Systematic Review and Meta-Analysis

Medicine®

OPEN

Impact of demographic characteristics and antihyperglycemic and cardiovascular drugs on the cardiorenal benefits of SGLT2 inhibitors in patients with type 2 diabetes mellitus

A protocol for systematic review and meta-analysis

Rong Chang, PhD[a], Shu-Yan Liu, MS[b], Li-Min Zhao, MD[c,*]

Abstract

Background: It is unclear whether demographic characteristics and baseline use of hypoglycemic and cardiovascular drugs significantly affect the efficacy of sodium-glucose transporter 2 (SGLT2) inhibitors on cardiorenal outcomes in patients with type 2 diabetes mellitus (T2DM).

Methods: Randomized trials assessing the efficacy of SGLT2 inhibitors on cardiorenal outcomes in adult patients with T2DM were included in analysis. Three endpoints of interest were major adverse cardiovascular events (MACE), hospitalization for heart failure or cardiovascular death (HHF or CV death), and kidney composite outcome (KCO). We performed random-effects meta-analysis using the aggregate data of hazard ratios (HRs) and 95% confidence intervals (CIs). Subgroup analyses were done according to 17 factors of interest, including 7 factors related to demographic characteristics and 10 related to baseline use of antihyperglycemic and cardiovascular drugs such as renin–angiotensin system (RAS) inhibitor. We conducted meta-regression analyses to calculate *P* values for subgroup differences.

Results: Seven trials were included in this meta-analysis. Compared with placebo, SGLT2 inhibitors significantly lowered the risk of MACE (HR 0.90, 95% CI 0.84–0.97) regardless of demographic characteristics and baseline use of insulin, statin or ezetimibe, RAS inhibitor, beta-blocker, and diuretic ($P_{subgroup}$ from 0.088–0.981); that of HHF or CV death (HR 0.78, 95% CI 0.71–0.85) regardless of demographic characteristics and baseline use of 10 antihyperglycemic and cardiovascular drugs ($P_{subgroup}$ from 0.147–0.999); and that of KCO (HR 0.63, 95% CI 0.57–0.69) regardless of demographic characteristics and baseline use of statin or ezetimibe, RAS inhibitor, and diuretic ($P_{subgroup}$ from 0.073–0.918).

Conclusions: The cardiorenal benefits of SGLT2 inhibitors were consistent in a broad population of T2DM patients. The findings of this meta-analysis suggest that SGLT2 inhibitors should be recommended in T2DM patients for the prevention of cardiorenal events, regardless of various demographic characteristics and baseline use of various hypoglycemic and cardiovascular drugs.

Abbreviations: CI = confidence interval, DPP-4i = dipeptidyl peptidase-4 inhibitor, GLP-1RA = GLP-1 receptor agonist, HHF or CV death = hospitalization for heart failure or cardiovascular death, HR = hazard ratio, KCO = kidney composite outcome, MACE = major adverse cardiovascular events, MRA = mineralocorticoid receptor antagonist, PRISMA = preferred reporting items for systematic reviews and meta-analyses, RAS = renin–angiotensin system, SBP = systolic blood pressure, SGLT2 = sodium-glucose cotransporter 2, T2DM = type 2 diabetes mellitus.

Keywords: cardiovascular drugs, demographic characteristics, hypoglycemic drugs, sodium-glucose cotransporter 2 inhibitors, type 2 diabetes mellitus

Editor: Leena Mallik.

The authors have no funding and conflicts of interests to disclose.

Supplemental Digital Content is available for this article.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

[a] Cardiovascular Department, Shenzhen Longhua District Central Hospital, Shenzhen, China, [b] Department of Endocrinology, The Second Affiliated Hospital of Kunming Medical University, Kunming, China, [c] Department of General Medicine, Shenzhen Longhua District Central Hospital, Shenzhen, China.

[*] Correspondence: Li-Min Zhao, Department of General Medicine, Shenzhen Longhua District Central Hospital, Guanlan Avenue 187, Longhua District, Shenzhen City 518110, China (e-mail: zlmrain@sohu.com).

Copyright © 2021 the Author(s). Published by Wolters Kluwer Health, Inc.
This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial License 4.0 (CCBY-NC), where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.

How to cite this article: Chang R, Liu SY, Zhao LM. Impact of demographic characteristics and antihyperglycemic and cardiovascular drugs on the cardiorenal benefits of SGLT2 inhibitors in patients with type 2 diabetes mellitus: a protocol for systematic review and meta-analysis. Medicine 2021;100:47(e27802).

Received: 25 May 2021 / Received in final form: 1 October 2021 / Accepted: 26 October 2021

http://dx.doi.org/10.1097/MD.0000000000027802

1. Introduction

There are several meta-analyses[1–7] which have revealed the distinct benefits of sodium-glucose cotransporter 2 (SGLT2) inhibitors on cardiorenal outcomes in patients with type 2 diabetes mellitus (T2DM). Unfortunately, none of these prior meta-analyses[1–7] completely assessed those clinically important factors which probably affected the cardiorenal efficacy of SGLT2 inhibitors in T2DM patients. However, as for the optimal application of this new class of hypoglycemic agents, it is very important to know whether SGLT2 inhibitors are applicable for T2DM subpopulations with specific demographic characteristics, or those with/without baseline use of specific antihyperglycemic drugs or cardiovascular drugs. Moreover, at present there is some new evidence of cardiorenal outcomes with SGLT2 inhibitors in T2DM patients from 3 large randomized trials, namely the VERTIS CV trial[8] evaluating ertugliflozin in T2DM patients with established cardiovascular disease, the SOLOIST-WHF trial[9] evaluating sotagliflozin in T2DM patients with worsening heart failure, and the SCORED trial[10] evaluating sotagliflozin in T2DM patients with chronic kidney disease. However, all the previous meta-analyses, aiming to assess the cardiorenal efficacy of SGLT2 inhibitors in the clinically important subgroups of T2DM patients, failed to incorporate 2 or 3 of the new trials.[8–10] Hence, we aimed to include all the randomized trials that focused on cardiorenal endpoints with SGLT2 inhibitors in T2DM patients to perform an updated meta-analysis, in order to explore whether various factors related to demographic characteristics and those related to baseline use of hypoglycemic and cardiovascular drugs affect the efficacy of SGLT2 inhibitors on cardiorenal endpoints in patients with T2DM.

2. Methods

We report this meta-analysis in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[11] The according PRISMA checklist is given in (Table S1, Supplemental Content, which provides the PRISMA checklist, http://links.lww.com/MD/G5110).

2.1. Inclusion criteria and risk of bias assessment

We utilized the separate search strategies for PubMed and Embase (see Table S2, Supplemental Content, which details the separate search strategies for the 2 databases, http://links.lww.com/MD/G511) to search relevant studies from the start date of databases to January 8th, 2021. We included those randomized trials which aimed at assessing the effect of SGLT2 inhibitors compared to placebo on cardiorenal endpoints in adult patients with T2DM. Three cardiorenal outcomes interesting for us were major adverse cardiovascular events (MACE), hospitalization for heart failure or cardiovascular death (HHF or CV death), and kidney composite outcome (KCO). MACE was a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke; and KCO was a composite of doubling of serum creatinine or sustained 40% reduction in the estimated glomerular filtration rate, initiation of renal-replacement therapy or occurrence of end-stage kidney disease, or renal death.

Seventeen factors of interest consisted of 7 factors relevant with demographic characteristics, 5 factors relevant with baseline use of antihyperglycemic drugs, and 5 factors relevant with baseline use of cardiovascular drugs. Subgroups defined by demographic characteristics were subgroups with age (<65 year, or ≥65 year), sex (male, or female), region (North America, Central/South America, Europe, or other), ethnicity (Caucasian, or Non-Caucasian), body mass index (<30 kg/m^2, or ≥30 kg/m^2), blood pressure control (systolic blood pressure ≥140 or diastolic blood pressure ≥90 mm Hg, or systolic blood pressure < 140 and diastolic blood pressure < 90 mm Hg), and duration of diabetes (<10 year, or ≥10 year). Subgroups defined by baseline use of antihyperglycemic drugs were subgroups with sulfonylurea or thiazolidinedione use (yes, or no), metformin use (yes, or no), dipeptidyl peptidase-4 inhibitor (DPP-4i) use (yes, or no), GLP-1 receptor agonist (GLP-1RA) use (yes, or no), and insulin use (yes, or no). Subgroups defined by baseline use of cardiovascular drugs were subgroups with statin or ezetimibe use (yes, or no), mineralocorticoid receptor antagonist (MRA) use (yes, or no), renin–angiotensin system (RAS) inhibitor use (yes, or no), beta-blocker use (yes, or no), and diuretic use (yes, or no).

Study selection according to the inclusion criteria, risk of bias assessment for included studies, and data extraction from included studies, were separately completed by 2 authors. Discussion between them or the arbitrament by a third author addressed all the divergences encountered in the above assignments. The quality assessment for included trials was performed on the basis of the Cochrane risk of bias assessment tool.[12]

2.2. Statistical analysis

Using the aggregate survival data of hazard ratios (HRs) and 95% confidence intervals (CIs) extracted from included studies, we performed random-effects meta-analysis with the method of DerSimonian & Laird. Heterogeneity across studies was assessed by I^2 statistic. Subgroup analyses were done for the 3 outcomes of interest, respectively according to each of the 17 factors of interest. When there was 1 subgroup including less than 2 studies, we quitted doing corresponding subgroup analysis. P values for subgroup differences were calculated by meta-regression analyses, and $P_{subgroup} < 0.05$ denotes statistical significance. All the statistical analyses conducted in this meta-analysis were completed in the Stata/SE software (version 15.1).

2.3. Ethical statement

The data analyzed in this study were extracted from previously published studies, and thus ethical approval was not necessary.

3. Results

3.1. Characteristics of included trials

After performing study selection according to the inclusion criteria, we ultimately included the following 7 trials in this meta-analysis: CREDENCE trial[13] regarding canagliflozin, DECLARE–TIMI 58 trial[14] regarding dapagliflozin, CANVAS Program trial[15] regarding canagliflozin, EMPA-REG OUTCOME trial[16] regarding empagliflozin, VERTIS CV trial[8] regarding ertugliflozin, SCORED trial[10] regarding sotagliflozin, and SOLOIST-WHF trial[9] regarding sotagliflozin. The process of study selection is detailed in (Figure S1, Supplemental Content, which presents the flow diagram of study selection, http://links.lww.com/MD/G505). The included trials involved a total of 58,783 patients with T2DM, and all of the trials were high-quality studies with low risk of bias (see Figure S2, Supplemental

Content, which shows each trial with the low risk of bias, http://links.lww.com/MD/G506).

3.2. Meta-analyses

As is summarized in Figure 1, compared to placebo, SGLT2 inhibitors significantly lowered the risk of MACE (HR 0.90, 95% CI 0.84–0.97), regardless of 7 factors related to demographic characteristics and regardless of baseline use of insulin, statin or ezetimibe, RAS inhibitor, beta-blocker, and diuretic ($P_{subgroup}$ from 0.088–0.981). These meta-analysis results are detailed in (Figure S3, Supplemental Content, which illustrates the effects of SGLT2 inhibitors on MACE according to various factors, http://links.lww.com/MD/G507). The relevant data was not sufficient to assess the impact of sulfonylurea or thiazolidinedione, metformin, DPP-4i, GLP-1RA, and MRA on the efficacy of SGLT2 inhibitors on MACE.

As is summarized in Figure 2, compared to placebo, SGLT2 inhibitors significantly lowered the risk of HHF or CV death (HR 0.78, 95% CI 0.71–0.85), regardless of 7 factors related to

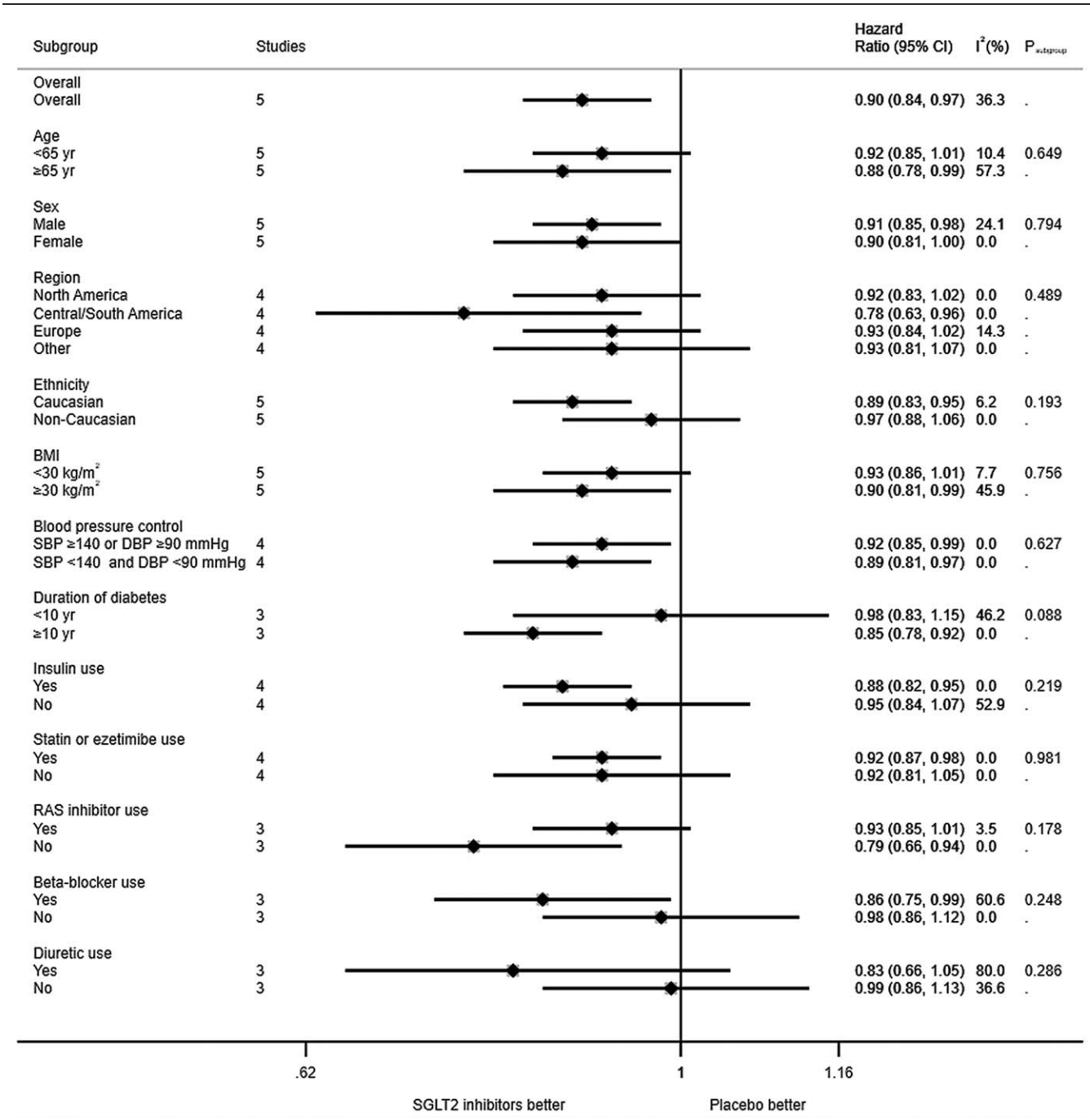

Figure 1. Efficacy of SGLT2 inhibitors on MACE, stratified by 7 factors related to demographic characteristics and baseline use of insulin, statin or ezetimibe, RAS inhibitor, Beta-blocker, and diuretic. MACE = major adverse cardiovascular events, RAS = renin–angiotensin system, SGLT2 = sodium-glucose cotransporter 2.

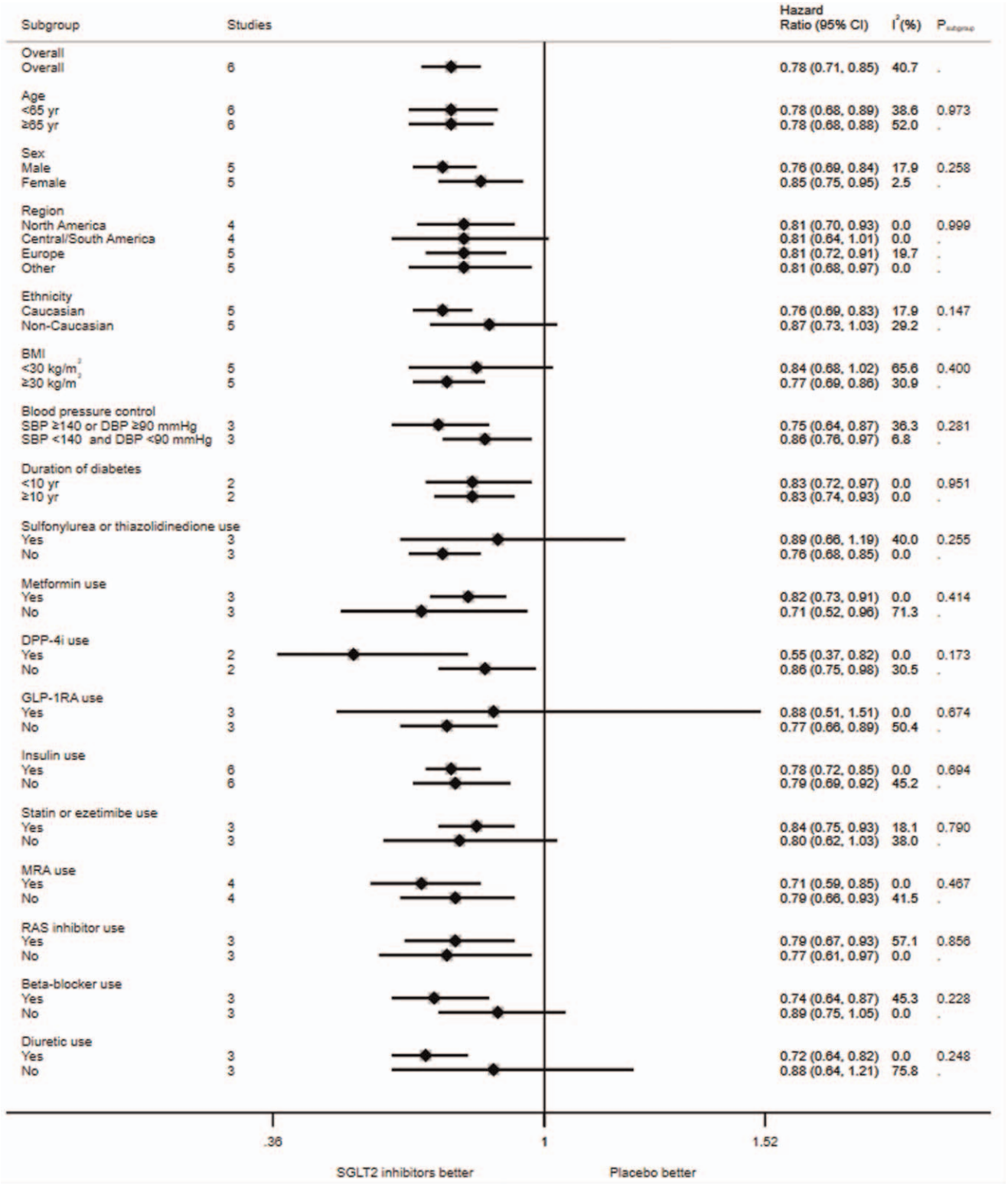

Figure 2. Efficacy of SGLT2 inhibitors on the composite of HHF or CV death, stratified by 7 factors related to demographic characteristics and baseline use of 10 antihyperglycemic and cardiovascular drugs. HHF or CV death = hospitalization for heart failure or cardiovascular death, SGLT2 = sodium-glucose cotransporter 2.

demographic characteristics and regardless of baseline use of 10 antihyperglycemic and cardiovascular drugs ($P_{subgroup}$ from 0.147 to 0.999). These meta-analysis results are detailed in (Figure S4, Supplemental Content, which illustrates the effects of SGLT2 inhibitors on the composite of HHF or CV death according to various factors, http://links.lww.com/MD/G508).

As is summarized in Figure 3, compared to placebo, SGLT2 inhibitors significantly lowered the risk of KCO (HR 0.63, 95%

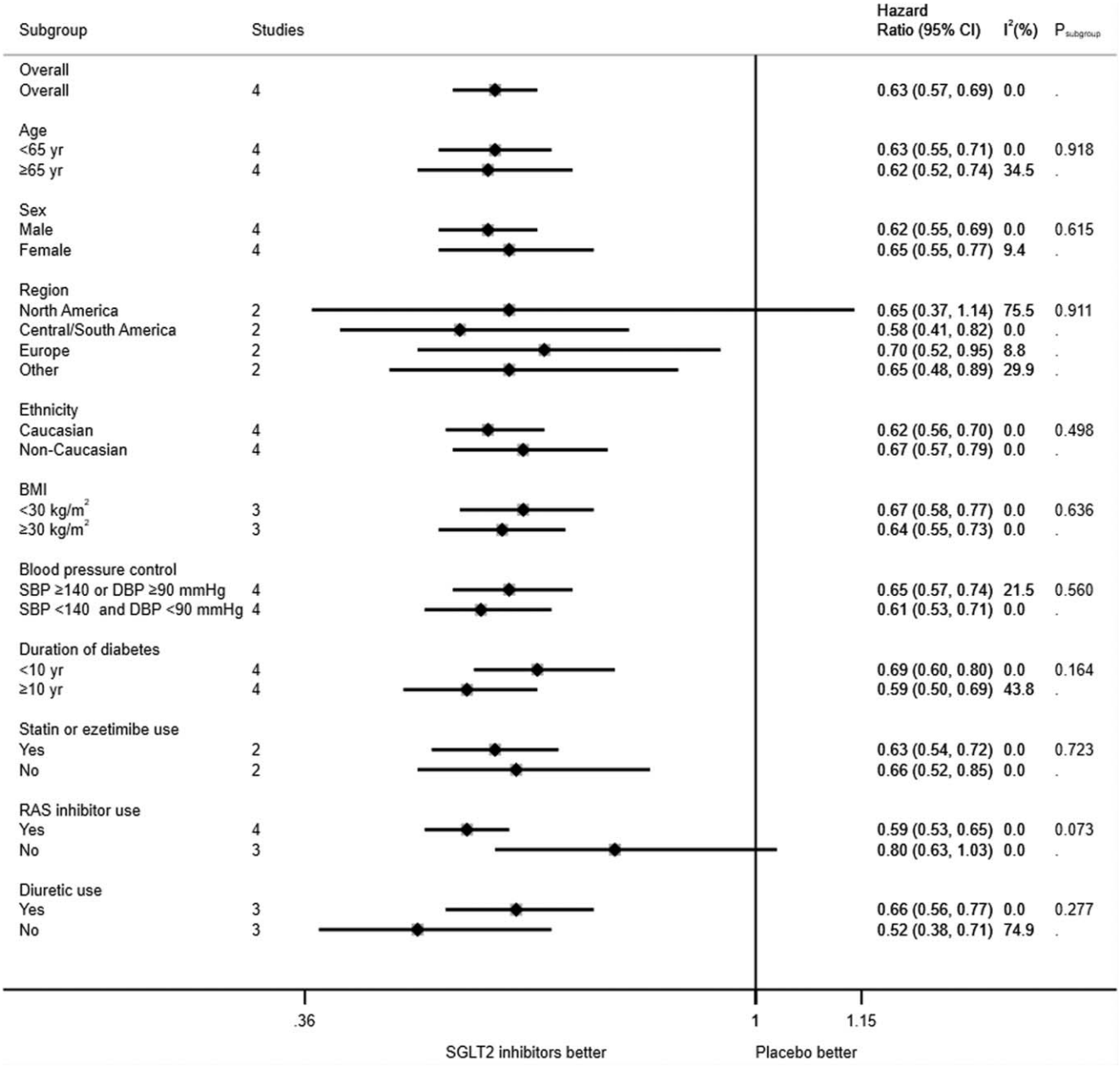

Figure 3. Efficacy of SGLT2 inhibitors on KCO, stratified by 7 factors related to demographic characteristics and baseline use of statin or ezetimibe, RAS inhibitor, and diuretic. KCO = kidney composite outcome, RAS = renin–angiotensin system, SGLT2 = sodium-glucose cotransporter 2.

CI 0.57–0.69), regardless of 7 factors related to demographic characteristics and regardless of baseline use of statin or ezetimibe, RAS inhibitor, and diuretic ($P_{subgroup}$ from 0.073–0.918). These meta-analysis results are detailed in (Figure S5, Supplemental Content, which illustrates the effects of SGLT2 inhibitors on KCO according to various factors, http://links.lww.com/MD/G509). The relevant data was not sufficient to assess the impact of sulfonylurea or thiazolidinedione, metformin, DPP-4i, GLP-1RA, insulin, MRA, and beta-blocker on the efficacy of SGLT2 inhibitors on KCO.

4. Discussion

This updated meta-analysis included all the large randomized trials that focused on the cardiorenal effects of SGLT2 inhibitors in T2DM patients, including the 3 new ones,[8–10] and produced the following 3 findings.

First, SGLT2 inhibitors could reduce the risk of MACE by 10% (HR 0.90, 95% CI 0.84–0.97) in T2DM patients, and this benefit was independent of 7 factors related to demographic characteristics and independent of baseline use of 5 hypoglycemic and cardiovascular drugs. Second, SGLT2 inhibitors could reduce the risk of HHF or CV death by 22% (HR 0.78, 95% CI 0.71–0.85) in T2DM patients, and this benefit was independent of 7 factors related to demographic characteristics and independent of baseline use of 10 hypoglycemic and cardiovascular drugs. Last, SGLT2 inhibitors could reduce the risk of KCO by 37% (HR 0.63, 95% CI 0.57–0.69) in T2DM patients, and this benefit was independent of 7 factors related to demographic characteristics and independent of baseline use of 3 cardiovascu-

lar drugs. These findings of this meta-analysis suggest that SGLT2 inhibitors should be recommended in T2DM patients for the prevention of cardiorenal events, regardless of various demographic characteristics and regardless of baseline use of various hypoglycemic and cardiovascular drugs.

Several previous meta-analyses[3–5,7] identified that the cardiorenal benefits of SGLT2 inhibitors were consistent across T2DM subgroups with or without history of cardiovascular disease and history of heart failure, and were consistent across T2DM subgroups with different levels of estimated glomerular filtration rate, glycosylated hemoglobin and albuminuria. Thus, in this meta-analysis we did not re-assess the above 5 factors, but assessed 17 other important factors, namely, age, sex, region, ethnicity, body mass index, blood pressure control, duration of diabetes, sulfonylurea or thiazolidinedione, metformin, DPP-4i, GLP-1RA, insulin, statin or ezetimibe, MRA, RAS inhibitor, beta-blocker, and diuretic. Although a prior meta-analysis[3] evaluated the impact of demographic characteristics and baseline use of insulin, statin or ezetimibe, RAS inhibitor, beta-blocker, and diuretic on the cardiorenal benefits of SGLT2 inhibitors, that meta-analysis[3] failed to include the 3 new trials[8–10] of VERTIS CV,[8] SOLOIST-WHF[9] and SCORED,[10] and failed to evaluate the impact of baseline use of sulfonylurea or thiazolidinedione, metformin, DPP-4i, GLP-1RA, and MRA. Thus, this updated meta-analysis provides the most comprehensive analysis on whether various demographic characteristics and various hypoglycemic and cardiovascular drugs have significant effects on the cardiorenal benefits of SGLT2 inhibitors in patients with T2DM.

The original studies included in this meta-analysis all were high-quality studies with low risk of bias, which is 1 strength of this study. Oppositely, 1 limitation of this study is that the relevant data was not sufficient enough to assess the impact of some factors, such as DPP-4i use and GLP-1RA use, on the efficacy of SGLT2 inhibitors on MACE and KCO. This needs to be further investigated.

In conclusion, the cardiorenal benefits of SGLT2 inhibitors were consistent in a broad population of T2DM patients. The findings of this meta-analysis suggest that SGLT2 inhibitors should be recommended in T2DM patients for the prevention of cardiorenal events, regardless of various demographic characteristics and baseline use of various hypoglycemic and cardiovascular drugs.

Author contributions

Conceptualization: Li-Min Zhao.
Data curation: Rong Chang, Shu-Yan Liu, Li-Min Zhao.
Formal analysis: Shu-Yan Liu.
Writing – original draft: Rong Chang.
Writing – review & editing: Li-Min Zhao.

References

[1] Zelniker TA, Wiviott SD, Raz I, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet 2019;393:31–9.
[2] Neuen BL, Young T, Heerspink H, et al. SGLT2 inhibitors for the prevention of kidney failure in patients with type 2 diabetes: a systematic review and meta-analysis. Lancet Diabetes Endocrinol 2019;7:845–54.
[3] Qiu M, Liu SY, Gu JS, et al. Do reductions in risk of cardiorenal events with SGLT2 inhibitors in type 2 diabetes vary with baseline characteristics? A meta-analysis. Endocrine 2020;69:688–91.
[4] Qiu M, Ding LL, Zhang M, et al. SGLT2 inhibitors for prevention of cardiorenal events in people with type 2 diabetes without cardiorenal disease: a meta-analysis of large randomized trials and cohort studies. Pharmacol Res 2020;161:105175.
[5] Arnott C, Li Q, Kang A, et al. Sodium-glucose cotransporter 2 inhibition for the prevention of cardiovascular events in patients with type 2 diabetes mellitus: a systematic review and meta-analysis. J Am Heart Assoc 2020;9:e14908.
[6] Qiu M, Ding LL, Zhang M, et al. GLP-1RAs and SGLT2is reduce cardiovascular events independent of reductions of systolic blood pressure and body weight: a meta-analysis with meta-regression. Diabetes Ther 2020;11:2429–40.
[7] Mcguire DK, Shih WJ, Cosentino F, et al. Association of SGLT2 inhibitors with cardiovascular and kidney outcomes in patients with type 2 diabetes: a meta-analysis. JAMA Cardiol 2021;6:148–58.
[8] Cannon CP, Pratley R, Dagogo-Jack S, et al. Cardiovascular outcomes with ertugliflozin in type 2 diabetes. N Engl J Med 2020;383:1425–35.
[9] Bhatt DL, Szarek M, Steg PG, et al. Sotagliflozin in patients with diabetes and recent worsening heart failure. N Engl J Med 2021;384:117–28.
[10] Bhatt DL, Szarek M, Pitt B, et al. Sotagliflozin in patients with diabetes and chronic kidney disease. N Engl J Med 2021;384:129–39.
[11] Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6:e1000097.
[12] Higgins JP, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.
[13] Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med 2019;380:2295–306.
[14] Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2019;380:347–57.
[15] Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017;377:644–57.
[16] Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117–28.