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SYSTEMATIC REVIEW

Effects of DPP-4 inhibitors, GLP-1 receptor agonists, SGLT-2 inhibitors and sulphonylureas on mortality, cardiovascular and renal outcomes in type 2 diabetes: A network meta-analyses-driven approach

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Abstract

Aims: The aim of our meta-analyses was to compare the effects of glucose-lowering drugs on mortality, cardiovascular and renal endpoints for a range of type 2 diabetes (T2D) subgroups defined by their specific cardiovascular risk profile.

Methods: Meta-analyses comparing drugs within the classes of GLP-1RAs and SGLT-2 inhibitors were performed and compared to sulphonylureas and DPP-4 inhibitors with available cardiovascular outcome trials. The comparison between the different classes of glucose-lowering drugs included analyses of T2D populations with low risk and high risk for cardiovascular disease including populations with established cardiovascular disease and/or kidney disease. Outcomes included mortality, major cardiovascular adverse events (MACE), hospitalisation for heart failure (HHF) and a composite renal endpoint as applied in the underlying clinical trials.

Results: SGLT-2 inhibitors and GLP-1RAs showed beneficial effects on mortality and MACE compared to the classes of DPP-4 inhibitors and sulphonylureas. SGLT-2 inhibitors were shown to be the most effective treatment in terms of HHF and kidney disease. Metformin was used as background therapy for the vast majority of participants in all included studies. Overall, the absolute effects of SGLT-2 inhibitors and GLP-1RAs on these important outcomes were evident for patients with established or at high risk for cardiovascular disease but limited for the low-risk subgroup.

Conclusions: The findings from our analyses substantiate the relevance of treatment with SGLT-2 inhibitors or GLP-1RAs as an add-on to metformin in patients with T2D and a high risk for cardiovascular disease, and furthermore, support the

recommendation for SGLT-2 inhibitor treatment in patients with T2D and heart failure or established kidney disease.

KEYWORDS

cardiovascular outcomes, DPP-IV inhibitor, effectiveness, GLP-1 receptor agonist, mortality, network meta-analysis, SGLT2 inhibitor, sulphonylureas, renal outcomes

1 | INTRODUCTION

The positive cardiovascular outcome trials for drugs within the classes of glucagon-like peptide 1 receptor agonists (GLP-1RAs) and sodium-glucose cotransporter-2 inhibitors (SGLT-2 inhibitors) as an add-on to metformin have prompted the recommendation as well as a widespread use of these compounds for the treatment of patients with type 2 diabetes (T2D).[1] The main clinical trials within this field have primarily investigated the treatment effects in T2D populations at high risk of cardiovascular disease, and furthermore, no head-to-head cardiovascular safety studies with a mutual comparison of GLP-1RAs and SGLT-2 inhibitors or against other glucose-lowering drugs such as sulphonylureas (SUs) or dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors) have been performed.[2–11] A network meta-analysis from 2021 by Palmer et al. has examined the benefits and harms of GLP-1RAs and SGLT-2 inhibitors in relation to one another in adults with T2D and different cardiovascular risk profiles.[12] However, this analysis was based on the clinical trials for all approved drugs within these two classes, including compounds with limited clinical relevance and without documented cardiovascular benefit.

The objective of our study was to compare the effects of relevant GLP-1RAs, SGLT-2 inhibitors, SUs and DPP-4 inhibitors for a range of T2D subgroups defined by their specific cardiovascular risk profile. We performed network meta-analyses with comparisons of drugs within the classes of GLP-1RAs and SGLT-2 inhibitors using prespecified definitions for clinically significant treatment effects with respect to important clinical outcomes (mortality, major cardiovascular adverse events [MACE], hospitalisation for heart failure [HHF] and kidney disease). The specified clinically equivalent GLP-1RAs and SGLT-2 inhibitors were compared to SUs and DPP-4 inhibitors with available cardiovascular outcome trials. The results presented in this article formed part of the basis for a recent T2D treatment recommendation from the Danish Medicines Council.[13]

What's new?

- Cardiovascular outcome trials for GLP-1RAs and SGLT-2 inhibitors have reported beneficial effects in patients with T2D.
- Drugs considered to be clinically equivalent within the classes of SGLT-2 inhibitors and GLP-1RAs as well as DPP-4 inhibitors and SUs were compared in terms of effects on hard outcomes. Our results substantiate the relevance of treatment with SGLT-2 inhibitors (or GLP-1RAs) in patients with T2D and concomitant high risk for cardiovascular disease.
- The lack of clinically relevant effects on hard outcomes in patients considered at low risk for cardiovascular disease should be taken into consideration when applying these relatively high-cost medicines.

2 | METHODS

2.1 | Search strategy and study selection

Originally, a systematic literature search for reviews and meta-analyses was performed based on the three databases Cochrane, MEDLINE and EMBASE. After this initial search, we identified a newer comprehensive network meta-analysis by Palmer et al. that was found to cover the relevant literature up to August 2020 with respect to the above-specified outcomes.[12] This network meta-analysis was evaluated to be of high quality after independent review from two persons using AMSTAR 2.[14] A supplementary search was conducted for relevant randomised clinical trials published within the period from January 2020 to February 2021 (Appendix S1, pages 1–6). Independent screening of literature and data extraction were performed by two persons.

The systematic literature search identified a range of cardiovascular outcome trials that have examined the effects of various GLP-1RAs,[2–7] SGLT-2 inhibitors,[8–11,15] DPP-4 inhibitors[16–20] and the SU glimepiride[17] in patients with T2D. The GLP-1RAs albiglutide and lixisenatide are not marketed and are considered clinically obsolete in Denmark, and in addition, no cardiovascular safety study has been performed for exenatide twice daily. Thus, these compounds were excluded from our analyses. An overview of the clinical trials included in our network meta-analyses is outlined in Table 1.

TABLE 1 Overview of the clinical trials included in our network meta-analyses.

Trial	Intervention (target dose)	Established CVD at baseline	Duration of follow-up	Study outcomes	Risk of bias
GLP-1RAs					
EXSCEL Add-on AHAs (metformin ≈75%)	Exenatide 2 mg QW ($n = 7356$) versus placebo ($n = 7396$)	73%	38 months	Mortality, MACE, HHF, kidney disease	Low
LEADER Add-on to AHAs (metformin ≈75%)	Liraglutid 1.8 mg QD ($n = 4668$) versus placebo ($n = 4672$)	81%	46 months	Mortality, MACE, HHF, kidney disease	Low
PIONEER-6 Add-on to AHAs (metformin ≈75%)	Oral semaglutide 14 mg QD ($n = 1591$) versus placebo ($n = 1592$)	85%	16 months	Mortality, MACE, HHF	Low
REWIND Add-on to AHAs (metformin ≈80%)	Dulaglutide 1.5 mg ($n = 4949$) QW versus placebo ($n = 4952$)	32%	65 months	Mortality, MACE, HHF, kidney disease	Low
SUSTAIN-6 Add-on to AHAs (metformin ≈75%)	sc. semaglutide 0.5 mg/1 mg QW ($n = 1648$) versus placebo ($n = 1649$)	83%	25 months	Mortality, MACE, HHF, kidney disease	Low
SGLT-2 inhibitors					
CANVAS + CANVAS-Renal Add-on to AHAs (metformin ≈75%)	Canagliflozin 100 mg/300 mg QD ($n = 5795$) versus placebo ($n = 4347$)	66%	43 months	Mortality, MACE, HHF, kidney disease	Low
CREDENCE Add-on to AHAs (metformin ≈60%)	Canagliflozin 100 mg QD ($n = 2202$) versus placebo ($n = 2199$)	50%	31 months	Mortality, MACE, HHF, kidney disease	Low
DECLARE-TIMI Add-on to AHAs (metformin ≈80%)	Dapagliflozin 10 mg QD ($n = 8582$) versus placebo ($n = 8578$)	41%	50 months	Mortality, MACE, HHF, kidney disease	Low
EMPA-REG Add-on to AHAs (metformin ≈75%)	Empagliflozin 10 mg/25 mg QD ($n = 4687$) versus placebo ($n = 2333$)	100%	37 months	Mortality, MACE, HHF	Low
VERTIS CV Add-on to AHAs (metformin ≈75%)	Ertugliflozin 5 mg/15 mg QD ($n = 5499$) versus placebo ($n = 2747$)	100%	42 months	Mortality, MACE, HHF, kidney disease	Low
DPP-4 inhibitors and SUs					
CARMELINA Add-on to AHAs (metformin ≈50%)	Linagliptin 5 mg QD ($n = 3494$) versus placebo ($n = 3485$)	57%	26 months	Mortality, MACE, HHF, kidney disease	Low
CAROLINA Add-on to AHAs (metformin ≈80%)	Linagliptin 5 mg QD ($n = 3023$) versus glimepiride 1–4 mg QD ($n = 3010$)	42%	76 months	Mortality, MACE, HHF	Low
EXAMINE Add-on to AHAs (metformin ≈65%)	Alogliptin 25 mg/12.5 mg/6.25 mg QD ($n = 2701$) versus placebo ($n = 2679$)	100%	18 months	Mortality, MACE	Low
SAVOR-TIMI Add-on to AHAs (metformin ≈70%)	Saxagliptin 5 mg/2.5 mg QD ($n = 8280$) versus placebo ($n = 8212$)	78%	25 months	Mortality, MACE, HHF, kidney disease	Low
TECOS Add-on to AHAs (metformin ≈80%)	Sitagliptin 100 mg/50 mg QD ($n = 7332$) versus placebo (7339)	100%	36 months	Mortality, MACE, HHF	Low

Abbreviations: AHA, antihyperglycemic agent; HHF, hospitalisation for heart failure; MACE, major adverse cardiovascular event; QD, once daily; QW, once weekly; sc., subcutaneous.

(Continues)

2.2 | Population, interventions, comparators and outcomes

The analyses comparing drugs within the classes of GLP-RAs and SGLT-2 inhibitors were performed based on the overall intention-to-treat (ITT) populations from the relevant clinical trials (Table 1). The comparison between the different classes of glucose-lowering drugs included analyses of populations with low risk and high risk for cardiovascular disease as well as populations with established cardiovascular disease and/or kidney disease. Low-risk and high-risk patients were defined by the presence of ≤2 or ≥3 cardiovascular risk factors, respectively, as described in the network meta-analysis by Palmer et al.[12]

The comparison within the class of GLP-1RAs included the drugs exenatide once weekly, dulaglutide, liraglutide as well as subcutaneous (sc.) semaglutide and oral semaglutide. The drugs canagliflozin, dapagliflozin, empagliflozin and ertugliflozin were included in the comparison within the class of SGLT-2 inhibitors. These analyses were applied to specify the drugs considered clinically equivalent within the classes of GLP-1RAs and SGLT-2 inhibitors, and the relevant compounds were subsequently included in a comparison between classes that also comprised the DPP-4 inhibitors alogliptin, linagliptin, saxagliptin and sitagliptin as well as the SU glimepiride. No cardiovascular outcome trials have investigated the safety of the remaining SUs or the DPP-4 inhibitor vildagliptin.

Our network meta-analyses included the outcomes of mortality, MACE, HHF, and a composite outcome for kidney disease as defined in the relevant clinical trials. MACE was in all the included trials defined as a composite of cardiovascular death, non-fatal myocardial infarction (MI) and non-fatal stroke. HHF was defined by hospital admission due to clinical manifestations of heart failure including the requirement for initiation or up-titration of relevant treatment (e.g. diuretics). The composite endpoint for kidney disease was not fully consistent between the included trials but was in general characterised by a composite of a sustained decrease of more than 30%–50% in the estimated glomerular filtration rate (eGFR), sustained end-stage kidney disease (eGFR <15 and/or renal replacement therapy) or death with renal disease as the underlying cause (i.e., renal death). However, renal death was not included in the REWIND and SUSTAIN-6 trials for dulaglutide and sc. semaglutide.[5,6] In addition, the new onset of persistent macroalbuminuria was included as part of the composite renal outcome in all trials for GLP-1RAs.[2,4–6]

As described in the protocol for this work, the Danish Medicines Council applied prespecified definitions of clinically significant treatment effects for the included outcomes. For mortality, an absolute risk reduction of 1% over a period of 5 years was considered clinically significant. For the remaining outcomes, absolute risk reductions of 2% at 5-year follow-up were applied as the cut-off for clinical significance.[21]

2.3 | Quality of evidence

The certainty of the results from our network meta-analyses was evaluated by GRADE (grading of recommendations assessment, development, and evaluation).[22] The clinical trials applied in our analyses were all included in the high-quality network meta-analysis by Palmer et al. that reported these trials to have a low risk of bias[12] (Table 1).

Overall, the clinical trials in our analyses included a few T2D patients with a low risk of cardiovascular disease, which led to a downgrade of the quality of evidence to moderate for the group of low-risk patients (≤2 cardiovascular risk factors) due to indirect evidence (*indirectness*).

Based on the relative effect estimates from our analyses (Appendix S1, pages 7–23) we downgraded the certainty of evidence for some specific comparisons within the classes of GLP-1RAs and SGLT-2 inhibitors due to wide confidence intervals (*imprecision*). The downgrade included estimates for oral and sc. semaglutide versus other GLP-1RAs in terms of mortality and HHF, oral semaglutide versus other GLP-1RAs in terms of MACE, sc. semaglutide versus other GLP-1RAs in terms of the composite kidney endpoint as well as estimates for empagliflozin and ertugliflozin versus other SGLT-2 inhibitors with respect to HHF and the composite endpoint for kidney disease. As a result, the evidence for these specific estimates was evaluated to be of low quality for the group of low-risk patients and of moderate quality for the remaining groups (high-risk and established cardiovascular disease or kidney disease).

The lack of consistency for the composite kidney endpoint between trials for the different drug classes resulted in a downgrade for *indirectness* due to lack of comparability between the studies. Thus, the evidence was assessed to be of low quality in the group of low-risk patients and of moderate quality in the remaining groups for comparisons between drug classes with respect to the composite kidney endpoint.

2.4 | Statistical analyses

Comparative effect analyses for mortality, MACE, HHF and the composite kidney endpoint were performed by indirect comparisons through the placebo arms of the

included clinical trials. Odds ratios (ORs) and confidence intervals (CIs) for pairwise comparisons between interventions were estimated using a fixed effects network meta-analysis analysed with R version 4.0.0 using packages meta and netmeta. The absolute risk reductions for the overall population (ITT) were estimated based on ORs for the pairwise comparisons and the median risk in the placebo arms. These estimates were thereby based on the actual follow-up periods of the relevant clinical trials.

The comparison between drug classes included estimates of 5-year absolute risk reductions in subgroups classified by baseline cardiovascular risk. These analyses were based on the ORs in the overall ITT population combined with the estimated 5-year risk at baseline for each subgroup, as described in the network meta-analysis by Palmer et al.[12] MACE was not included as an outcome in Palmer et al., and therefore no baseline 5-year risk estimates were accessible for this endpoint.[12] Instead, the baseline risk estimates for non-fatal MI (identical to the estimate for non-fatal stroke) were applied for effect analyses in the various subgroups. Subgroup analyses have not been performed for the composite renal endpoint due to the lack of valid 5-year risk estimates at baseline for this outcome. However, an estimation of 5-year absolute risk reductions in the overall ITT population was included for comparisons between DPP-4 inhibitors, GLP-1RAs and SGLT-2 inhibitors. Assuming a constant ratio of exponential distribution, this analysis was based on the median risks of the placebo groups alongside the hazard ratios of the pairwise comparisons.

3 | RESULTS

3.1 | Comparison of treatment effects within the class of GLP-1RAs

The effects of the GLP-1RAs dulaglutide, exenatide QW, liraglutide, sc. semaglutide and oral semaglutide were compared in terms of mortality, MACE, HHF and the composite kidney outcome. The results are shown in Table 2.

The apparent beneficial effect of sc. semaglutide compared to exenatide QW for the composite renal endpoint was the only observed statistically significant difference between the GLP-1RAs for the outcomes MACE, HHF or kidney disease. The analysis showed reduced mortality following treatment with oral semaglutide compared to dulaglutide, exenatide QW and sc. semaglutide. However, mortality was included as an exploratory secondary endpoint in the PIONEER-6 trial for oral semaglutide that did not reach statistically significance for the primary study outcome MACE.[7] Furthermore, the reported beneficial effect of oral semaglutide on mortality seems contradictory in terms of a classic exposure-response relationship, as no beneficial effect on mortality was shown for sc. semaglutide compared to placebo despite an evidently higher steady state semaglutide exposure after sc. compared to oral treatment.[6,23]

The proportion of patients with established cardiovascular disease at baseline was consistent between the trials of exenatide QW, liraglutide, oral semaglutide and sc. semaglutide (73–85%),[2,4,6,7] whereas this fraction was substantially smaller in the REWIND trial of dulaglutide (32%).[5] In contrast to the remaining trials, the REWIND trial did not classify the presence of objective cardiovascular risk factors (e.g. abnormal cardiac stress test or atherosclerosis by diagnostic imaging) as established disease.[5]

Based on the results from our analyses, we evaluated the included GLP-1RAs to be clinically equivalent with respect to effects on mortality as well as cardiovascular and renal outcomes. As a result, the compounds dulaglutide, exenatide QW, liraglutide, oral semaglutide and sc. semaglutide were all included in the comparison against the classes of SGLT-2 inhibitors, DPP-4 inhibitors, and the SU glimepiride.

3.2 | Comparison of treatment effects within the class of SGLT-2 inhibitors

The effects of the SGLT-2 inhibitors canagliflozin, dapagliflozin, empagliflozin and ertugliflozin were compared for effects on mortality, MACE, HHF and kidney disease. The results from our analyses are presented in Table 3.

The analyses for HHF and the composite kidney outcome showed no statistically significant differences between the SGLT-2 inhibitors, whereas empagliflozin was found to reduce mortality compared to all the other SGLT-2 inhibitors. This apparent beneficial effect of empagliflozin might at least partly be explained by a higher proportion of patients with established cardiovascular disease at baseline in the EMPA-REG study (100%) compared to the trials for canagliflozin and dapagliflozin (41%–66%).[8,10,11,15] Ertugliflozin demonstrated no statistically significant treatment effects compared to placebo in terms of mortality, MACE or the composite renal outcome, and furthermore, a statistically significant increased occurrence of MACE was evident compared to canagliflozin.

Based on the results from our analyses, we evaluated canagliflozin, dapagliflozin and empagliflozin to be clinically equivalent in terms of effects on cardiovascular and renal outcomes, whereas ertugliflozin was considered clinically inferior and therefore not included in the comparison against the classes of GLP-1RAs, DPP-4 inhibitors and the SU glimepiride.

TABLE 2 Comparison of estimated absolute effects of GLP-1RAs on mortality, MACE, HHF and the composite outcome of kidney disease.

Intervention	Dulaglutide	Exenatide QW	Liraglutide	Oral semaglutide	Sc. semaglutide	Placebo
Mortality						
Dulaglutide	N/A	0.23 (−0.84; 1.48)	0.40 (−0.75; 1.76)	2.98 (0.21; 7.30)*	−1.03 (−3.18; 1.95)	−0.77 (−1.55; 0.09)
Exenatide QW	−0.23 (−1.27; 0.98)	N/A	0.17 (−0.94; 1.49)	2.75 (0.06; 6.95)*	−1.26 (−3.34; 1.63)	−1.00 (−1.76; −0.17)*
Liraglutide	−0.40 (−1.50; 0.88)	−0.17 (−1.27; 1.11)	N/A	2.57 (−0.07; 6.73)	−1.43 (−3.50; 1.45)	−1.18 (−2.02; −0.22)*
Oral semaglutide	−2.98 (−4.62; −0.33)*	−2.75 (−4.39; −0.10)*	−2.57 (−4.23; 0.11)	N/A	−4.01 (−5.89; −0.69)*	−3.75 (−5.36; −1.20)*
Sc. semaglutide	1.03 (−1.41; 4.39)	1.26 (−1.18; 4.62)	1.43 (−1.04; 4.86)	4.01 (0.40; 10.06)*	N/A	0.26 (−2.07; 3.41)
Placebo	0.77 (−0.08; 1.72)	1.00 (0.15; 1.95)*	1.18 (0.20; 2.28)*	3.75 (0.76; 8.32)*	−0.26 (−2.52; 2.81)	N/A
MACE						
Dulaglutide	N/A	−0.45 (−1.87; 1.16)	0.27 (−1.26; 2.00)	0.97 (−2.11; 5.06)	1.81 (−0.67; 4.91)	−1.28 (−2.39; −0.07)*
Exenatide QW	0.45 (−1.02; 2.11)	N/A	0.72 (−0.75; 2.37)	1.42 (−1.73; 5.58)	2.26 (−0.26; 5.38)	−0.83 (−1.80; 0.22)
Liraglutide	−0.27 (−1.76; 1.43)	−0.72 (−2.10; 0.85)	N/A	0.71 (−2.30; 4.71)	1.54 (−0.88; 4.57)	−1.55 (−2.62; −0.37)*
Oral semaglutide	−0.97 (−3.80; 2.81)	−1.42 (−4.22; 2.29)	−0.71 (−3.53; 3.07)	N/A	0.84 (−2.42; 5.43)	−2.25 (−4.95; 1.29)
Sc. semaglutide	−1.81 (−3.91; 0.85)	−2.26 (−4.32; 0.32)	−1.54 (−3.65; 1.11)	−0.84 (−3.84; 3.43)	N/A	−3.09 (−5.03; −0.70)*
Placebo	1.28 (0.07; 2.61)*	0.83 (−0.20; 1.95)	1.55 (0.34; 2.86)*	2.25 (−0.99; 6.46)	3.09 (0.57; 6.15)*	N/A
HHF						
Dulaglutide	N/A	−0.04 (−0.74; 0.88)	0.21 (−0.49; 1.12)	0.21 (−1.19; 2.72)	−0.49 (−1.53; 1.05)	−0.19 (−0.71; 0.44)
Exenatide QW	0.04 (−0.68; 0.96)	N/A	0.25 (−0.46; 1.16)	0.25 (−1.17; 2.77)	−0.46 (−1.51; 1.09)	−0.15 (−0.67; 0.47)
Liraglutide	−0.21 (−0.87; 0.64)	−0.25 (−0.90; 0.59)	N/A	0.00 (−1.30; 2.33)	−0.71 (−1.67; 0.73)	−0.40 (−0.88; 0.17)
Oral semaglutide	−0.21 (−1.52; 2.13)	−0.25 (−1.55; 2.09)	−0.00 (−1.30; 2.33)	N/A	−0.71 (−2.13; 2.04)	−0.40 (−1.66; 1.79)
Sc. semaglutide	0.49 (−0.71; 2.27)	0.46 (−0.74; 2.23)	0.71 (−0.49; 2.47)	0.71 (−1.06; 4.08)	N/A	0.31 (−0.79; 1.85)
Placebo	0.19 (−0.37; 0.85)	0.15 (−0.39; 0.80)	0.40 (−0.14; 1.05)	0.40 (−1.03; 2.88)	−0.31 (−1.31; 1.12)	N/A
Kidney disease						
Dulaglutide	N/A	0.26 (−1.17; 0.81)	0.43 (−0.56; 1.61)	N/A	1.62 (−0.01; 3.81)	−0.98 (−1.52; −0.39)*
Exenatide QW	0.26 (−0.69; 1.37)	N/A	0.69 (−0.47; 2.09)	N/A	1.88 (0.12; 4.28)*	−0.72 (−1.51; 0.18)
Liraglutide	−0.43 (−1.35; 0.67)	−0.69 (−1.72; 0.57)	N/A	N/A	1.19 (−0.42; 3.41)	−1.41 (−2.20; −0.48)*
Sc. semaglutide	−1.62 (−2.81; 0.01)	−1.88 (−3.12; −0.16)*	−1.19 (−2.46; 0.58)	N/A	N/A	2.60 (−3.74; −1.05)*
Placebo	0.98 (0.35; 1.66)*	0.72 (−0.16; 1.71)	1.41 (0.42; 2.55)*	N/A	2.60 (0.79; 4.99)*	N/A

Note: Results are presented as absolute risk reductions (%-points) with 95% CIs. White: ⨁⨁⨁⨁ High-quality evidence according to GRADE. Grey: ⨁⨁⨁◯ Downgraded to moderate quality of evidence for imprecision.

Abbreviations: HHF, hospitalisation for heart failure; MACE, major adverse cardiovascular event; N/A, not applicable; QD, once daily; QW, once weekly; sc., subcutaneous.

*$p < 0.05$.

TABLE 3 Comparison of estimated absolute effects of SGLT-2 inhibitors on mortality, MACE, HFF and the composite outcome of kidney disease.

Intervention	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin	Placebo
Mortality					
Canagliflozin	N/A	−0.50 (−1.60; 0.77)	1.48 (0.08; 3.18)*	−0.51 (−1.76; 0.98)	−1.09 (−1.90; −0.19)*
Dapagliflozin	0.50 (−0.66; 1.86)	N/A	1.98 (0.51; 3.77)*	−0.01 (−1.32; 1.56)	−0.59 (−1.42; 0.33)
Empagliflozin	−1.48 (−2.61; −0.10)*	−1.98 (−3.10; −0.62)*	N/A	−1.99 (−3.20; −0.48)*	−2.58 (−3.53; −1.45)*
Ertugliflozin	0.51 (−0.83; 2.10)	0.01 (−1.31; 1.57)	1.99 (0.39; 3.97)*	N/A	−0.59 (−1.65; 0.63)
Placebo	1.09 (0.17; 2.12)*	0.59 (−0.29; 1.57)	2.58 (1.23; 4.16)*	0.59 (−0.55; 1.89)	N/A
MACE					
Canagliflozin	N/A	−1.24 (−2.50; 0.18)	−0.31 (−1.88; 1.52)	−1.90 (−3.38; −0.19)*	−1.92 (−2.84; −0.93)*
Dapagliflozin	1.24 (−0.16; 2.81)	N/A	0.93 (−0.81; 2.94)	−0.66 (−2.29; 1.21)	−0.68 (−1.68; 0.40)
Empagliflozin	0.31 (−1.31; 2.19)	−0.93 (−2.54; 0.94)	N/A	−1.59 (−3.38; 0.53)	−1.61 (−2.96; −0.08)*
Ertugliflozin	1.90 (0.17; 3.88)*	0.66 (−1.06; 2.63)	1.59 (−0.45; 3.97)	N/A	−0.02 (−1.43; 1.54)
Placebo	1.92 (0.85; 3.08)*	0.68 (−0.37; 1.82)	1.61 (0.07; 3.35)*	0.02 (−1.38; 1.59)	N/A
HHF					
Canagliflozin	N/A	−0.40 (−0.91; 0.25)	−0.11 (−0.73; 0.75)	−0.26 (−0.87; 0.57)	−1.33 (−1.71; −0.89)*
Dapagliflozin	0.40 (−0.19; 1.16)	N/A	0.30 (−0.43; 1.29)	0.14 (−0.57; 1.11)	−0.93 (−1.36; −0.42)*
Empagliflozin	0.11 (−0.55; 1.00)	−0.30 (−0.95; 0.59)	N/A	−0.15 (−0.89; 0.90)	−1.23 (−1.78; −0.51)*
Ertugliflozin	0.26 (−0.42; 1.18)	−0.14 (−0.82; 0.77)	0.15 (−0.63; 1.27)	N/A	−1.08 (−1.65; −0.34)*
Placebo	1.33 (0.74; 2.03)*	0.93 (0.36; 1.61)*	1.23 (0.40; 2.30)*	1.08 (0.27; 2.11)*	N/A
Kidney disease					
Canagliflozin	N/A	−0.49 (−0.96; 0.10)	0.28 (−0.47; 1.34)	−0.65 (−1.28; 0.18)	−1.40 (−1.77; −0.97)*
Dapagliflozin	0.49 (−0.08; 1.18)	N/A	0.77 (−0.11; 1.98)	−0.17 (−0.89; 0.78)	−0.91 (−1.30; −0.48)*
Empagliflozin	−0.28 (−0.95; 0.67)	−0.77 (−1.42; 0.15)	N/A	−0.93 (−1.67; 0.16)	−1.68 (−2.29; −0.85)*
Ertugliflozin	0.65 (−0.14; 1.69)	0.17 (−0.60; 1.16)	0.93 (−0.11; 2.44)	N/A	−0.75 (−1.42; 0.10)
Placebo	1.40 (0.83; 2.06)*	0.91 (0.42; 1.47)*	1.68 (0.63; 3.10)*	0.75 (−0.08; 1.78)	N/A

Note: Results are presented as absolute risk reductions (%-points) with 95% CIs. White: ⨁⨁⨁⨁ High-quality evidence according to GRADE. Grey: ⨁⨁⨁◯ Downgraded to moderate quality of evidence for imprecision.

Abbreviations: HHF, hospitalisation for heart failure; MACE, major adverse cardiovascular event; N/A, not applicable; QD, once daily; QW, once weekly; sc., subcutaneous.

*$p < 0.05$.

3.3 | Comparison of treatment effects between the classes of DPP-4 inhibitors, GLP-1RAs, SGLT-2 inhibitors and SUs

The effects on mortality, MACE, HHF and the composite kidney outcome were compared between the specified clinically equivalent drugs within the classes of GLP-1RAs (dulaglutide, exenatide once weekly, liraglutide, sc. semaglutide and oral semaglutide) and SGLT-2 inhibitors (canagliflozin, dapagliflozin and empagliflozin) as well as DPP-4 inhibitors (alogliptin, linagliptin, saxagliptin and sitagliptin) and the SU glimepiride with available cardiovascular outcome trials. Results for the overall population are presented in Table 4.

Our analyses showed treatment with SGLT-2 inhibitors to elicit statistically significant reductions in mortality compared to DPP-4 inhibitors and the SU glimepiride. SGLT-2 inhibitor treatment was also found to cause a statistically significant reduction in MACE compared to DPP-4 inhibitors. Furthermore, reductions in HHF and the composite kidney outcome were shown compared to DPP-4 inhibitors and GLP-1RAs. A sensitivity analysis was performed to examine the effects of SGLT-2 inhibitors on MACE compared to a specified selection of GLP-1RAs consisting of the compounds dulaglutide, liraglutide and sc. semaglutide that have all demonstrated beneficial placebo-corrected effects in terms of this outcome.[2,5,6] The result was consistent with the primary analysis, and thus,

TABLE 4 Comparison of estimated absolute effects of DPP-4 inhibitors, GLP-1RAs, SGLT-2 inhibitors and SUs in terms of mortality, MACE, HHF and the composite kidney outcome.

Intervention	DPP-4 inhibitors	GLP-1RAs	SGLT-2 inhibitors	SU	Placebo
Mortality					
DPP-4 inhibitors	N/A	1.03 (0.35; 1.78)*	1.15 (0.43; 1.94)*	−0.73 (−1.78; 0.47)	0.10 (−0.39; 0.64)
GLP-1RAs	−1.03 (−1.63; −0.38)*	N/A	0.11 (−0.50; 0.79)	−1.77 (−2.83; −0.50)*	−0.93 (−1.35; −0.48)*
SGLT-2 inhibitors	−1.15 (−1.76; −0.47)*	−0.11 (−0.72; 0.55)	N/A	−1.88 (−2.94; −0.62)*	−1.04 (−1.50; −0.55)*
SU	0.73 (−0.41; 2.05)	1.77 (0.43; 3.34)*	1.88 (0.52; 3.48)*	N/A	0.84 (−0.41; 2.29)
Placebo	−0.10 (−0.60; 0.42)	0.93 (0.45; 1.43)*	1.04 (0.52; 1.60)*	−0.84 (−1.97; 0.48)	N/A
MACE					
DPP-4 inhibitors	N/A	1.28 (0.39; 2.23)*	1.34 (0.41; 2.34)*	−0.25 (−1.78; 1.47)	−0.01 (−0.66; 0.67)
GLP-1RAs	−1.28 (−2.08; −0.42)*	N/A	0.06 (−0.76; 0.95)	−1.53 (−3.10; 0.28)	−1.29 (−1.85; −0.70)*
SGLT-2 inhibitors	−1.34 (−2.18; −0.44)*	−0.06 (−0.88; 0.82)	N/A	−1.59 (−3.17; 0.23)	−1.35 (−1.96; −0.71)*
SU	0.25 (−1.30; 2.00)	1.53 (−0.24; 3.56)	1.59 (−0.20; 3.65)	N/A	0.24 (−1.43; 2.14)
Placebo	0.01 (−0.64; 0.69)	1.29 (0.67; 1.94)*	1.35 (0.67; 2.07)*	−0.24 (−1.88; 1.63)	N/A
HHF					
DPP-4 inhibitors	N/A	0.41 (−0.05; 0.95)	1.26 (0.76; 1.83)*	0.61 (−0.22; 1.70)	0.20 (−0.15; 0.58)
GLP-1RAs	−0.41 (−0.83; 0.06)	N/A	0.84 (0.41; 1.34)*	0.20 (−0.62; 1.30)	−0.22 (−0.51; 0.10)
SGLT-2 inhibitors	−1.26 (−1.58; −0.88)*	−0.84 (−1.16; −0.47)*	N/A	−0.64 (−1.25; 0.18)	−1.06 (−1.30; −0.79)*
SU	−0.61 (−1.30; 0.29)	−0.20 (−0.97; 0.84)	0.64 (−0.14; 1.69)	N/A	−0.42 (−1.15; 0.55)
Placebo	−0.20 (−0.52; 0.16)	0.22 (−0.09; 0.56)	1.06 (0.71; 1.45)*	0.42 (−0.42; 1.52)	N/A
Kidney disease					
DPP-4 inhibitors	N/A	1.93 (1.05; 2.93)*	2.80 (1.81; 3.92)*	N/A	0.92 (0.16; 1.77)*
GLP-1RAs	−1.93 (−2.59; −1.18)*	N/A	0.86 (0.28; 1.52)*	N/A	−1.01 (−1.36; −0.63)*
SGLT-2 inhibitors	−2.80 (−3.41; −2.08)*	−0.86 (−1.36; −0.31)*	N/A	N/A	−1.87 (−2.28; −1.43)*
Placebo	−0.92 (−1.60; −0.18)*	1.01 (0.59; 1.45)*	1.87 (1.30; 2.49)*	N/A	N/A

Note: Results are presented as absolute risk reductions (%-points) with 95% CIs. White: ⨁⨁⨁⨁ High-quality evidence according to GRADE. Grey: ⨁⨁⨁◯ Downgraded to moderate quality of evidence for indirecness.

Abbreviations: HHF, hospitalisation for heart failure; MACE, major adverse cardiovascular event; N/A, not applicable.

*$p < 0.05$.

no statistically significant difference between SGLT-2 inhibitors and GLP-1RAs was evident for the outcome MACE (HR 1.03 [0.91; 1.16]) after exclusion of exenatide QW and oral semaglutide that have not demonstrated statistically significant effects on MACE compared to placebo.[4,7]

GLP-1RA treatment was shown to reduce mortality compared to DPP-4 inhibitors and the SU glimepiride. In addition, the occurrence of MACE and the composite renal outcome was reduced compared to DPP-4 inhibitors. It should be noted that estimates for mortality and cardiovascular outcomes for the class of SUs were based solely on data from the CAROLINA trial examining linagliptin versus glimepiride in a population with 42% of patients having established cardiovascular disease at baseline.[17] As a natural consequence, the relatively wide confidence intervals for the comparison of SUs against the classes of SGLT-2 inhibitors and GLP-1RAs pose a risk of a type II error for the MACE outcome. The proportion of patients with established cardiovascular disease included in the trials for DPP-4 inhibitors was overall consistent with the conditions in the trials for SGLT-2 inhibitors and GLP-1RAs (Table 1).

No trials for SUs with the inclusion of a relevant renal outcome have been identified, whereas the analysis for DPP-4 inhibitors was based on data from the CARMELINA and SAVOR-TIMI trials for linagliptin and saxagliptin. The proportion of patients with micro- or macroalbuminuria at baseline was overall consistent between studies (approximately 10%), with the exception of the CREDENCE trial for canagliflozin (100%) and the CAROLINA study examining linagliptin and glimepiride (approximately 40%).[15,17]

3.4 | Subgroup analyses based on cardiovascular risk profile

The primary objective of our analyses was to compare the included drug classes with respect to important clinical outcomes for a range of subgroups classified by baseline cardiovascular risk. The estimated 5-year absolute risk reductions are presented in Table 5.

Treatment with SGLT-2 inhibitors or GLP-1RAs was shown to cause statistically significant reductions in mortality compared to DPP-4 inhibitors and the SU glimepiride for all five subgroups. A gradual increasing effect in absolute terms was observed in relation to rising baseline cardiovascular risk, and thus, the numerical effects were relatively limited in the low-risk group with 5-year absolute risk reductions between 0.30% and 0.55% corresponding to numbers needed to treat (NNTs) within the range of 182 to 334. The same tendency was evident for SGLT-2 inhibitors and GLP-1RAs compared to DPP-4 inhibitors in terms of MACE, whereas no statistically significant differences were observed for these two drug classes compared to the SU glimepiride.

Only SGLT-2 inhibitors showed statistically significant reductions in HHF, which was evident compared to DPP-4 inhibitors and GLP-1RAs for all risk groups. Once again, the largest absolute risk reductions were present in subgroups with a substantial baseline risk for cardiovascular disease. No subgroup analysis has been performed for the composite kidney outcome due to the lack of valid baseline risk estimates for this endpoint. An analysis based on the overall ITT population found SGLT-2 inhibitors to elicit significant 5-year absolute risk reductions for the composite kidney outcome compared to both DPP-4 inhibitors and GLP-1RAs. In addition, GLP-1RAs were shown to cause a statistically significant risk reduction compared to DPP-4 inhibitors for the composite renal outcome.

4 | DISCUSSION

The results from our network meta-analyses point to beneficial treatment effects of SGLT-2 inhibitors and GLP-1RAs on mortality and MACE compared to DPP-4 inhibitors and the SU glimepiride in T2D patients with high risk for cardiovascular disease including populations with established cardiovascular or kidney disease. In addition, SGLT-2 inhibitors were shown to be the most effective treatment choice in terms of HHF and kidney disease prevention. Overall, the magnitude of the observed beneficial effects of SGLT-2 inhibitors and GLP-1RAs were determined by baseline cardiovascular risk, and thus, the effect estimates for the low-risk subgroup were small and not considered to be of clinical relevance according to our predefined cut-off values. Metformin was used as a standard background therapy for the majority of participants (roughly 75%) in all the included studies.

The work presented in this paper is to a large extent based on the methodological approach from the recent comprehensive network meta-analysis by Palmer et al. that has compared the effects of SGLT-2 inhibitors and GLP-1RAs.[12] Strengths of our analyses included the inclusion of only drugs considered to be clinically equivalent within the classes of SGLT-2 inhibitors and GLP-1RAs as well as the comparison with drugs from the classes of DPP-4 inhibitors and SUs with available cardiovascular outcome trials. Furthermore, our analyses addressed the composite cardiovascular and renal endpoints applied in the underlying clinical trials. An equivalent effect on MACE was observed between SGLT-2 inhibitors and GLP-1RAs, which was substantiated by the consistent result from a sensitivity analysis including only the GLP-1RAs

TABLE 5 Comparison of estimated absolute 5-year treatment effects of DPP-4 inhibitors, GLP-1RAs, SGLT-2 inhibitors and SUs in subgroups defined by their baseline 5-year cardiovascular risk profile. Results are presented as absolute risk reductions (%-points) with 95% CIs.

Baseline risk (baseline 5-year risk)	SGLT-2 inhibitors versus GLP-1RAs	SGLT-2 inhibitors versus DPP-4 inhibitors	SGLT-2 inhibitors versus SU	GLP-1RAs versus SU	GLP-1RAs versus DPP-4 inhibitors	SU versus DPP-4 inhibitors
Mortality						
Low risk (20 per 1000)	−0.03 (−0.20; 0.15)	−0.32 (−0.50; −0.14)*	−0.55 (−0.84; −0.18)*	−0.51 (−0.82; −0.15)*	−0.30 (−0.46; −0.10)*	0.22 (−0.13; 0.58)
High risk (70 per 1000)	−0.11 (−0.69; 0.51)	−1.07 (−1.69; −0.47)*	−1.83 (−2.81; −0.58)*	−1.68 (−2.73; −0.50)*	−1.00 (−1.55; −0.33)*	0.72 (−0.43; 1.68)
Established CVD (120 per 1000)	−0.19 (−1.14; 0.84)	−1.75 (−2.76; −0.76)*	−2.97 (−4.60; −0.93)*	−2.73 (−4.47; −0.81)*	−1.64 (−2.54; −0.54)*	1.16 (−0.68; 2.73)
Established CKD (170 per 1000)	−0.26 (−1.56; 1.13)	−2.35 (−3.74; −1.01)*	−3.98 (−6.21; −1.23)*	−3.65 (−6.03; −1.08)*	−2.20 (−3.42; −0.72)*	1.55 (−0.90; 3.65)
Established CVD + CKD (265 per 1000)	−0.36 (−2.23; 1.59)	−3.29 (−5.27; −1.40)*	−5.52 (−8.74; −1.68)*	−5.05 (−8.48; −1.46)*	−3.07 (−4.82; −1.00)*	2.11 (−1.21; 5.05)
MACE						
Low risk (30 per 1000)[a]	−0.03 (−0.23; 0.23)	−0.38 (−0.59; −0.12)*	−0.45 (−0.87; 0.06)	−0.42 (−0.84; 0.09)	−0.35 (−0.59; −0.12)*	0.06 (−0.41; 0.48)
High risk (58 per 1000)[a]	−0.05 (−0.44; 0.44)	−0.72 (−1.11; −0.22)*	−0.84 (−1.64; 0.11)	−0.78 (−1.58; 0.17)	−0.66 (−1.11; −0.22)*	0.11 (−0.77; 0.90)
Established CVD (108 per 1000)[a]	−0.09 (−0.79; 0.78)	−1.27 (−1.97; −0.39)*	−1.49 (−2.93; 0.20)	−1.39 (−2.83; 0.29)	−1.17 (−1.97; −0.39)*	0.20 (−1.35; 1.59)
Established CKD (120 per 1000)[a]	−0.10 (−0.87; 0.85)	−1.39 (−2.16; −0.42)*	−1.64 (−3.22; 0.21)	−1.53 (−3.11; 0.32)	−1.29 (−2.16; −0.42)*	0.21 (−1.48; 1.75)
Established CVD + CKD (190 per 1000)[a]	−0.14 (−1.30; 1.26)	−2.05 (−3.20; −0.62)*	−2.41 (−4.79; 0.31)	−2.24 (−4.61; 0.46)	−1.89 (−3.20; −0.62)*	0.31 (−2.12; 2.57)
HHF						
Low risk (5 per 1000)	−0.13 (−0.18; −0.07)*	−0.20 (−0.24; −0.14)*	−0.10 (−0.19; 0.03)	−0.03 (−0.15; 0.13)	−0.06 (−0.13; 0.01)	−0.09 (−0.20; 0.04)
High risk (30 per 1000)	−0.77 (−1.04; −0.44)*	−1.15 (−1.43; −0.81)*	−0.59 (−1.14; 0.18)	−0.19 (−0.88; 0.76)	−0.37 (−0.74; 0.06)	−0.56 (−1.18; 0.25)
Established CVD (80 per 1000)	−1.98 (−2.71; −1.12)*	−2.95 (−3.70; −2.05)*	−1.53 (−2.97; 0.46)	−0.49 (−2.27; 1.90)	−0.94 (−1.89; 0.15)	−1.41 (−3.03; 0.61)
Established CKD (105 per 1000)	−2.55 (−3.50; −1.44)*	−3.79 (−4.77; −2.63)*	−1.97 (−3.85; 0.58)	−0.63 (−2.93; 2.42)	−1.20 (−2.43; 0.20)	−1.81 (−3.90; 0.78)
Established CVD + CKD (235 per 1000)	−5.16 (−7.17; −2.87)*	−7.54 (−9.61; −5.15)*	−4.02 (−8.07; 1.15)	−1.23 (−5.95; 4.56)	−2.29 (−4.73; 0.37)	−3.49 (−7.77; 1.45)
Kidney disease						
ITT-population	−1.35 (−2.33; −0.47)*	−4.18 (−5.85; −2.72)*	N/A	N/A	−2.83 (−4.32; −1.51)*	N/A

Note: White: ⨁⨁⨁⨁ High-quality evidence according to GRADE; Grey: ⨁⨁⨁◯ Downgraded to moderate quality of evidence for indirectness (only few patients with low risk in studies); Dark grey: ⨁⨁◯◯ Downgraded to low quality of evidence for indirectness (only few patients with low risk in studies and lack of comparison of endpoint definition).

Abbreviations: CVD, cardiovascular disease; CKD, chronic kidney disease; HHF, hospitalisation for heart failure; ITT, intention-to-treat; MACE, major adverse cardiovascular event; N/A, not applicable.

[a]Baseline risk estimates for non-fatal MI.

*$p < 0.05$.

dulaglutide, liraglutide and sc. semaglutide that have all demonstrated beneficial placebo-corrected effects in terms of MACE.

Evaluation by GRADE identified the general lack of low-risk patients in the clinical trials as the most consistent challenge for the quality of evidence. Heterogeneity in study populations and the varying definitions of the composite renal outcome between the included trials also constitute limitations. However, the use of a random effects model as an alternative to the applied fixed effect model did not elicit any substantial changes in the results. Also, such heterogeneity seems inevitable, as network meta-analyses are performed to deal with the absence of head-to-head cardiovascular safety studies. The network meta-analysis by Palmer et al. did not include risk estimates for MACE and the application of baseline risk estimates for myocardial infarction in our 5-year MACE analysis poses an additional potential limitation. Thus, this might have instigated an underestimation of the effect estimates for MACE in our subgroup analyses, but we consider any marked impact on the comparison between GLP-1RAs and SGLT-2 inhibitors to be unlikely due to the absence of relative and absolute differences between these drug classes. Finally, it should be noted that data from the DAPA-HF, DAPA-CKD and EMPEROR-Reduced trials investigating the effects of dapagliflozin and empagliflozin in patients with heart failure or kidney disease were not included in our analyses, as these clinical outcome trials included both patients with and without T2D.[24–26]

The findings from our analyses are in line with the results from the meta-analysis by Palmer et al. that reported equivalent beneficial effects of SGLT-2 inhibitors and GLP-1RAs on mortality and non-fatal MI compared to placebo as well as a superior effect of SGLT-2 inhibitors in terms of HHF. In contrast to our results, Palmer et al. described similar effects of SGLT-2 inhibitors and GLP-1RAs on kidney failure, which could be due to the less extensive definition of the kidney endpoint (eGFR <15 or start of kidney replacement treatment) in this study. The analysis by Palmer et al. reported GLP-1RAs to hold beneficial effects compared to SGLT-2 inhibitors for the endpoint non-fatal stroke (OR 1.20 [1.03; 1.41]).[12] This was mainly a result of the failure of SGLT-2 inhibitors to reduce non-fatal stroke compared to placebo (OR 1.01 (95% CI [0.89; 1.14])) despite that the SGLT-2 inhibitors reduced other cardiovascular endpoints compared to placebo (MACE OR 0.87 [0.82; 0.93]) and showed no difference compared to GLP-1RAs in our analysis (MACE OR 0.99 [0.91; 1.09]). A meta-analysis from 2022 by Wei et al. has specifically evaluated the effect of GLP-1RA treatment on the outcome of stroke and reported a reduced risk ratio of 0.83 [0.73; 0.95] for total stroke after treatment with GLP-1RAs compared to placebo, which corresponds to an absolute risk reduction of 0.27% and a number needed to treat of roughly 370 persons for a period of 1.3 to 5.4 years based on the included clinical trials.[27]

In conclusion, the results from our analyses substantiate the relevance of treatment with SGLT-2 inhibitors or GLP-1RAs in patients with T2D and concomitant high risk for cardiovascular disease, and furthermore, support the recommendation for SGLT-2 inhibitor treatment in patients with T2D and heart failure or established kidney disease. The lack of clinically relevant effects on mortality, cardiovascular and renal outcomes in the low-risk subgroup should be taken into consideration when deciding whether to use these compounds with higher costs in low-risk T2D populations.

CONFLICT OF INTEREST STATEMENT

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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