Diabetologia (2021) 64:2676–2686
https://doi.org/10.1007/s00125-021-05529-w

ARTICLE

The efficacy and safety of novel classes of glucose-lowering drugs for cardiovascular outcomes: a network meta-analysis of randomised clinical trials

Donna Shu-Han Lin[1,2,3] · Jen-Kuang Lee[1,3,4,5,6] · Chi-Sheng Hung[1,3,4,6] · Wen-Jone Chen[1,2,3,7]

Received: 13 January 2021 / Accepted: 23 April 2021 / Published online: 18 September 2021

Abstract

Aims/hypothesis Several cardiovascular outcome trials on sodium–glucose cotransporter 2 inhibitors (SGLT2i) have been released recently, including trials enrolling patients with congestive heart failure (CHF) and chronic kidney disease (CKD). Comparisons of the efficacy and safety of SGLT2i, glucagon-like peptide-1 receptor agonists (GLP-1RA) and dipeptidyl peptidase-4 inhibitors (DPP-4i) thus require an update. Assessments in patient subgroups, i.e., as stratified by age or the presence of CHF, CKD or atherosclerotic cardiovascular disease (ASCVD), are also currently lacking.

Methods We searched the PubMed, Embase and Cochrane databases for relevant studies published up until 5 December 2020. RCTs comparing SGLT2i, GLP-1RA and DPP-4i with placebo (or other controls) or with each other with cardiovascular (CV) or renal outcomes were eligible for inclusion. The primary efficacy endpoint was 3-point major adverse cardiovascular events (3P-MACE), which are defined as CV death, non-fatal myocardial infarction and non-fatal ischaemic stroke. All-cause mortality, hospitalisation for heart failure (HHF) and composite renal outcomes were also analysed. Pre-specified subgroup analyses of 3P-MACE were also performed.

Results A total of 21 trials with 170,930 participants were included in this network meta-analysis. Both GLP-1RA and SGLT2i were associated with lower risks of 3P-MACE than placebo (RR 0.89, 95% CI 0.84, 0.94 and RR 0.88, 95% CI 0.83, 0.94, respectively). GLP-1RA and SGLT2i were also associated with lower risks of 3P-MACE than DPP-4i (RR 0.89, 95% CI 0.82, 0.98 and RR 0.89, 95% CI 0.81, 0.97, respectively). A comparison between SGLT2i and GLP-1RA demonstrated no difference in their risks of 3P-MACE (RR 0.99, 95% CI 0.91, 1.08). Only GLP-1RA was associated with a lower risk of stroke compared with placebo (RR 0.85, 95% CI 0.76, 0.94). SGLT2i is superior to GLP-1RA in reducing HHF (RR 0.76, 95% CI 0.68, 0.84) and renal outcomes (RR 0.78, 95% CI 0.65, 0.93). Subgroup analyses indicated that the benefits of SGLT2i and GLP-1RA were more pronounced in elderly patients, white and Asian patients, those with established ASCVD and those with longer durations of diabetes mellitus and worse glycaemic control.

Conclusions/interpretation SGLT2i and GLP-1RA are superior to DPP-4i in terms of CV and renal outcomes. GLP-1RA is the only drug class that reduces the risk of stroke. SGLT2i is superior in reducing HHF and renal outcomes. Therefore, the choice between SGLT2i and GLP-1RA should be individualised according to patient profiles.

PROSPERO registration number: CRD42020206600.

Donna Shu-Han Lin and Jen-Kuang Lee contributed equally to this study.

✉ Chi-Sheng Hung
petrehcs@gmail.com

[1] Division of Cardiology, Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan

[2] Division of Cardiology, Department of Internal Medicine, National Taiwan University Hospital Hsin-Chu Branch, Hsin-Chu, Taiwan

[3] Cardiovascular Center, National Taiwan University Hospital, Taipei, Taiwan

[4] Department of Internal Medicine, National Taiwan University College of Medicine, Taipei, Taiwan

[5] Department of Laboratory Medicine, National Taiwan University College of Medicine, Taipei, Taiwan

[6] Telehealth Center, National Taiwan University Hospital, Taipei, Taiwan

[7] Department of Emergency Medicine, National Taiwan University College of Medicine and Hospital, Taipei, Taiwan

Research in context

What is already known about this subject?

- Cardiovascular outcome trials of glucose-lowering drugs shifted the goals of diabetes management from focusing on glycaemic control only to actively improving cardiovascular (CV) outcomes
- SGLT2i trials have expanded their study populations from diabetes patients only to also include patients with congestive heart failure or chronic kidney disease but not diabetes

What is the key question?

- How do DPP-4i, GLP-1RA and SGLT2i compare in terms of cardiovascular and composite renal outcomes?

What are the new findings?

- SGLT2i and GLP-1RA are superior to DPP-4i in terms of CV and renal outcomes
- GLP-1RA is the only drug class that reduces the risk of stroke
- SGLT2i is superior in reducing hospitalisation for heart failure and renal outcomes

How might this impact on clinical practice in the foreseeable future?

- Our results may guide choices between SGLT2i and GLP-1RA in clinical practice

Keywords Cardiovascular outcome trial · Composite renal outcome · CVOT · DPP4 · Meta-analysis · SGLT-2

Abbreviations

3P-MACE	3-Point major adverse cardiovascular events
ASCVD	Atherosclerotic cardiovascular disease
CHF	Congestive heart failure
CKD	Chronic kidney disease
CV	Cardiovascular
CVOT	Cardiovascular outcome trial
DPP-4i	Dipeptidyl peptidase-4 inhibitors
GLP-1RA	Glucagon-like peptide-1 receptor agonists
HHF	Hospitalisation for heart failure
IPD	Individual patient-level data
MACE	Major adverse cardiovascular events
MI	Myocardial infarction
SGLT2i	Sodium–glucose cotransporter 2 inhibitors

Introduction

Type 2 diabetes mellitus is a highly prevalent chronic disease, affecting approximately 8.5% of the adult population worldwide [1]. Diabetes is associated with high risk for atherosclerotic cardiovascular disease (ASCVD) [2]; in fact, ASCVD accounts for more than 60% of deaths among individuals with diabetes [3, 4]. Historically, the development of antidiabetic agents had focused on glucose-lowering effects only. Since 2008, however, the United States Food and Drug Administration (FDA) has mandated that randomised placebo-controlled cardiovascular outcome trials (CVOTs) be completed for all new glucose-lowering candidate drugs to confirm their cardiovascular (CV) safety before approval [5, 6]. Intriguingly, various CVOTs have shown not only that sodium–glucose cotransporter 2 inhibitors (SGLT2i) [7–10] and glucagon-like peptide-1 receptor agonists (GLP-1RA) [11–16] are safe, but that they even provide better results than placebo in terms of CV outcomes. These results shifted the goals of diabetes management from focusing on glycaemic control only to actively improving CV outcomes.

Although the effects of SGLT2i and GLP-1RA on CV events have been scrutinised in previous meta-analyses [17–19], new data on this subject continue to be released, such that an update is warranted. As evidence of the efficacy of SGLT2i continues to grow, trials on these drugs have expanded their study populations from diabetes patients only to also include patients with congestive heart failure (CHF) or chronic kidney disease (CKD) but not diabetes. The Dapagliflozin in Patients with Chronic Kidney Disease (DAPA-CKD) [20] trial was the first published SGLT2i CVOT that extended the enrolled population to patients with CKD either with or without diabetes. Over a median follow-up period of 2.4 years, the composite renal outcome was reduced by 39% in the dapagliflozin group compared with the placebo group, with significant concomitant reductions in major adverse cardiovascular events (MACE) and hospitalisation for heart failure (HHF). The DAPA-HF [21] trial was the first SGLT2i CVOT that specifically enrolled patients with CHF and a left ventricular ejection fraction of 40% or less. Over a median follow-up period of 18.2 months, the composite outcome of CV death or HHF was reduced significantly, by 26%, in the dapagliflozin

group compared with the placebo group. Trials targeting patients with CHF or CKD with or without diabetes that followed included the EMPEROR-Reduced [22], SCORED [23] and SOLOIST-WHF [24] trials. These studies have added to the existing body of data and shed new light on the performance of SGLT2i and GLP-1RA in non-diabetic patients and the mechanisms of their hypoglycaemia-independent effects.

Current guidelines on the choice of glucose-lowering agents recommend an individualised approach considering the patient's CV comorbidities, with SGLT2i or GLP-1RA suggested in patients who have established ASCVD, CHF or CKD, independent of HbA_{1c} levels. However, data directly comparing SGLT2i and GLP-1RA are lacking, and further evidence is needed to guide clinical choices between these two types of agents. In addition, past conclusions from subgroup analyses of CVOTs were often limited by patient number, and direct comparisons of the effects of SGLT2i and GLP-1RA in various subgroups would be highly beneficial in terms of optimising the treatment of diabetes.

Since the release of the latest guideline updates and the most recent meta-analysis, at least five large outcome trials of SGLT2i have been published. In this current network meta-analysis, we included 21 RCTs in our analysis, including the most recently published trials, namely, the SOLOIST-WHF and SCORED trials. We aimed to compare the relative efficacy of SGLT2i, GLP-1RA and dipeptidyl peptidase-4 inhibitor (DPP-4i) in terms of clinical outcomes. Besides a main analysis including MACE (a composite endpoint composed of myocardial infarction [MI], stroke, and CV death), all-cause mortality, HHF and composite renal outcomes, the effects of these drugs in several subgroups – e.g., as stratified by age or the presence of ASCVD, CHF or CKD – were also assessed.

Methods

The protocol of this study has been registered in PROSPERO (number CRD42020206600). The meta-analysis was performed according to the guidelines provided in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P).

Data sources and search strategies Patients eligible for inclusion were those with or without diabetes who participated in randomised trials conducted to evaluate one of the three classes of novel glucose-lowering agents (SGLT2i, GLP-1RA or DPP-4i) with pre-specified follow-up for CV or renal outcomes or for all-cause mortality. The PubMed, Embase and Cochrane databases were searched for English-language studies published from the inception of each database up until 5 December 2020. The search scope was limited to published outcome trials (i.e., those with CV outcomes, heart failure outcomes or renal outcomes) evaluating novel glucose-lowering drug classes, including the SGLT2i, GLP-1RA and DPP-4i classes, in patients with or without diabetes. The search keywords included 'sodium–glucose cotransporter 2 inhibitor', 'glucagon-like peptide-1 receptor agonist', 'dipeptidyl peptidase-4 inhibitor', 'major adverse cardiovascular event (MACE)', 'cardiovascular risk', 'cardiovascular event', 'heart failure', 'renal outcome', 'chronic kidney disease', and their synonyms and related keywords.

Outcomes The primary outcome was the standard 3-point MACE (3P-MACE), which consisted of CV death, non-fatal myocardial infarction (MI) and non-fatal ischaemic stroke. The secondary outcomes were CV death, fatal or non-fatal MI, fatal or non-fatal ischaemic stroke, all-cause mortality, HHF and the composite renal outcome. The definitions of composite renal outcomes varied across the included trials, but most of them were composed of an eGFR decline greater than 40% or 50% and progressed to end-stage renal disease. Definitions of the composite renal outcomes in each of the included trials are listed in electronic supplementary material (ESM) Table 1.

Data extraction The following data were extracted for the included studies: name of trial, year of publication, total number of patients, patient demographics (including age and sex), definition of population (diabetes, CHF or CKD), and information regarding subgroup variables (age, sex, BMI, BP control, race, use of metformin, ASCVD, diabetes duration, HbA_{1c}, eGFR, and CHF history) (Table 1). As for the extraction of outcome data, we extracted the sample size and number of events in each arm. For some situations, especially the subgroup analysis, we extracted the reported HR or adjusted HR that had been calculated by the study authors. We used the Cochrane Risk of Bias tool to assess the risk of bias for the studies enrolled in our analysis.

Statistical analysis The comparison of outcomes among the different glucose-lowering drug classes was made using the frequentist approach and multivariate meta-analysis estimated by restricted maximum likelihood. Pooled random-effects RRs, which were calculated directly from the reported tabular table (sample size and number of events), were chosen as the summary statistics. The pairwise comparisons among the treatment (SGLT2i, GLP-1RA and DPP-4i) and control groups were made using visual forest plots rather than tables. The overall heterogeneity of all the comparisons was assessed using the I^2 statistic, in which values of >25%, >50% and >75% corresponded to mild, moderate, and high heterogeneity, respectively. There were no direct comparisons between any two classes in all the trials; therefore, there was no evaluation of inconsistency between the direct and indirect effects

Table 1 Study-level characteristics of included RCTs

Trial	Year	Intervention arm	No. of participants	Median follow-up, years	Mean/median age, years	Female, %	BMI, kg/m^2 [a]	HbA_{1c}, mmol/mol (%) [a]	Baseline metformin, %	Baseline eGFR, ml min^{-1} [1.73 m]$^{-2}$ [a]	eGFR <60 ml min^{-1} [1.73 m]$^{-2}$, %	Prior ASCVD, %	Prior CHF, %
EMPA-REG OUTCOME	2015	Empagliflozin	7020	3.1	63	29	30.6	65 (8.1)	73	74	26	99	10
CANVAS	2017	Canagliflozin	10,142	2.4	63	36	32.0	67 (8.3)	77	77	20	66	14
DECLARE-TIMI 58	2019	Dapagliflozin	17,160	4.2	64	37	32.1	67 (8.3)	82	85	7	41	10
DAPA-HF	2019	Dapagliflozin	4744	1.5	66	23	28.2	NR	73	65	40	100	100
CREDENCE	2019	Canagliflozin	4401	2.6	63	34	31.3	67 (8.3)	66	56	59	50	15
VERTIS CV	2020	Ertugliflozin	8246	3.5	64	30	32	66 (8.2)	76	76	22	100	23
DAPA-CKD	2020	Dapagliflozin	4304	2.4	62	33	29.4	NA	NR	43	89	38	11
EMPEROR-Reduced	2020	Empagliflozin	3730	1.3	67	24	28.0	NA	NR	62	48	100	100
SOLOIST-WHF	2020	Sotagliflozin	1222	0.75	69	33	30.4	54 (7.1)	NR	49	NA	100	100
SCORED	2020	Sotagliflozin	10,584	1.3	69	44	32	67 (8.3)	NR	44	(eGFR <45) 52	NA	31
ELIXA	2015	Lixisenatide	6068	2.1	60	30	30.2	61 (7.7)	76	76	23	100	22
SUSTAIN-6	2016	Semaglutide	3297	2.1	54	39	NR	72 (8.7)	76	75	28.5	83	24
LEADER	2016	Liraglutide	9340	3.8	64	36	NR	72 (8.7)	73	75	23	81	18
EXSCEL	2017	Exenatide	14,752	3.2	62	38	NR	65 (8.1)	74	76	18	73	16
Harmony Outcomes	2018	Albiglutide	9463	1.6	64	31	32.3	73 (8.8)	81	79	23	100	20
REWIND	2019	Dulaglutide	9901	5.4	66	46	32.3	56 (7.3)	57	75	22	32	9
PIONEER 6	2019	Semaglutide	3182	1.3	66	32	32.3	66 (8.2)	51	74	27	85	NR
EXAMINE	2013	Alogliptin	5380	1.5	61	32	28.7	64 (8.0)	NA	71	29	100	28
SAVOR-TIMI 53	2013	Saxagliptin	16,492	2.1	65	33	31.2	64 (8.0)	69	73	(eGFR <50) 16	78	13
TECOS	2015	Sitagliptin	14,523	3.0	65	29	30.2	55 (7.2)	81	75	NR	100	18
CARMELINA	2019	Linagliptin	6979	2.2	66	37	31.4	64 (8.0)	54	55	62	57	27

NA, not available; NR, not recorded

[a] These are expressed as mean values

in this network meta-analysis. The potential publication bias was assessed using the visual funnel plot (control as the reference category) with the Egger's test in the traditional meta-analysis.

Focusing on 3P-MACE, we conducted several subgroup analyses according to pre-specified subgroup variables, including age (dichotomised by 65 years), sex, BMI (dichotomised by 30 kg/m^2), BP control (lower BP levels: good; higher BP levels: poor), race (white, black and Asian), use of metformin at baseline, pre-existing ASCVD, diabetes duration (dichotomised by 10 years), HbA_{1c} at baseline (lower vs higher), baseline renal function (eGFR ≥60 vs <60 ml min^{-1} [1.73 m]$^{-2}$), and the diagnosis of CHF. The network meta-analysis was carried out using the statistical package 'netmeta' (version 1.2-1; updated by 16 April 2020) in R (version 3.6.3).

Results

Results of the search The initial search identified 762 citations. After critical assessment of these papers, 21 RCTs fulfilled the inclusion criteria (Fig. 1), with a total of 170,930 participants.

Study characteristics The characteristics of the 21 included studies are presented in Table 1. The enrolled studies were published from 2013 to 2020. Of these studies, ten compared SGLT2i (the EMPA-REG OUTCOME, CANVAS, DECLARE-TIMI 58, DAPA-HF, CREDENCE, VERTIS CV, DAPA-CKD, EMPEROR-Reduced, SOLOIST-WHF, and SCORED studies), seven compared GLP-1RA (the ELIXA, SUSTAIN-6, LEADER, EXSCEL, Harmony Outcomes, REWIND, and PIONEER 6 studies), and four compared DPP-4i (the EXAMINE, SAVOR-TIMI 53, TECOS, and CARMELINA studies) against placebo. At present, however, there have still been no trials conducted to directly compare the CV outcomes of these three classes of glucose-lowering agents.

Risk of bias All the 21 trials met the criteria for low risk of bias. The detailed results of the risk-of-bias assessments are provided in the supplementary materials (ESM Fig. 1).

3P-MACE and the individual components ESM Fig. 2 shows the network of comparisons for the outcomes in these studies. Figure 2a–d shows the results of all the clinical outcomes. The results showed that both GLP-1RA and SGLT2i were associated with lower risks for 3P-MACE than placebo (RR 0.89, 95% CI 0.84, 0.94 and RR 0.88, 95% CI 0.83, 0.94,

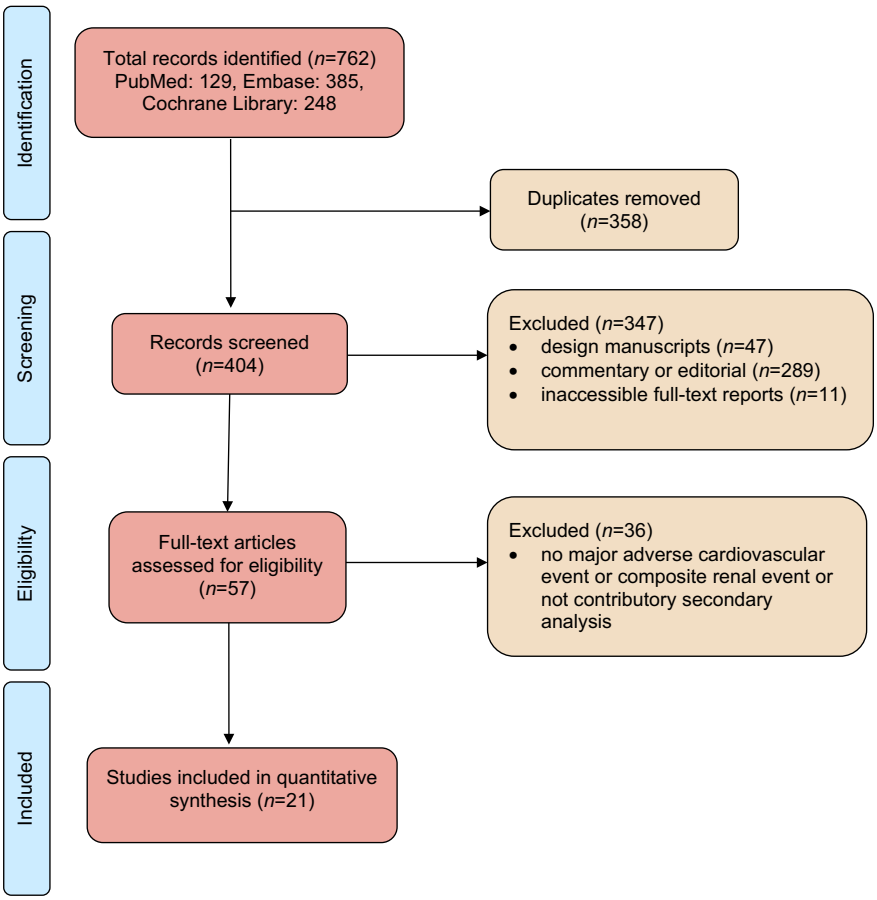

Fig. 1 PRISMA flow chart for the identification, inclusion and exclusion of studies

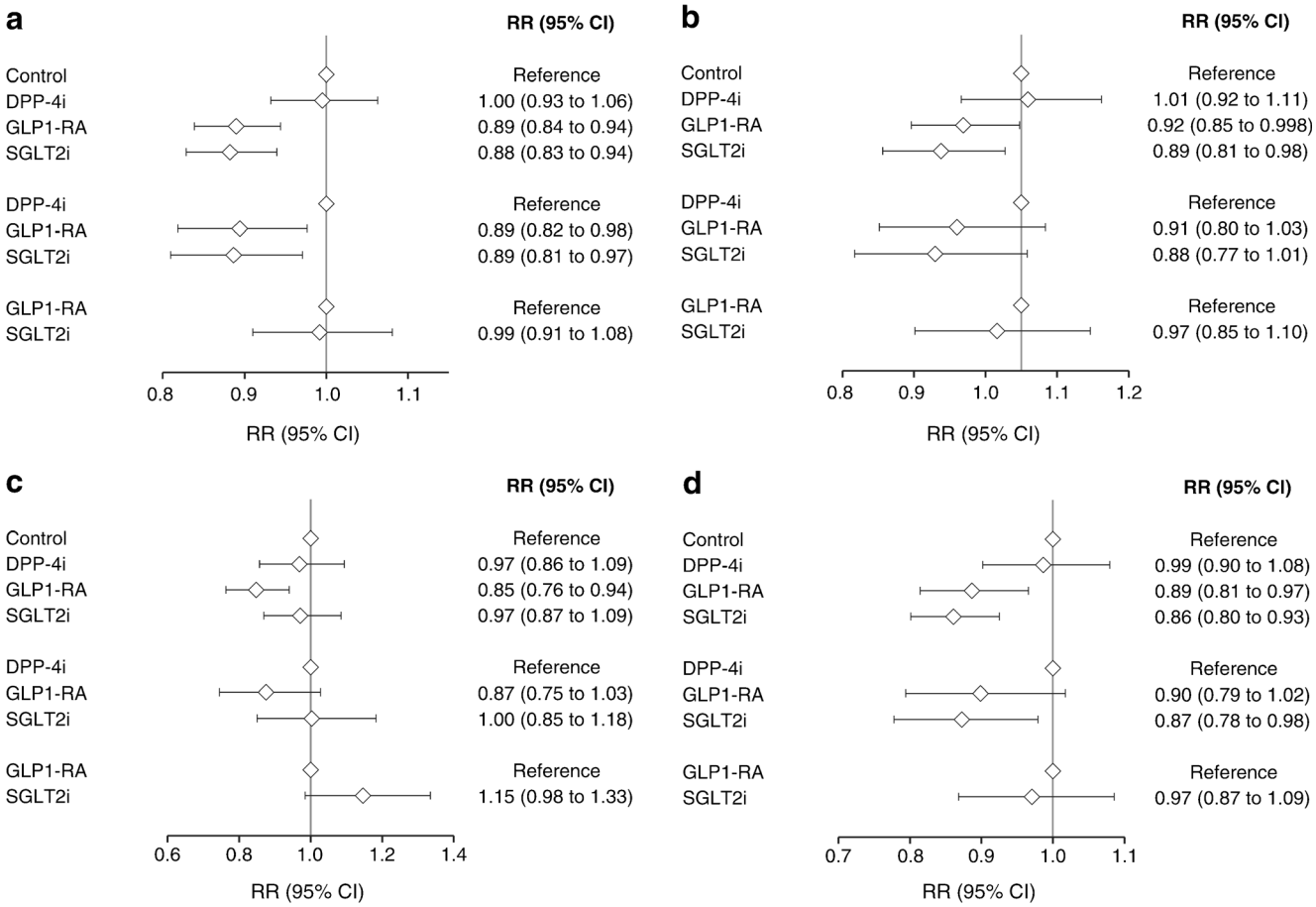

Fig. 2 Forest plot of the network meta-analysis of 3P-MACE (**a**), fatal or non-fatal MI (**b**), fatal or non-fatal ischaemic stroke (**c**), and CV death (**d**)

respectively). GLP-1RA and SGLT2i were also associated with lower risks of 3P-MACE than DPP-4i (RR 0.89, 95% CI 0.82, 0.98 and RR 0.89, 95% CI 0.81, 0.97, respectively). The comparison between SGLT2i and GLP-1RA demonstrated no difference in their risks of 3P-MACE (RR 0.99, 95% CI 0.91, 1.08). The comparison between DPP-4i and placebo also suggested no difference in their frequencies of 3P-MACE (Fig. 2a). In addition, the overall heterogeneity was moderate, with an I^2 of 30.9% (95% CI 0%, 62.2%).

As for fatal or non-fatal MI, both GLP-1RA and SGLT2i were associated with lower risks than placebo (RR 0.92, 95% CI 0.85, 0.998 and RR 0.89, 95% CI 0.81, 0.98, respectively). SGLT2i and GLP-1RA were also associated with lower risks than DPP-4i, although the differences in risks were not statistically significant (Fig. 2b). In terms of fatal or non-fatal stroke, only the GLP-1RA class was associated with lower risks than placebo (RR 0.85, 95% CI 0.76, 0.94). The results also demonstrated that the GLP-1RA class was associated with a lower risk of stroke than SGLT2i and DDP4i, although the differences in risks were not statistically significant (Fig. 2c). With respect to CV death, both GLP-1RA and SGLT2i were associated with lower risks than placebo (RR 0.89, 95% CI 0.81, 0.97 and RR 0.86, 95% CI 0.80, 0.93, respectively). Noticeably, both SGLT2i (to a significant degree) and GLP-1RA (to a borderline significant degree) were also associated with lower risks for CV death than DPP-4i. The comparison between SGLT2i and GLP-1RA revealed no difference in terms of CV mortality (Fig. 2d). In addition, the overall heterogeneity levels of MI, stroke and CV death were low ($I^2 = 24.3\%$), low ($I^2 = 7.8\%$), and low ($I^2 = 16.5\%$), respectively.

Other clinical outcomes The results demonstrated that both GLP-1RA and SGLT2i were associated with lower risks of all-cause mortality than placebo (RR 0.89, 95% CI 0.83, 0.96, and RR 0.87, 95% CI 0.81, 0.93, respectively). Both SGLT2i (to a significant degree) and GLP-1RA (to a borderline significant degree) were also associated with reduced risks of all-cause mortality compared with DPP-4i. The comparison between SGLT2i and GLP-1RA showed similar effects for the two classes on all-cause mortality (Fig. 3a). Regarding HHF, the SGLT2i class was associated with reduced risks compared with the other three groups. On the other hand, the GLP-1RA class was also associated with lower risks for HHF than DPP-4i and placebo (Fig. 3b). In terms of renal outcomes, the SGLT2i class was associated with lower risks

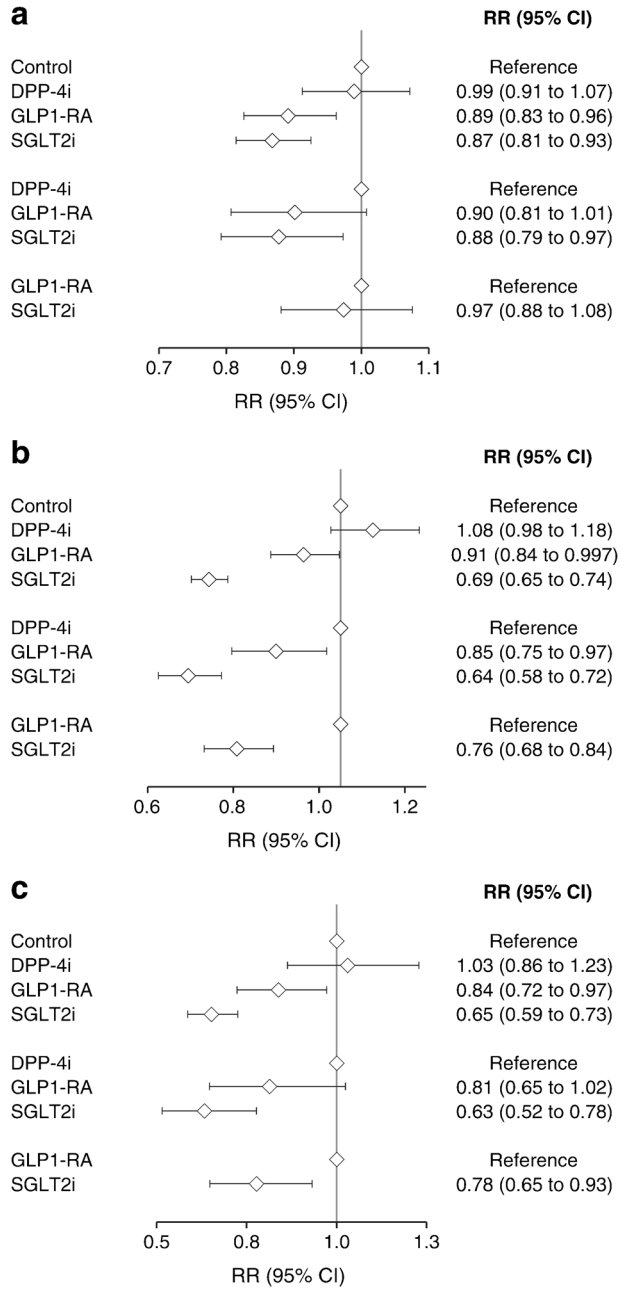

Fig. 3 Forest plot of the network meta-analysis of all-cause death (**a**), HHF (**b**) and composite renal outcomes (**c**)

than the other three groups. Notably, the GLP-1RA class was also associated with lower risks of composite renal outcomes than placebo (to a significant degree) and DPP-4i (to a borderline significant degree) (Fig. 3c). In addition, the overall heterogeneity levels of all-cause death, HHF and composite renal outcome were moderate ($I^2 = 31.5\%$), low ($I^2 = 0\%$), and moderate ($I^2 = 58.5\%$), respectively.

Subgroup analysis for 3P-MACE Subgroup analyses showed that among individuals aged <65 years, only GLP-1RA significantly reduced 3P-MACE compared with placebo. Among those aged ≥65 years, the relative efficacy levels of each class of drugs were similar to those in the main analysis (Fig. 4a). The benefits of SGLT2i and GLP-1RA, as compared with either placebo or DPP-4i, were more apparent in the white and Asian populations (Fig. 4b). Among individuals with pre-existing ASCVD, the relative efficacy levels of these glucose-lowering agents were similar to those in the main analysis, while in those without established ASCVD, the analysis showed no clear superiority of one type of agent compared with another (Fig. 4c). Among individuals with diabetes duration <10 years, only GLP-1RA significantly reduced 3P-MACE compared with placebo. However, the relative efficacy levels of these glucose-lowering agents were similar to those in the main analysis in patients with diabetes duration ≥10 years (Fig. 4d). Other subgroup analyses, including analyses of sex, BMI, BP control, use of metformin, HbA_{1c} level, eGFR and history of CHF, are illustrated in ESM Figs 3–9.

Publication bias and heterogeneity ESM Figs 10–16 demonstrate the funnel plot along with Egger's test on the seven outcomes. Some asymmetry was noted in MACE ($p = 0.034$), CV death ($P = 0.098$) and all-cause mortality ($p = 0.108$), indicating a potential threat of publication bias. ESM Table 2 lists the heterogeneity (expressed as I^2 derived from the traditional meta-analysis) in each class of the drugs and the overall drugs. It should be noted that heterogeneity within each class of drug was smaller than the overall heterogeneity on HHF and composite renal outcome, suggesting there were more homogeneous effects within classes and difference between classes.

Discussion

In this network meta-analysis, we included the most updated data from RCTs of SGLT2i, GLP-1RA and DPP-4i that were designed to assess their efficacy in terms of CV or renal outcomes. Our analyses confirmed several findings. First, when compared with placebo, both SGLT2i and GLP-1RA significantly reduced the risks of MACE, death from any cause, HHF and composite outcome of renal events. Regarding the components of MACE, when compared with placebo, both SGLT2i and GLP-1RA reduced the risks of MI and CV death; however, only the GLP-1RA class was associated with a lower risk of stroke (ESM Fig. 17). Second, the DPP-4i class was similar to placebo in terms of MACE, all the components of MACE, death from any cause, HHF and composite outcome of renal events. Third, when compared with GLP-1RA, SGLT2i led to significantly lower risks of HHF and renal events, but were associated with an increased risk of stroke that almost reached statistical significance. GLP-1RA and SGLT2i were otherwise similar in terms of MACE,

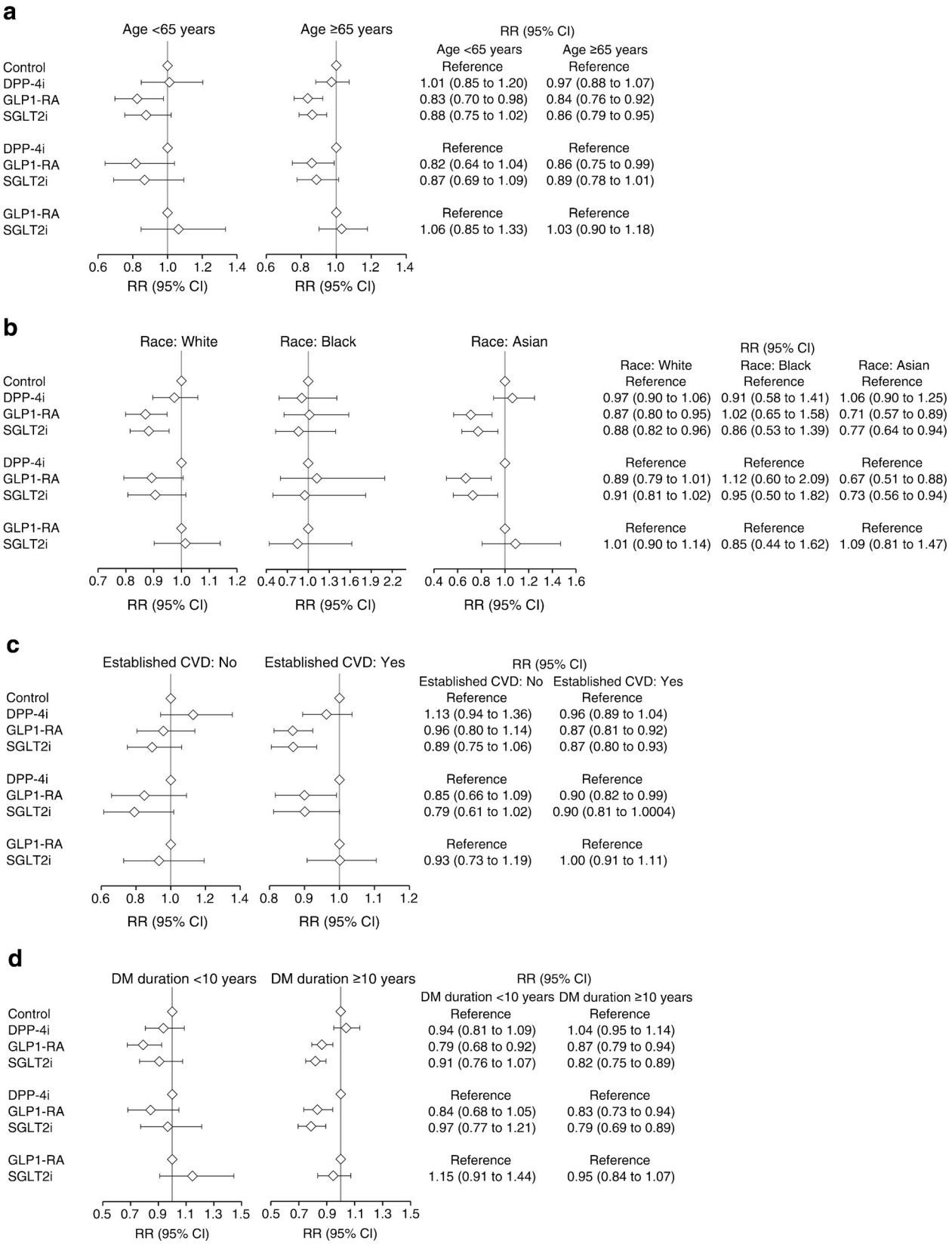

Fig. 4 Subgroup analysis of 3P-MACE by age group (**a**), race (**b**), established ASCVD (**c**) and duration of diabetes (**d**). DM, diabetes mellitus

MI, CV death and all-cause mortality. In addition to the above-mentioned results, subgroup analyses revealed that the efficacy levels of GLP-1RA and SGLT2i in reducing MACE are more pronounced in those older than 65 years, in Asians and white people, in those with established ASCVD, and in those with diabetes for over 10 years (ESM Fig. 18).

Both SGLT2i and GLP-1RA have demonstrated benefits in terms of reducing CV events, but via entirely distinct mechanisms [6]. GLP1 receptors are present in the brain, pancreas and stomach, and are responsible for the control of centrally mediated satiety, sympathetic activation, postprandial insulin release and gastrointestinal motility inhibition [6]. The actions of GLP-1RA are complex, not only enhancing the aforementioned effects of GLP1 receptors, but ultimately leading to anti-atherogenic effects. In addition to actions via the incretin system, GLP-1RA has also demonstrated anti-inflammation, endothelial function enhancement, and plaque stabilisation effects through other pathways [25–27]. This in in contrast to SGLT2i, which exert actions primarily through glucosuria and natriuresis, with subsequently reduced tubuloglomerular feedback, improved intraglomerular hypertension and hyperfiltration, and decreased cardiac preload and afterload [28, 29]. These actions lead to reduced myocardial stress and ventricular arrhythmias. SGLT2i exhibit their effects primarily through haemodynamic changes and less through anti-atherogenic effects. The results of our analysis and prior studies conform with this concept. Both GLP-1RA and SGLT2i are effective in reducing risks of MACE, death from any cause, HHF, and composite outcome of renal events when compared with placebo. When the components of MACE are examined, however, only the GLP-1RA class significantly reduces the risk of stroke. A direct comparison between GLP-1RA and SGLT2i was consistent with this finding, while just missing statistical significance. This likely reflects the effects of GLP-1RA on plaque stabilisation. On the other hand, SGLT2i outperformed GLP-1RA in terms of reducing HHF and renal events, findings which are also compatible with its haemodynamic influences.

In our analysis, GLP-1RA failed to reach statistical significance in terms of stroke reduction when directly compared with SGLT2i (SGLT2i HR 1.15, 95% CI 0.98, 1.33). The efficacy levels of SGLT2i and GLP-1RA in terms of the reduction of stroke risk have been inconsistent across individual studies. In a network meta-analysis by Fei et al [19], when comparing SGLT2i, GLP-1RA and DPP-4i to placebo, the GLP-1RA class was also the only class of drugs to demonstrate a significant reduction in strokes. However, a direct comparison between SGLT2i and GLP-1RA was not conducted by Fei et al. Tsapas et al [30] also examined the effectiveness of glucose-lowering agents in a network meta-analysis with a subgroup analysis of patients stratified by CV risk. They found that SGLT2i and GLP-1RA did not differ in terms of their risks of stroke in patients with low CV risk, but GLP-1RA significantly reduced stroke events compared with SGLT2i in patients with increased CV risk. Interestingly, when examining individual trials included in our analysis, most trials involving SGLT2i reported either similar incidence rates of stroke in the intervention and placebo arms or just slightly fewer events in the intervention arm. However, in the most recently published SCORED [23] study – an RCT that enrolled patients with diabetes, concomitant CKD, and risk for CV disease – there were approximately 1.5 times the number of stroke events in the placebo arm compared with the sotagliflozin group. Notably, however, this was not observed in the SOLOIST-WHF [24] study, in which sotagliflozin was compared with placebo in patients with diabetes who were recently hospitalised for worsening heart failure. Sotagliflozin is, currently, the SGLT2i with the highest affinity for sodium–glucose cotransporter 1 (SLGT1) receptors. Whether the protective effects against stroke are limited to sotagliflozin, or more specifically, sotagliflozin in patients with CKD, is unknown, and requires further study.

It has been postulated that SGLT2i and GLP-1RA may not only serve as secondary means of preventing CV events, but that they may also play a role in primary prevention. In the present meta-analysis, the effects of SGLT2i, GLP-1RA and DPP-4i were examined separately in patients with and without pre-existing ASCVD. In the subgroup analysis, patients without established ASCVD taking SGLT2i, GLP-1RA, DPP-4i and placebo had comparable MACE. On the other hand, in patients with pre-existing ASCVD, both SGLT2i and GLP-1RA were associated with lower risks of MACE compared with placebo; this effect was also present when compared with DPP-4i, although the differences in risks were less significant. In a systematic review and meta-analysis by Zelniker et al [18], the authors reported that SGLT2i and GLP-1RA reduced MACE to similar extents in patients with diabetes, but only in those with established ASCVD. This finding conforms with the results of our analysis. Thus, as of today, evidence only supports SGLT2i and GLP-1RA as secondary means of preventing MACE in patients with ASCVD.

In the subgroup analysis of the present study, we evaluated the effects of SGLT2i, GLP-1RA and DPP-4i in white, black and Asian individuals. SGLT2i, GLP-1RA and DPP-4i exhibited no differences in terms of reducing MACE compared with placebo in the black population. However, both SGLT2i and GLP-1RA led to lower risks of MACE when compared with placebo in white people and Asians, similar to the results of our main analysis. When comparing SGLT2i and GLP-1RA against DPP-4i, a significant reduction of MACE was seen only in Asians. Differences in the epidemiology of ASCVD and its risk factors among various races have been well reported in the past. For example, the prevalence levels of several CV risk factors, such as hypertension, diabetes and obesity, were found to be higher among African Americans than among white people [31, 32]. Conversely, the triacylglycerol/HDL-cholesterol ratio, an atherogenic index that is an independent predictor of MI, is generally lower in

black people and higher in Asians [33]. Several non-traditional risk factors, such as inflammatory markers, have been proposed to play a role in ASCVD in South Asians, in whom coronary artery disease occurs at younger ages [34, 35]. The variable effects of risk factors on CV outcomes across different ethnic groups reflects the complex interplay between genetic background and ASCVD. Why and how the efficacy of SGLT2i and GLP-1RA in reducing MACE varies across races is largely unknown and will likely require investigations at the genomic and proteomic levels to fully elucidate.

There were several limitations in this study. First, there were seven outcomes and 14 subgroup analyses and the family-wise type 1 error would be much higher than 0.05. This is due to the lack of adjustment for multiple comparison in the current study, and therefore there would be a few false positive results (ESM Tables 3–14). The obtained conclusions from this study should be taken more conservatively. Second, the subgroup analysis was presented descriptively without statistical tests. There are some developed approaches to deal with the covariate effects in the network meta-analysis when using the individual patient-level data (IPD). However, using the aggregated information regarding patient characteristics in a network meta-regression is vulnerable to ecological bias, according to previous reports [36, 37]. Therefore, future network meta-analysis with IPD is warranted to confirm the conclusions obtained from the subgroup analysis.

Conclusions In the current network meta-analysis including 21 CVOTs of SGLT2i, GLP-1RA and DPP-4i, both SGLT2i and GLP-1RA were associated with lower risks of MACE, death from any cause, HHF and composite outcome of renal events. The effects of DPP-4i were neutral and similar to those of placebo. The GLP-1RA class was superior in terms of reducing the risk of stroke, whereas SGLT2i led to significantly lower risks of HHF and renal events. The efficacy levels of GLP-1RA and SGLT2i in reducing MACE were more pronounced in elderly patients, in Asians and white people, in those with pre-existing ASCVD, and in those with diabetes for longer durations. These results may guide choices between SGLT2i and GLP-1RA in clinical practice, although further validation by studies directly comparing these two classes of drugs would be beneficial.

Supplementary Information The online version contains peer-reviewed but unedited supplementary material available at https://doi.org/10.1007/s00125-021-05529-w.

Acknowledgements We thank Alfred HF Lin, and Zoe YZ Syu, Raising Statistics Consultant Inc. New Taipei City, Taiwan, for their assistance with the statistical analysis during the completion of the manuscript.

Data availability The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Funding This research was supported by the Ministry of Science and Technology of Taiwan (MOST 108-2221-E-002-163-, MOST 109-2221-E-002 -083) and National Taiwan University Hospital (107-EDN11, 108-N4406, 108EDN02, 109-O20, 109-S4579, 109-EDN11).

Authors' relationships and activities The authors declare that there are no relationships or activities that might bias, or be perceived to bias, their work.

Contribution statement All authors significantly contributed to the manuscript and approved the final version for publication. WJC and JKL contributed to the study design, data acquisition, analysis and manuscript revision. JKL and CSH contributed to data acquisition, interpretation of data and manuscript revision. DSHL contributed to data analysis, interpretation of data, manuscript drafting and revision. JKL is the guarantor of this work.

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