapa)	-48.18	6.16	1.7%	-48.18 [-60.25, -36.11]	-
chumm-Draeger 2014 (2.5mgbidDapa)	-38.07	5.63	1.7%	-38.07 [-49.10, -27.04]	-
chumm-Draeger 2014 (5mgbidDapa)	-39.26	6.33	1.7%	-39.26 [-51.67, -26.85]	
eino 2014 (0.5mgLuseo)	-15.4648	8.487796	1.6%	-15.46 [-32.10, 1.17]	
eino 2014 (2.5mgLuseo)	-27.3608	8.487796	1.6%	-27.36 [-44.00, -10.73]	-
eino 2014 (5mgLuseo)	-23.792	9.659552	1.5%	-23.79 [-42.72, -4.86]	
eino 2018 (2.5mgLuseo)	2.974	5.97774	1.7%	2.97 [-8.74, 14.69]	+
himizu 2020 (10mgEmpa)	-59.48	11.134656	1.4%	-59.48 [-81.30, -37.66]	
tenlöf 2013 (100mgCana)	-48.8365	5.6445	1.7%	-48.84 [-59.90, -37.77]	-
teniot 2013 (300mgCana)	-52.6363	5.6195	1.7%	-52.64 [-63.65, -41.62]	
rojek 2011 (TomgDapa)	-27.36	6.8383	1.6%	-27.30 [-40.76, -13.96]	<u> </u>
aojek 2011 (2.5mgDapa) trojek 2011 (5mgDapa)	-22.6	0.4154	1.7%	-22.00 [-33.17, -10.03]	_
iojek zofi (ongolaja) Izkanan 2015 (10maEmpa)	-21.30	/.1826	1.0%	-27.30 [-41.44, -13.28]	-
ikkanen 2015 (TomgEmpa)	-33.04	4.4070	1.7.90	-33.04 [-41.00, -24.40]	-
(eher 2015 (2011gEnipa)	-30.23	4.403J 5.1174	1.7%	-30.23 [-30.33, -21.03]	-
(eber 2016 (10mgDana)	-17.844	6.06696	1.7%	-17.84 [-29.745.95]	
(ilding 2013a (100mgCana)	-30.6927	9.5308	1.5%	-30.69 [-49.37 -12.01]	
(ilding 2013a (300mgCana)	-34,2997	9.1273	1.5%	-34.30 [-52.19, -16.41]	
(ilding 2013b (12.5mglpra)	-37.8	8.7009	1.6%	-37.80 [-54.85, -20.75]	
(ilding 2013b (150mglpra)	-29.2	10.3624	1.5%	-29.20 [-49.51, -8.89]	
(ilding 2013b (300mglpra)	-30.8	9.633	1.5%	-30.80 [-49.68, -11.92]	
(ilding 2013b (50mglpra)	-27.1	8.6754	1.6%	-27.10 [-44.10, -10.10]	
ale 2014 (100mgCana)	13.0044	15.9708	1.2%	13.00 [-18.30, 44.31]	+
ale 2014 (300mgCana)	11.7458	14.1163	1.3%	11.75 [-15.92, 39.41]	+
ang 2015 (10mgDapa)	-18.4	45.49747413	0.3%	-18.40 [-107.57, 70.77]	
ang 2015 (5mgDapa)	-19	45.8853539	0.3%	-19.00 [-108.93, 70.93]	
ang 2018 (10mgDapa)	-9.5168	6.370308	1.7%	-9.52 [-22.00, 2.97]	7
anchi 2019 (10mgEmpa)	-97	11.3842	1.4%	-97.00 [-119.31, -74.69]	
0015 (10 5 - )	-18.3516	41.1540138	0.4%	-18.35 [-99.01, 62.31]	
nman 2015 (10mgEmpa)				20 56 1 00 00 57 061	
nman 2015 (10mgEmpa) nman 2015 (25mgEmpa)	-20.5642	40.06509016	0.4%	-20.56 [-99.09, 57.96]	
nman 2015 (10mgEmpa) inman 2015 (25mgEmpa) xtal (95% CI)	-20.5642	40.06509016	0.4%	-20.00 [-99.09, 07.90]	
nman 2015 (10mgEmpa) nman 2015 (25mgEmpa) xtal (95% Cl)	-20.5642	40.06509016	0.4% 100.0%	-20.56 [-99.09, 57.96] -31.48 [-37.35, -25.60]	· · · · ·



# 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.*,<sup>30</sup> Griffin *et al.*,<sup>64</sup> Ramírez-Rodríguez *et al.*<sup>33</sup> and Stack *et al.*<sup>71</sup> had a sample size of 24, 20, 24 and 36, respectively. One trial<sup>30</sup> 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 metaanalyses which quantify the serum urate-lowering properties of SGLT2 inhibitors in patients with T2DM.<sup>21–23</sup> 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.<sup>23</sup> This is in contrast to our study, as well as Xin *et al.*<sup>21</sup> and Chino *et al.*,<sup>30</sup> which did not find any significant dose-dependent difference in the urate-lowering effects of SGLT2 inhibitors.<sup>21,22</sup> 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.<sup>30,72</sup> Urate is freely filtered by the kidney and most of it is reabsorbed in the S1 segment of the proximal convoluted tubule (PCT).<sup>73,74</sup> 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 GLUT9 isoform 2 (SLC2A9b) found on the apical membrane of epithelial cells in the S1 segment of the PCT, involved in the excretion of urate.<sup>9</sup> Therefore, when SGLT2 is inhibited, the increased concentration of glucose within the lumen of the PCT competes with urate for GLUT9 isoform 2.<sup>30</sup> In addition to being found in the PCT, GLUT9 isoform 2 is also found in the collecting ducts, where it mediates urate reabsorption.<sup>75</sup> 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.<sup>30</sup> This uricosuric effect is also seen with phloridzin, a non-selective SGLT inhibitor, which induces uricosuria in healthy subjects.<sup>76</sup>

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.<sup>22</sup> 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,77 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<sup>78</sup> and for the prevention of gouty arthritis.<sup>79,80</sup> 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.<sup>19</sup> Given the strong association between urate levels and many other comorbidities,<sup>14</sup> 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,<sup>22,30</sup> 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.

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Elliot Yeung Chong: Data curation; Validation.

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**Ching-Hui Sia:** Conceptualization; Methodology; Supervision; Validation; Writing – review & editing.

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

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### Supplemental material

Supplemental material for this article is available online.

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