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Cardiovascular and kidney benefits of SGLT-2is and GLP-1RAs according to baseline blood pressure in type 2 diabetes: a systematic meta-analysis of cardiovascular outcome trials

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ABSTRACT

***Objectives*::** Using a systematic meta-analysis, we investigated if patients with type 2 diabetes (T2D) and with varying baseline blood pressure (BP) differ in the cardiorenal benefits received from sodium–glucose co-transporter 2 inhibitors (SGLT-2is) and glucagon-like peptide 1 receptor agonists (GLP-1RAs). *Design:* Randomized, placebo-controlled, cardiovascular outcome trials (CVOTs) of SGLT-2is and GLP-1RAs were identified from MEDLINE, Embase, and the Cochrane Library up to April 2024. Hazard ratios (HRs) with 95% CIs were pooled. The differential treatment effect by baseline BP category within each trial was estimated as the ratio of the HR (RHR) and pooled. *Results:* Seventeen publications based on 9 unique CVOTs (4 SGLT-2is and 5 GLP-1RAs) were eligible. In participants with normal baseline BP, comparing SGLT-2is with placebo, the HRs (95% CIs) were 0.88 (0.79-0.97) for major adverse cardiovascular events (MACE), 0.73 (0.59-0.91) for heart failure (HF) hospitalization, 0.78 (0.65-0.94) for composite CVD death/HF hospitalization, and 0.55 (0.41-0.73) for composite renal outcome. The corresponding estimates for participants with higher baseline BP were 0.88 (0.81-0.96), 0.67 (0.57-0.79), 0.73 (0.65-0.82), and 0.61 (0.48-0.77), respectively. In participants with normal baseline BP, GLP-RAs had no strong effect on MACE, stroke and nephropathy, but reduced stroke and nephropathy risk in those with higher baseline BP. Estimated RHRs showed no statistical evidence that baseline BP modified the cardiorenal benefits of SGLT-2is and GLP-1RAs. *Conclusions:* In patients with T2D, the cardiorenal benefits of treatment with SGLT2-Is and GLP1-RAs were similar in patients with normal baseline BP compared to those with a higher baseline BP. **:**

KEYWORDS
SGLT-2i; GLP-1RA; type 2 diabetes; blood pressure; cardiovascular disease; kidney disease; randomized controlled trial

Introduction

Type 2 diabetes (T2D) represents a significant global health challenge, with its incidence rising alarmingly in recent decades. Alongside its metabolic disturbances, T2D confers an increased risk of both macrovascular and microvascular complications. Elevated blood pressure or hypertension is a common comorbidity in individuals with T2D; it has been reported that elevated blood pressure occurs in 50-80% of patients with T2D [1,2]. Hypertension is a strong and independent risk factor for vascular complications. The combination of hypertension and diabetes heightens the risk of macrovascular and microvascular complications than those with either condition in isolation [3,4].

Optimal management of T2D extends beyond glycaemic control. It necessitates comprehensive risk factor management, particularly cardiovascular determinants such as dyslipidaemia and hypertension [5]. Blood pressure control is very paramount, as optimal control has been robustly linked to reductions in adverse cardiovascular and renal outcomes [6,7]. The cornerstone of achieving optimal blood pressure targets has traditionally rested upon standard antihypertensive agents, such as renin-angiotensin-aldosterone system (RAAS) inhibitors, beta-blockers, calcium-channel blockers, and diuretics; these therapies mainly focus on blood pressure reduction [8]. Emerging from the shadows of conventional diabetes care are the sodium-glucose cotransporter-2 inhibitors (SGLT-2is) and glucagon-like peptide-1 receptor agonists (GLP-1RAs). These agents are not just known for their glycaemic efficacy but also for their potential in reducing the risk of adverse cardiovascular outcomes [9–12]. Their cardiovascular benefits are believed to stem from non-glycaemic pleiotropic effects on the cardiovascular system. These include ameliorating insulin resistance, inducing weight loss, improving lipid profiles, and

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direct salutary actions on cardiac and vascular endothelial function [13]. Notably, a reduction in blood pressure has also been observed [10,11,13], suggesting a multifactorial benefit that could be especially relevant for those with co-existing hypertension. These newer agents have been consistently demonstrated to produce modest to substantial reductions in blood pressure [14,15]. The SGLT-2is act by blocking the reuptake of sodium and glucose in the proximal tubules and may cause reductions in blood pressure *via* reductions in intravascular volume, weight loss, electrolyte reabsorption, lowering of uric acid, and decrease in arterial stiffness [16,17]. The blood pressure lowering effects of GLP-1RAs may also be *via* several pathways including natriuresis and weight loss [18,19].

It is well known that both optimal blood pressure control and these newer antidiabetic agents independently attenuate the risk of cardiovascular and kidney complications. It has been reported that GLP-1RAs and SGLT-2is produce greater reductions in blood pressure in those with higher baseline blood pressure [20,21]. Regardless of baseline comorbidities, glycaemic control, or cardiovascular risk, SGLT-2is and GLP-1RAs offer consistent cardiovascular and kidney benefits [22,23]. Despite this, the extent to which the treatment benefits of SGLT-2is and GLP-1RAs differ by baseline blood pressure control is not clear. It will also be clinically relevant to know if patients with adequate or inadequate control of blood pressure at baseline can be safely treated with these agents. Though a number of cardiovascular outcome trials (CVOTs) of SGLT-2is and GLP-1RAs have reported outcomes among subgroups of patients with varying baseline blood pressure, the evidence has been inconsistent across these trials. Hence, there is a need to synthesise the data. Using a systematic meta-analysis of CVOTs of SGLT-2is and GLP-1RAs in T2D, the aim of this study is to investigate if patient populations with varying baseline blood pressure differ in the cardiovascular and kidney benefits received from SGLT-2is and GLP-1RAs.

Materials and methods

Data sources and search strategy

This systematic review and meta-analysis adhered to a predetermined protocol and was registered in the PROSPERO prospective register of systematic reviews under the identifier CRD42023474599. The study was reported in accordance with the PRISMA guidelines, detailed in Supplementary material 1. Our team executed a comprehensive search of databases including MEDLINE, Embase, and the Cochrane Library, spanning their inception to 15 April 2024, without imposing language constraints. This search merged free-text queries and MeSH terms pertinent to T2D, SGLT-2is, GLP-1RAs, baseline blood pressure and CVD and kidney outcomes. We specifically utilized an RCT design filter in our search strategy. A detailed breakdown of our search algorithm can be found in Supplementary material 2. The initial screening of titles and abstracts from the retrieved citations was undertaken by one researcher (SKK) to assess their suitability for inclusion. This phase employed Rayyan, an online bibliographic software designed to streamline the screening process through semi-automation [24]. Subsequently, full-text articles deemed potentially relevant were acquired and assessed, a task collaboratively undertaken by two researchers (SKK and RSD). Any disagreements on the inclusion of a study or article were settled through discussions. To capture any potentially overlooked studies during the systematic search, we manually scoured the reference lists of pertinent studies and review articles. Furthermore, citing references were cross-checked using the Web of Science.

Study selection and eligibility criteria

Studies eligible for inclusion were randomized, placebo-controlled cardiovascular outcome trials (CVOTs) examining either SGLT-2is or GLP-1RAs in adult patients with T2D. There were no restrictions regarding comorbidities or background medications used by patients. These studies needed to have provided data on cardiovascular and/or kidney outcomes stratified by baseline blood pressure categories. Our pre-established cardiovascular outcomes included: (i) major adverse cardiovascular events (MACE) defined as the composite of death from cardiovascular causes, nonfatal myocardial infarction (MI), or nonfatal stroke (composite cardiovascular outcome); (ii) individual components of MACE; (iii) heart failure (HF) hospitalization; (iv) composite of CVD death or HF hospitalization; (v) other vascular outcomes as reported by the studies; and (vi) all-cause mortality. For kidney outcomes, we pre-specified: (i) composite outcome of end-stage kidney disease, doubling of creatinine level or death from renal causes (composite renal outcome); (ii) individual components of composite renal outcome; (iii) other renal outcomes (e.g. nephropathy); and (iv) composite renal and cardiovascular outcome.

Data extraction

We employed a data collection form that had been designed and utilized in prior reviews [25–27]. This form was adapted to fit the needs of our current analysis. The primary extraction of data from the qualified studies was conducted by an experienced reviewer (SKK), while a secondary verification for precision using the source articles was undertaken by another reviewer (RSD). Any discrepancies that arose during this phase were addressed on discussion. Where available, and classified by baseline blood pressure categories, we extracted the following data: date of publication; geographical location; study participants details, such as average age, gender distribution, and duration of T2D at the outset; study design characteristics like randomization procedures, allocation concealment tactics, blinding methodology, and follow-up durations; detailed information on the intervention and control groups; and relevant outcomes, and their hazard ratios (HRs) with 95% confidence intervals (CIs). In instances where studies presented forest plots

without explicitly indicating the HRs and the associated 95% CIs, we resorted to using Plotdigitizer. This online tool facilitates the extraction of data directly from graphical representations, converting image data into a numerical format. The tool is accessible at https://plotdigitizer.com/app

Risk of bias and certainty of evidence

To assess the risk of bias in each included trial, we employed the Cochrane Collaboration's risk of bias tool [28]. This instrument evaluates seven potential sources of bias: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other potential biases. Based on these criteria, each study was categorized as having a low, unclear, or high risk of bias. To rate the certainty of the evidence for each outcome, we utilized the Grading of Recommendations Assessment, Development and Evaluation (GRADEpro) tool (https://gdt.gradepro.org), which considers factors like study limitations, effect inconsistency, precision, relevance, and publication bias [29]. The certainty of the evidence was classified into one of four categories: high, moderate, low, or very low.

Statistical analysis

For all time-to-event outcomes, we employed HRs with 95% CIs as our summary measures of effect. To account for the impact of heterogeneity, random-effects models were employed in aggregating the HRs [30]. When suitable, fixed-effects models were also applied in parallel analyses. When studies published more than one estimate of the association according to several blood pressure subgroups (e.g. SBP <120 and SBP 130-139 mmHg), a within-group summary estimate was obtained using a fixed effect analysis. The degree of statistical heterogeneity among studies was determined using standard chi-square tests complemented by the I^2 statistic [31,32]. In our pre-specified protocol, we intended to: (i) explore for sources of heterogeneity using stratified analysis and random effects meta-regression and (ii) assess for small study effects (e.g. publication bias) using formal tests such as Begg's funnel plots [33] and Egger's regression symmetry test [34]. However, these steps could not be undertaken because each outcome stratified by baseline blood pressure categories relied on aggregated analyses from fewer than 10 studies. We estimated the differential treatment effects (i.e. interaction coefficients) by baseline blood pressure category within each RCT as the ratio of the HRs (RHR) [35]; then RHRs were combined across RCTs [36]. An RHR <1 (i.e. a smaller hazard ratio in patients with normal baseline blood pressure vs. those with elevated baseline blood pressure) indicates a greater treatment effect in participants with normal baseline blood pressure. We regarded all tests as two-tailed, and any resulting p-values at or below 0.05 were deemed statistically significant. All analyses were conducted using Stata version MP 16 (Stata Corp, College Station, Texas).

Results

Study identification and selection

Figure 1 shows the study selection process. The search of relevant databases and manual scanning of reference lists of relevant studies identified 164 potentially relevant citations. After the initial screening of titles and abstracts, 44 articles remained for full text evaluation. Following detailed evaluation, 27 articles were excluded because (i) outcomes were not relevant ($n=15$), (ii) outcomes by blood pressure categories were not reported ($n=8$); (iii) they were reviews ($n=3$); and (iv) populations were not relevant ($n=1$). The remaining 17 articles comprising 9 distinct CVOTs met the inclusion criteria and were included in the review [10,11,37–51].

Study characteristics and risk of bias

The 9 CVOTs were published between 2015 and 2022 and conducted in multiple countries (ranging from 20-42 countries). Overall, the included studies involved 68,600 participants diagnosed with T2D. Baseline characteristics are reported in Table 1. Among these trials, 4 compared SGLT-2is with placebo (38,723 participants, SGLT-2i = 21,266, placebo = 17,457) and 5 compared GLP-1RAs with placebo (involving 29,877 participants, GLP-1RA = 14,931, placebo = 14,946). Based on the available data, we used the following blood pressure stratification as reported by the eligible studies: (i) normal baseline blood pressure or adequate blood pressure control (e.g. systolic blood pressure (SBP) <140 mmHg and/or diastolic blood pressure (DBP) <90) and (ii) elevated baseline blood pressure or inadequate blood pressure control (e.g. SBP ≥140 mmHg and/or DBP ≥90 mmHg). The average duration since T2D diagnosis before inclusion into the trials ranged from 9.5 to 15.8 years. Study participants were being managed on standard treatment therapies including background antihyperglycemic and antihypertensive medications before inclusion into the trial. Metformin was the most commonly used antihyperglycemic agent across trials, with usage ranging from 57.9% to 84.9%. Insulin use varied significantly, with 23.7% to 65.9% of patients receiving insulin therapy. Sulfonylureas were also widely used, with usage rates ranging from 27.8% to 50.6%. Regarding antihypertensive therapy, most patients were on at least one antihypertensive agent, with RAAS inhibitors (angiotensin-converting enzyme inhibitors/angiotensin receptor blockers) being the most frequently used, ranging from 50.3% to >99% across the trials. Beta-blockers and diuretics were also commonly prescribed, with usage rates of 40.1% to 65.2% for beta-blockers and 32.6% to 46.9% for diuretics. Other antihypertensive classes such as calcium channel blockers and mineralocorticoid receptor antagonists were less frequently used (Supplementary material 2). The mean/median age of participants ranged from 63 to 67 years. The mean/median duration of follow-up ranged from 1.3 to 5.4 years. Using the Cochrane Collaboration tool, all trials demonstrated low risk of bias in all domains (Supplementary material 4).

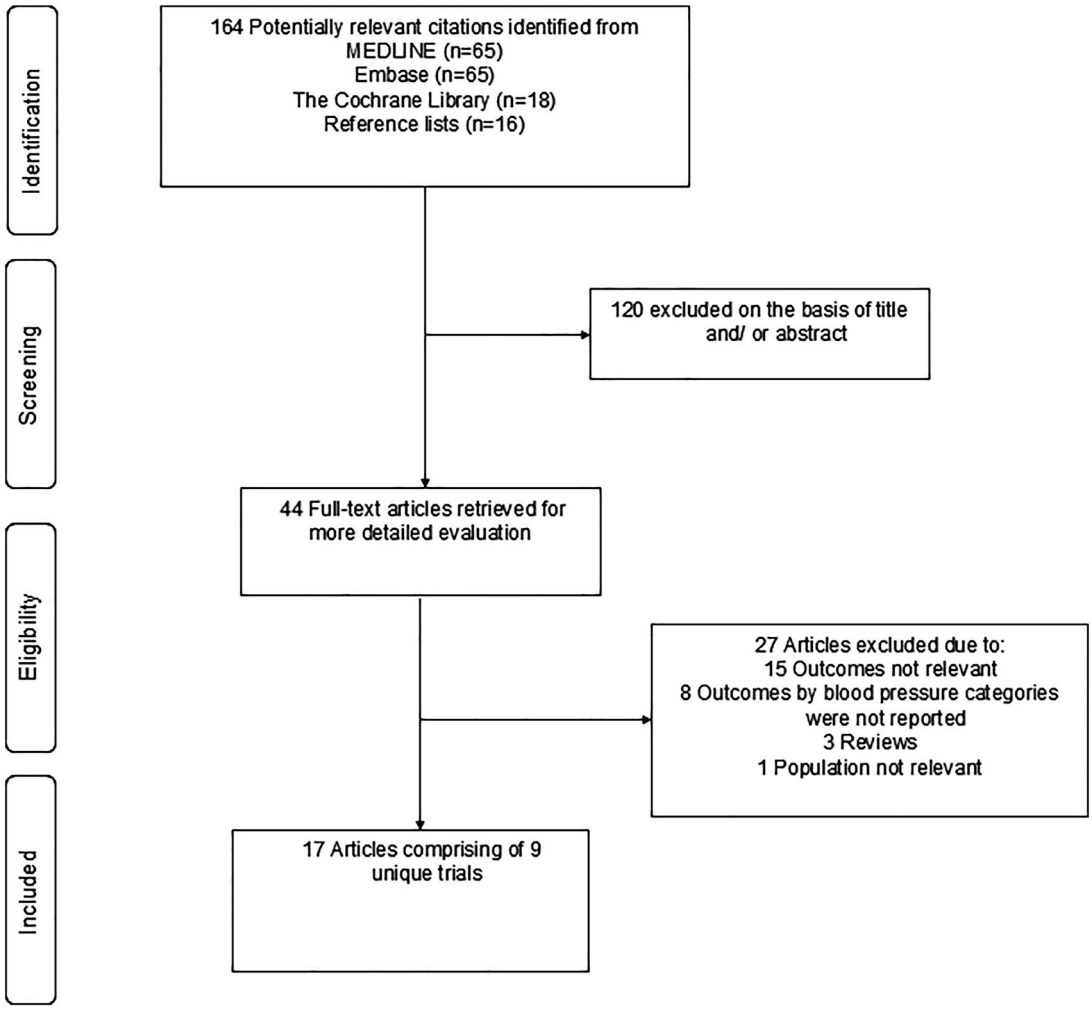

Figure 1. Selection of studies included in the meta-analysis.

SGLT-2is and outcomes stratified by baseline blood pressure

In participants with normal baseline blood pressure, allocation to SGLT-2is compared with placebo was associated with a significant reduction in MACE, CVD death, HF hospitalization, composite of CVD death or HF hospitalization, nephropathy, composite renal outcome, and composite renal or CVD outcome: HRs (95% CIs) of 0.88 (0.79-0.97), 0.67 (0.50-0.90), 0.73 (0.59-0.91), 0.78 (0.65-0.94), 0.59 (0.50-0.70), 0.55 (0.41-0.73) and 0.57 (0.39-0.83), respectively (Figure 2A). There was no significant evidence of an effect on stroke and atrial fibrillation: HRs (95% CIs) of 0.93 (0.72-1.19) and 0.91 (0.71-1.16), respectively.

In participants with elevated baseline blood pressure, allocation to SGLT-2is compared with placebo was associated with a significant reduction in MACE, CVD death, HF hospitalization, composite of CVD death or HF hospitalization, atrial fibrillation, nephropathy, composite renal outcome, and composite renal or CVD outcome: HRs (95% CIs) of 0.88 (0.81-0.96), 0.56 (0.40-0.79), 0.67 (0.57-0.79), 0.73 (0.65-0.82), 0.73 (0.59-0.91), 0.63 (0.52-0.76), 0.61 (0.48-0.77) and 0.73 (0.61-0.88), respectively (Figure 2B). There was no significant evidence of an effect on stroke: HR (95% CI) of 0.95 (0.76-1.18).

The overall results showed no statistical evidence that baseline blood pressure modified the cardiovascular and kidney benefits of SGLT-2is; the RHRs (95% CIs) for MACE, HF hospitalization, composite of CVD death or HF hospitalization, stroke, and composite renal outcome were 0.99 (0.93-1.05), 1.05 (0.85-1.31), 1.05 (0.92-1.21), 0.99 (0.90-1.09) and 0.83 (0.57-1.21), respectively (Figure 3). Single study results showed a larger beneficial effect of SGLT-2is on nephropathy and the composite renal and CVD outcome in patients with normal baseline blood pressure, with a larger beneficial effect on CVD death and atrial fibrillation in patients with elevated baseline blood pressure.

GLP-1RAs and outcomes stratified by baseline blood pressure

In participants with normal baseline blood pressure, there was no evidence of an effect on MACE, stroke and nephropathy when GLP-1RA was compared with placebo: HRs (95% CIs) of 0.97 (0.78-1.22), 0.85 (0.65-1.12) and 0.61 (0.27-1.35), respectively (Figure 4A).

In participants with elevated baseline blood pressure, allocation to GLP-1RAs compared with placebo was associated with a significant reduction in stroke and nephropathy,

Table 1. Baseline characteristics of CVOTs (2015–2022).

Author, year of publication	Study	Baseline population	Baseline year	Males, %	Mean/ median age, years	T2D duration, years	Location	Intervention (dose)	Follow-up, years	Intervention, N	Placebo, N
SGLT-2is											
Zinman, 2015; Fitchett, 2016; Wanner, 2016; Zinman, 2017	EMPA-REG OUTCOME	T2D at high cardiovascular risk, eGFR ≥30	2010-2013	71.4	67.1	NR	592 sites in 42 countries	Empagliflozin (10/25 mg)	3.1	4687	2333
Neal, 2017; Perkovic, 2018; Radholm, 2018; Zhou, 2019	CANVAS Program	T2D with high cardiovascular risk, eGFR > 30	2009, 2014	64.2	63.3	13.5	667 centres in 30 countries	Canagliflozin (100/300 mg)	3.6	5795	4347
Wiviott, 2019; Furtado, 2020; Zelniker, 2020	DECLARE-TMI 58	T2D who had or were at risk for ASCVD	2013-2018	62.6	63.9	11.0	882 sites in 33 countries	Dapagliflozin (10 mg)	4.2	8582	8578
Ye, 2021; Zhou, 2021	CREDENCE	T2D and albuminuric chronic kidney disease	2014-2017	66.1	63.0	15.8	690 sites in 34 countries	Canagliflozin (100 mg)	2.6	2202	2199
GLP-1RAs											
Leiter, 2020	LEADER	T2D with at least a cardiovascular condition	2010-2012	60.7	64.6	12.8	410 sites in 32 countries	Liraglutide (1.8 mg)	3.8	4668	4672
Leiter, 2020; Strain, 2022	SUSTAIN-6	T2D	2013	60.7	64.6	13.9	230 sites in 20 countries	Semaglutide (0.5/1.0 mg)	2.1	1648	1649
Gerstein, 2020	REWIND	T2D with and without previous CVD	2011-2013	53.7	66.2	9.5	371 sites in 24 countries	Dulaglutide (1.5 mg)	5.4	4949	4952
Strain, 2022	PIONEER 6	T2D and at high cardiovascular risk	2017	68.4	66.0	14.9	214 sites in 21 countries	Semaglutide (14 mg)	1.3	1591	1592
Ruff, 2022	FREEDOM CVO	T2D with or at risk for ASCVD	2013-2015	63.3	63.0	10.3	402 sites in 26 countries	Exanatide (20/60 mcg)	1.3	2075	2081

ASCVD, atherosclerotic cardiovascular disease; CVD, cardiovascular disease; CVOTs, cardiovascular outcome trials; DPP-4is, dipeptidyl peptidase-4 inhibitors; eGFR, estimated glomerular filtration rate; GLP-1RAs, glucagon-like peptide-1 receptor agonists; NR, not reported; SGLT-2is, sodium–glucose coransporter-2 inhibitors; T2D, type 2 diabetes.

Study Abbreviations: CANVAS, Canagliflozin Cardiovascular Assessment Study; CREDENCE, Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation; DECLARE-TMI 58, Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58; EMPA-REG OUTCOME, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients Removing Excess Glucose; LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; PIONEER, Peptide Innovation for Early Diabetes Treatment; REWIND, Researching Cardiovascular Events with a Weekly Incretin in Diabetes; SUSTAIN-6, Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes.

with no evidence of an effect on MACE: HRs (95% CIs) of 0.65 (0.51-0.84), 0.74 (0.63-0.86) and 0.91 (0.68-1.21), respectively (Figure 4B).

There was no statistical evidence that baseline blood pressure modified the cardiovascular and kidney benefits of GLP-1RAs; the RHRs (95% CIs) for MACE, stroke and nephropathy were 0.96 (0.66-1.40), 1.19 (0.86-1.66) and 0.76 (0.38-1.54), respectively (Figure 5).

GRADE summary of findings

In addition to MACE, we selected other outcomes based on their importance and how frequently they were reported by studies. The GRADE certainty of the evidence ranged from high to very low (Supplementary material 5).

Discussion

In pooled analysis of 9 unique randomized, placebo-controlled, CVOTs of SGLT-2is and GLP-1RAs in patients with T2D, we evaluated the cardiovascular and kidney efficacy of these novel agents stratified according to baseline blood pressure. The present analyses show that SGLT-2is and GLP-1RAs provide similar benefits on major cardiorenal outcomes across baseline blood pressure categories. Furthermore, there was no statistical evidence that baseline blood pressure modified their cardiovascular and kidney benefits. Single trial results showed potentially larger effect of SGLT-2is on nephropathy and the composite renal or CVD outcome in patients with normal baseline blood pressure, with a larger effect on CVD death and atrial fibrillation in patients with elevated baseline blood pressure. However, these single trial interaction results need to be interpreted with caution given well-known limitations such as inadequate statistical power [52].

Our review of the literature shows this is the first aggregate analysis to evaluate the cardiorenal efficacy of SGLT-2is and GLP-1RAs in T2D according to baseline blood pressure categories. However, a recent systematic review and meta-analysis by Rodriguez-Valadez and colleagues [23] investigated whether patients (with or without T2D) with varying baseline cardiovascular risks differed in cardiovascular and renal benefits from SGLT-2is and GLP-1RAs. Their results showed that the relative effects of novel drugs are preserved across baseline cardiovascular risk, whereas absolute benefits increase at higher risks, particularly with respect to HF [23]. Our study specifically investigated baseline blood pressure as a determinant of treatment efficacy and the analysis based on CVOTs of SGLT-2is showed that baseline blood pressure did not significantly modify the effect of SGLT-2is on HF hospitalization.

In this pooled analysis, cardiorenal benefits were observed in patients both with and without adequate blood pressure control at baseline. These findings contribute to the growing body of evidence demonstrating the cardiovascular and kidney efficacy of SGLT-2is and GLP-1RAs across a spectrum of risk factors including lipids [53,54], body mass index [55] and now blood pressure. The findings significantly expand

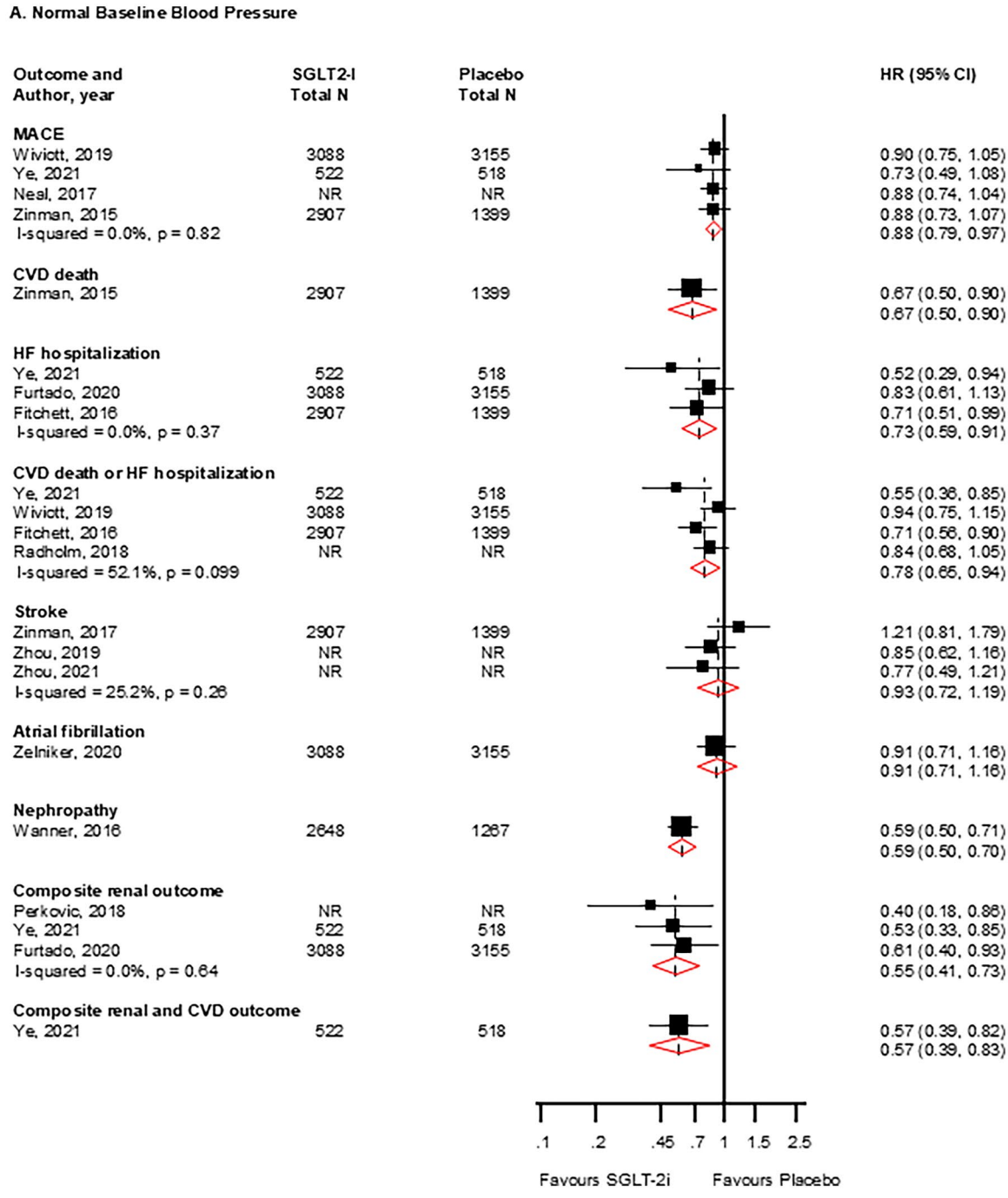

Figure 2. Risk for cardiorenal outcomes stratified by baseline blood pressure comparing SGLT-2is with placebo. (A) Normal baseline blood pressure; (B) Elevated baseline blood pressure CI, confidence interval (bars); CVD, cardiovascular disease; HR, hazard ratio; MACE, major adverse cardiovascular events; NR, not reported; SGLT-2i, sodium–glucose co-transporter 2 inhibitor.

the widespread utilization of SGLT-2is and GLP-1RAs. Prior research has indicated their considerable advantages in both obese and non-obese individuals [55], patients with and without diabetes [56], and individuals who exhibit low or high levels of albuminuria [57]. However, while these novel agents have shown significant efficacy in RCTs, it is important to recognize the potential gap between efficacy in RCTs and effectiveness in real-world settings, particularly in older and more complex patient populations typically seen in primary care. Randomized controlled trials often enrol relatively younger populations (mean age 60-65 years) with fewer comorbidities and less polypharmacy compared to the average diabetes population in primary care, which tends to be older and more burdened with multiple chronic conditions. Additionally, while the cardiometabolic benefits of SGLT-2is and GLP-1RAs, such as weight loss, improved lipid profiles, and modest reductions in blood pressure [10,11,13], are promising, their broader application in primary care requires careful consideration of factors such as patient safety, cost-effectiveness, and the potential challenges of managing polypharmacy. The generalizability of these findings to older and more complex populations must be

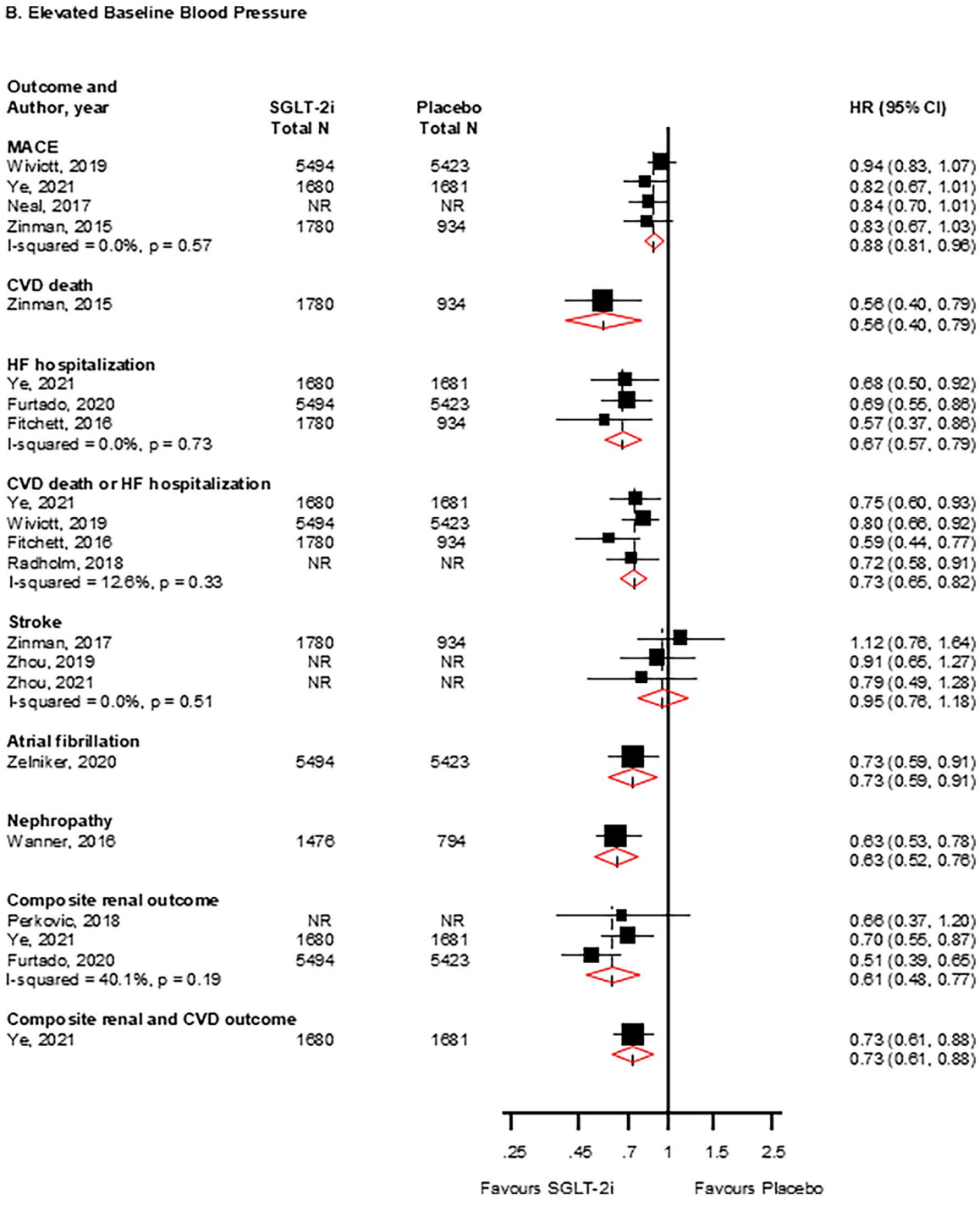

Figure 2. Continued.

approached with caution, and real-world studies will be necessary to confirm their effectiveness and safety in these groups. Therefore, while these agents offer important benefits, their use in primary care should be guided by a balanced assessment of their advantages and potential limitations.

When interpreting these data, one needs to consider the fact that participants in these trials were also on background antihypertensive therapy such as RAAS inhibitors. However, it has been previously shown that the cardiorenal benefits of SGLT-2is and GLP-1RAs are similar in users and non-users of RAAS inhibitors [26,41], which suggest that the cardiorenal benefits of these novel agents may be additive to the effects of these antihypertensive agents. The current findings are important for patients with elevated blood pressure and those whose hypertension may be difficult to control with standard therapies. Although no difference was observed between patients with high and low baseline blood pressure, the fact that similar cardiorenal benefits were observed across groups suggests that these agents may reduce the need for additional blood pressure medications. This could potentially enhance patient adherence and reduce the overall burden of polypharmacy. While these agents could still be considered as adjunctive therapies for blood pressure

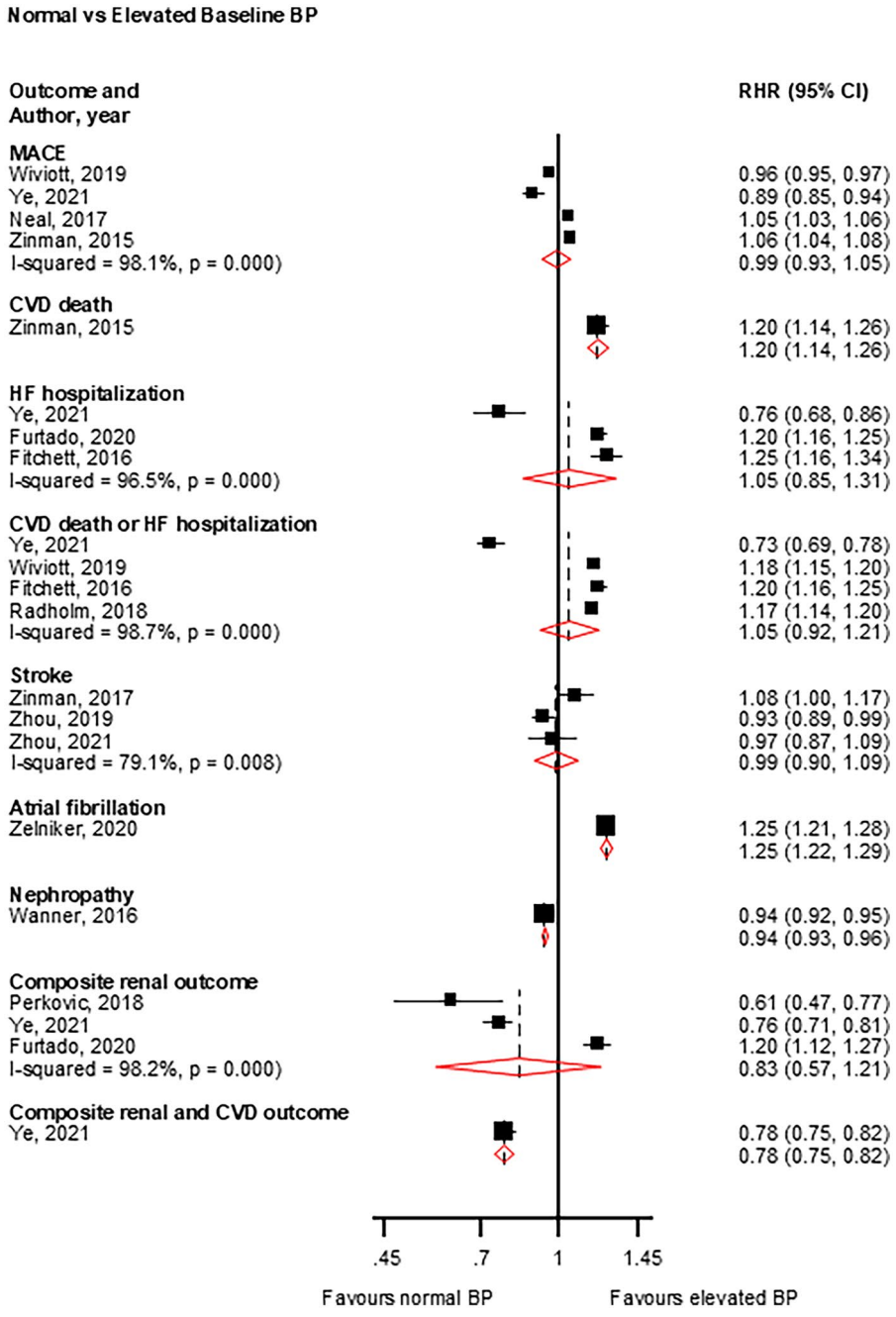

Figure 3. Differential cardiorenal treatment effect of SGLT-2is by baseline blood pressure. BP, blood pressure; CI, confidence interval (bars); CVD, cardiovascular disease; HF, heart failure; HR, hazard ratio; MACE, major adverse cardiovascular events; RHR, ratio of hazard ratio; SGLT-2i, sodium–glucose co-transporter 2 inhibitors. An RHR <1 (i.e., a smaller hazard ratio in participants with normal blood pressure vs. those with elevated blood pressure at baseline) indicates a greater treatment effect in participants with normal baseline blood pressure.

reduction, their primary value may lie in simplifying the treatment regimen for patients with T2D, while contributing to the reduction of cardiovascular and kidney risks.

There are several other strengths in addition to the ones mentioned previously. Unlike prior studies that assessed cardiovascular risk across various subgroups, our analysis specifically stratifies patients based on baseline blood pressure. This allows for an in-depth understanding of whether baseline blood pressure influences the cardiorenal benefits of SGLT-2is and GLP-1RAs in T2D patients. To the best of our knowledge, we included all known CVOTs in T2D that had reported outcomes by baseline pressure. We corresponded with the investigators of these CVOTs to ensure we included any trial that reported these data *via* additional publications. Given the challenges of interpreting trial-specific subgroup analysis and the limited power to detect interactions [52], we estimated trial-specific interactions (ratio of hazard ratios) and combined them using a meta-analytic approach. This methodology overcomes the challenges of trial-specific subgroup analysis and helps in the identification of who is most likely to benefit from a specific treatment [36]. The following

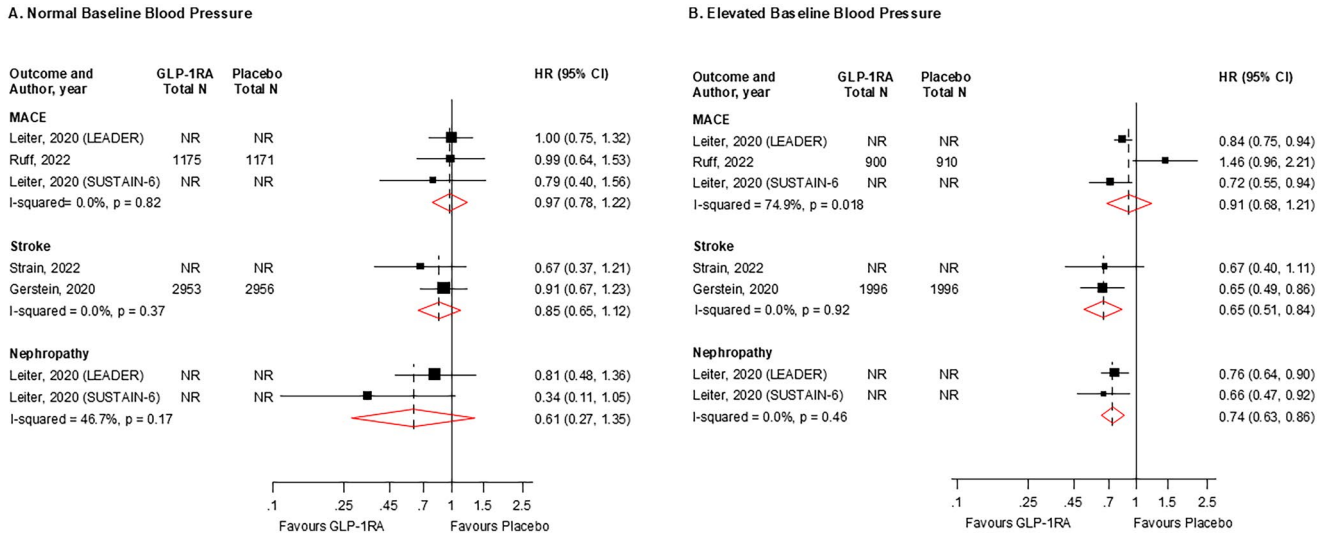

Figure 4. Risk for cardiorenal outcomes stratified by baseline blood pressure comparing GLP-1RAs with placebo. (A) Normal baseline blood pressure; (B) Elevated baseline blood pressure CI, confidence interval (bars); HR, hazard ratio; GLP-1RAs, glucagon-like peptide 1 receptor agonist; MACE, major adverse cardiovascular events; NR, not reported.

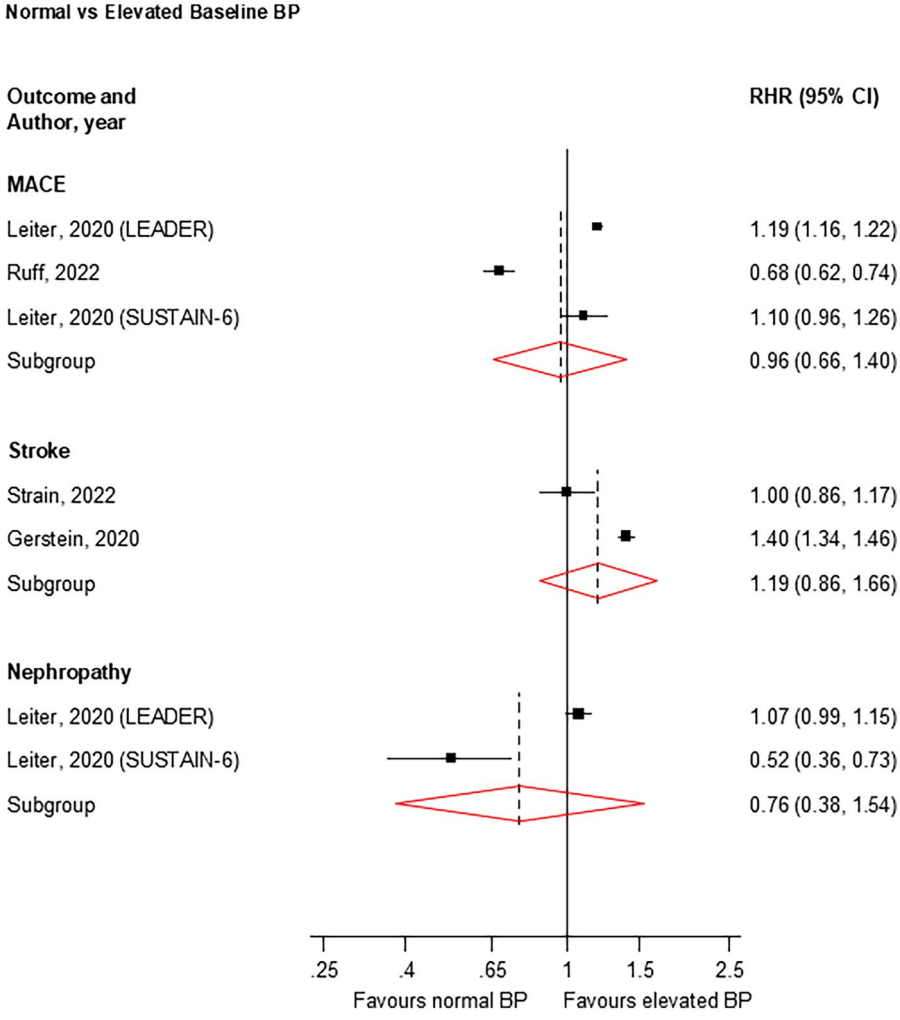

Figure 5. Differential cardiorenal treatment effect of GLP-1RAs by baseline blood pressure. BP, blood pressure; CI, confidence interval (bars); GLP-1RAs, glucagon-like peptide 1 receptor agonists; MACE, major adverse cardiovascular events; RHR, ratio of hazard ratio. An RHR <1 (i.e., a smaller hazard ratio in participants with normal blood pressure vs. those with elevated blood pressure at baseline) indicates a greater treatment effect in participants with normal baseline blood pressure.

limitations need to be considered in the interpretation of the results. First, of the 15 published placebo-controlled CVOTs of SGLT-2is and GLP-1RAs, 9 CVOTs (based on 17 publications) were identified to have reported outcomes by baseline blood pressure. We contacted investigators of the original trials to request additional data based on post-hoc analyses. However, none provided additional data beyond what had been reported in subsequent publications of the original trials. Due to the relatively few studies, there was limited data availability for the blood pressure categories, especially for trials of SGLT-2is which mostly reported mean SBP levels of <140 mmHg, suggesting a predominantly well-controlled blood pressure population. This might raise concerns about adequate statistical power to make broader inferences for patients with higher blood pressure levels. However, it's important to highlight that our analysis demonstrated consistent findings across all outcome measures, even within this context. Furthermore, the precision of our results is bolstered by mostly narrow 95% CIs observed, suggesting a lower likelihood of inadequate statistical power adversely impacting our conclusions. The limited number of trials also precluded accurate estimation of between-study heterogeneity, exploration of sources of heterogeneity, sensitivity analyses and assessment of small study effects. One of the inherent limitations in our meta-analysis, as with many such studies, is the variability in methodologies across the individual trials included, particularly in the measurement of blood pressure. This heterogeneity, while a common feature in meta-analyses, can potentially influence the interpretation of the combined data. Furthermore, considering the diverse patient populations and treatment settings in the original studies, there may be underlying differences in patient demographics, disease severities, and healthcare practices that could affect the generalizability of our findings. The studies included in our analysis did not report outcome data separately for patients with normal blood pressure who were or were not on blood pressure-lowering therapy, hence, we were unable to conduct separate analyses in these distinct patient subgroups. These data would have been invaluable in further elucidating the impact of concomitant blood pressure therapies on cardiorenal outcomes. The blood pressure cutoffs used in the included studies were based on the thresholds commonly reported in those trials (e.g. SBP <140 mmHg or DBP <90 mmHg), rather than the stricter targets recommended in current guidelines for high-risk patients, such as <130/80 mmHg. Though we pre-specified a long list of cardiovascular and kidney outcomes, most studies only reported a breakdown of the primary outcome (MACE) with a few reporting kidney outcomes. Our pooled data are based on results from trial-specific subgroup analysis. Furthermore, interaction estimates were not corrected for multiple testing given the limited number of studies. Finally, there was substantial heterogeneity across trials for some outcomes, which makes pooling somewhat controversial. Findings need to be interpreted with caution in the context of these limitations and access to individual level data from all published CVOTs may help clarify the current findings.

Conclusions

Pooled evidence from CVOTs of T2D demonstrates similar cardiorenal benefits of treatment with SGLT-2is and GLP-1RAs in patients with normal baseline blood pressure compared to those with a higher baseline blood pressure.

Disclosure statement

SS is in receipt of speaker honoraria from AstraZeneca, Boehringer Ingelheim, Janssen, Lilly, MSD, Abbott, Novo Nordisk, SB Communications, OmniaMed Communications, Roche, Napp Pharmaceuticals, NB Medical, and Amgen; advisory board honoraria from AstraZeneca, Lilly, Boehringer Ingelheim, Janssen, Abbott, MSD, Novo Nordisk, Takeda, and Sanofi; educational grants from Boehringer Ingelheim, Lilly, Novo Nordisk, and Takeda; and conference registration and subsistence from Boehringer Ingelheim, Janssen, Lilly, Novo Nordisk, Abbott, and Takeda. No other potential conflicts of interest relevant to this article were reported.

Author contributions

SKK conceived the study, conducted the systematic searches, was involved in the screening, data extraction, data analysis and drafted the article. SS, RSD, IKB, and AO were involved in screening, data extraction, data interpretation and provided critical feedback on subsequent versions of the article.

Data sharing statement

All extracted data are available upon request to the corresponding author.

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