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Sodium-glucose co-transporter-2 inhibitors in patients with chronic kidney disease with or without type 2 diabetes: systematic review and meta-analysis

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ABSTRACT

OBJECTIVE To examine cardiovascular and kidney benefits and harms of sodium-glucose co-transporter-2 (SGLT-2) inhibitors stratified by risk in adults with chronic kidney disease regardless of diabetes status.

DESIGN Systematic review and meta-analysis.

DATA SOURCES Ovid Medline, Embase, and Cochrane Central from database inception to 15 June 2024.

ELIGIBILITY CRITERIA FOR SELECTING STUDIES Randomised controlled trials that compared SGLT-2 inhibitors with placebo or standard care with no SGLT-2 inhibitors in adults with chronic kidney disease with a follow-up duration of ≥12 weeks were eligible. Secondary analyses based on subpopulations from randomised controlled trials and publications not in English language were excluded.

DATA SYNTHESIS Random effects meta-analyses were conducted, with effect estimates presented as risk ratios with 95% confidence intervals (CIs). Absolute treatment effects were estimated over a five year duration for individuals with varied risks of cardiovascular and kidney complications based on the Kidney Disease Improving Global Outcomes (KDIGO) risk stratification system. Certainty of evidence was assessed using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach.

RESULTS Evidence from 13 randomised controlled trials (29 614 patients) informed treatment effect estimates. In relative terms, SGLT-2 inhibitors reduced all cause death (risk ratio 0.85 (95% CI 0.74 to 0.98)), cardiovascular death (0.84 (0.74 to 0.96)), kidney failure (0.68 (0.60 to 0.77)), non-fatal stroke (0.73 (0.57 to 0.94)), non-fatal myocardial infarction (0.75 (0.60 to 0.93)), and admission to hospital for heart failure (0.68 (0.60 to 0.78)). No credible subgroup effects were found from diabetes status, heart failure status, estimated glomerular filtration rate, urinary albumin-to-creatinine ratio, and follow-up duration. Absolute effect estimates across these outcomes over a five year period varied across risk groups based on baseline risks of cardiovascular and kidney events. Effects of SGLT-2 inhibitors in the group at low risk included seven fewer all- cause deaths, four fewer admissions to hospital for heart failure per 1000 individuals, and no effects on kidney failure. Effects in the higher risk group included 48 fewer all cause deaths, 58 fewer kidney failures, and 25 fewer admissions to hospital for heart failure per 1000 individuals. Although SGLT-2 inhibitor use was associated with a relative increase in the risk of harms, including genital infection (2.66 (95% CI 2.07 to 3.42)), ketoacidosis (2.27 (1.30 to 3.95)), and symptomatic hypovolaemia (1.29 (1.15 to 1.44)), absolute differences for all harm outcomes were small.

CONCLUSIONS Among people who have chronic kidney disease either with type 2 diabetes or not, SGLT-2 inhibitors improved cardiovascular and kidney outcomes with varying degrees of absolute benefit depending on an individual's baseline risks of cardiovascular and kidney-related sequelae. Absolute benefits and harms stratified by risk and associated with SGLT-2 inhibitors should inform individual decision making at the patient level.

SYSTEMATIC REVIEW REGISTRATION PROSPERO CRD42022325483.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Sodium-glucose co-transporter-2 (SGLT-2) inhibitors showed benefits in reducing cardiovascular and kidney-related morbidity in individuals with chronic kidney disease and type 2 diabetes

⇒ Randomised controlled trials have evaluated the efficacy and safety of SGLT-2 inhibitors in people with chronic kidney disease irrespective of diabetes diagnosis

WHAT THIS STUDY ADDS

⇒ SGLT-2 inhibitors resulted in relative reductions in risks of all cause death by 15%, cardiovascular death by 16%, kidney failure by 32%, non-fatal myocardial infarction by 25%, non-fatal stroke by 27%, and admission to hospital for heart failure by 32% among adults with chronic kidney disease regardless of diabetes diagnosis

⇒ Anticipated absolute benefits varied across individuals' risks of cardiovascular and kidney-related complications, with individuals at higher risk of complications deriving incrementally greater benefit

⇒ SGLT-2 inhibitors were associated with little or no increased risk of harms such as genital infections, ketoacidosis, symptomatic hypovolaemia, acute kidney injury requiring dialysis, fractures, and lower limb amputations

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

⇒ When considering initiating SGLT-2 inhibitors for patients with chronic kidney disease irrespective of diabetes status, clinicians should consider the patients' anticipated risk of cardiovascular and kidney-related complications and associated benefits and harms of SGLT-2 inhibitor therapy in absolute terms

Introduction

Approximately 850 million adults live with chronic kidney disease worldwide. Globally, chronic kidney

disease results in 1.2 million deaths every year, with cardiovascular diseases being the leading cause of death.[1] Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers have been the mainstay of medical treatment for adults with chronic kidney disease for decades. However, individuals with chronic kidney disease carry a substantial residual risk of complications, including progression to kidney failure and cardiovascular events.[2]

Sodium-glucose co-transporter-2 (SGLT-2) inhibitors were initially developed as diabetes treatment medications. They subsequently proved to have protective effects on the cardiovascular system and on the kidney in adults who have type 2 diabetes, heart failure, or both.[3–5] More recently, two trials have shown large reductions in risks of kidney failure and death in addition to angiotensin-converting enzyme inhibitors or angiotensin receptor blockers for adults with chronic kidney disease with and with no diabetes.[6 7] One meta-analysis similarly showed cardiovascular and kidney benefits with SGLT-2 inhibitors, but was limited to large trials only and included only four trials that had adults with chronic kidney disease, and did not account for variable risks of cardiovascular and kidney complications across individuals when presenting absolute treatment effects.[8]

To inform evidence-based practice guidelines stratified by risk, we systematically reviewed all available randomised trial evidence regarding the efficacy and safety of SGLT-2 inhibitors for adults with chronic kidney disease, irrespective of type 2 diabetes status (box 1).

BOX 1 | LINKED ARTICLES IN THIS BMJ RAPID RECOMMENDATION CLUSTER

Research article: Zou X, Shi Q, Vandvik PO, et al. Sodium- glucose co-transporter-2 inhibitors in patients with chronic kidney disease with or without type 2 diabetes: systematic review and meta-analysis. *BMJ Med* 2024;3:e001009

Systematic review and meta-analysis of all available randomised trials that assessed sodium-glucose co-transporter-2 (SGLT-2) inhibitors

Practice article: Agarwal A, Zeng X, Li S. Sodium-glucose cotransporter-2 (SGLT-2) inhibitors for adults with chronic kidney disease: a clinical practice guideline. *BMJ* 2024; 387:e080257

A clinical practice guideline from the rapid recommendations process

MAGICapp version (https://app.magicapp.org/#/guideline/EezrQj)

Expanded version of the results with multilayered recommendations, evidence summaries, and decision aids for use across electronic devices

Methods

This review is linked to a BMJ Rapid Recommendation on SGLT-2 inhibitors for chronic kidney disease; the Rapid Recommendation series is a collaborative effort between the MAGIC Evidence Ecosystem Foundation (www.magicevidence.org) and *The BMJ* to produce trustworthy recommendations in response to practice changing evidence.[9] The parallel BMJ Rapid Recommendations guideline panel—comprised of patient partners, methodologists, general practitioners, internists, and nephrologists—defined the research question and the scope of the review. The panel included individuals free of financial and intellectual competing interests and was balanced by sex and geography. This systematic review summarised the relative effects of SGLT-2 inhibitors in adults with chronic kidney disease regardless of the presence of type 2 diabetes, which were then translated into absolute effects according to KDIGO strata for recommendations stratified by risk.[10 11] The study protocol for the systematic review is registered on PROSPERO (CRD42022325483).

Search strategy

We searched OVID Medline, Embase, and Cochrane Central Register of Controlled Trials for eligible randomised controlled trials and publications in English language from database inception to 15 June 2024. A supplementary search was conducted using ClinicalTrials.gov to identify ongoing or unpublished registered trials. The full search strategy is available in online supplemental appendix 1.

Eligibility criteria

Eligible trials of adults with chronic kidney disease (according to study-reported definitions) compared SGLT-2 inhibitor use to placebo or to standard care with no use of SGLT-2 inhibitors and followed up participants for at least 12 weeks. The guideline panel judged all-cause death, cardiovascular death, kidney failure, non-fatal myocardial infarction, non-fatal stroke, admission to hospital for heart failure, acute kidney injury requiring dialysis, and lower limb amputation as outcomes of critical patient importance; and bone fracture, genital infection, ketoacidosis, and symptomatic hypovolaemia as important outcomes. The review also included death related to the kidney as an important outcome for patients. Eligible studies reported on at least one outcome that is important to patients. Online supplemental appendices 2 and 3 provide detailed definitions for each outcome.

Study selection

XZo and YM independently reviewed titles and abstracts of identified hits, followed by full-text articles of potentially eligible studies. Discrepancies in judgements were resolved by team discussion.

Data extraction

XZo and YM independently extracted the following data: study characteristics (study acronym, first author, publication year, region, intervention, and follow-up duration), baseline characteristics of the included population (sample size, age, sex, proportion with pre-existing type 2 diabetes, estimated glomerular filtration rate, urinary albumin-to-creatinine ratio, and use of renin-angiotensin-aldosterone system inhibitors at baseline), and outcome data (number of events and total sample for all prespecified binary outcomes).

Risk of bias assessment

XZo and YM independently evaluated risk of bias specific to outcome using a revised Cochrane Risk of Bias Assessment Tool (ROB-2) with five domains: randomisation process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported results.[12] The risk of bias for each domain was judged as high risk of bias, low risk of bias, or some concern regarding risk of bias. Judgements within each domain led to an overall risk of bias rating for each outcome; discrepancies were resolved by discussion.

Data synthesis and analysis

We conducted a random effects meta-analysis using the Mantel-Haenszel approach, with pooled relative effects summarised as risk ratios with corresponding 95% confidence intervals (CIs) for all binary outcomes.[13] The heterogeneity variance was estimated by restricted maximum-likelihood estimator.[14] Continuity correction of 0.5 was used in studies with zero events in at least one of the arms (trials with zero events in all arms were excluded). For outcomes including ten or more trials, we assessed publication bias using a visual inspection of funnel plots and further evaluated statistically using Begg's rank test and Egger's regression test.[15–17]

Four subgroup analyses or meta-regression analyses were prespecified based on patients' characteristics (hypothesis specified in parenthesis):

- type 2 diabetes (larger benefit) versus no diabetes;
- an estimated glomerular filtration rate of <30 mL/min per 1.73 m² (larger benefit) versus a rate of ≥30 mL/min per 1.73 m²;
- a history of heart failure (larger benefit) versus no heart failure; and
- a higher urinary albumin-to-creatinine ratio level (larger benefit) versus a lower level (amended to meta-regression based on baseline median urinary albumin-to-creatinine ratio because of insufficient data).

For subgroup analyses, we used relative effects derived from the results of subgroup analyses if reported. A meta-regression by median follow-up duration was added due to the concern of varied follow-up durations across studies. The Instrument for assessing the Credibility of Effect Modification Analyses (ICEMAN) tool was used to assess credibility of subgroup effects.[18]

We conducted several sensitivity analyses to test the robustness of our results: (1) excluded trials stopping early for benefit; (2) excluded trials of dual SGLT-1 and SGLT-2 inhibitors (ie, sotagliflozin); (3) used a Bayesian binomial-normal hierarchial regression with a weakly informative prior to directly model the zero events in sparse data outcomes (ie, ketoacidosis and death related to the kidneys)[19]; (4) excluded trials of each specific SGLT-2 inhibitor one at a time; (5) conducted a meta-analysis of any acute kidney injury as an alternative outcome for acute kidney injury requiring dialysis; and (6) conducted a random effects meta-analysis with DerSimonian-Laird method and Hartung-Knapp adjustment. Fragility indices for outcomes with statistical significance aided in understanding the robustness of the estimates.[20]

Estimation of absolute treatment effects

Absolute effect estimates were anticipated using pooled relative effect estimates and baseline risk estimates that were stratified. In line with the linked practice paper, the Kidney Disease Improving Global Outcomes (KDIGO) 2012 classification system, which incorporates estimated glomerular filtration rate and level of albuminuria, was adopted to stratify adults based on their risk of cardiovascular and kidney complications. Accordingly, four risk categories were defined: low, moderate, high, and very high.[10] A large UK primary care cohort informed corresponding stratified baseline risks for all cause death, cardiovascular death, kidney failure, non-fatal stroke, non-fatal myocardial infarction, and admission to hospital for heart failure. The study-reported incidence rates per 100 patient years were transformed to baseline risks per 1000 adults over five year time frames for each risk category (online supplemental appendix 4).[21] In the absence of available risk-stratified baseline risks for other outcomes (death related to kidney, acute kidney injury requiring dialysis, bone fracture, lower limb amputation, genital infection, ketoacidosis, and symptomatic hypovolaemia), we estimated baseline risks using single-group meta-analyses of control arm event rates across included trials.[22]

Assessment of certainty of the evidence

For every outcome of interest, we assessed the certainty of available evidence using the GRADE approach.[23] Certainty started as high and was rated down where appropriate for any of the following five domains: risk of bias, imprecision, inconsistency, indirectness, and publication bias. Imprecision was judged using outcome-specific minimal important differences informed by panel discussions and existing literature (see online supplemental appendix 5).[24] The decision

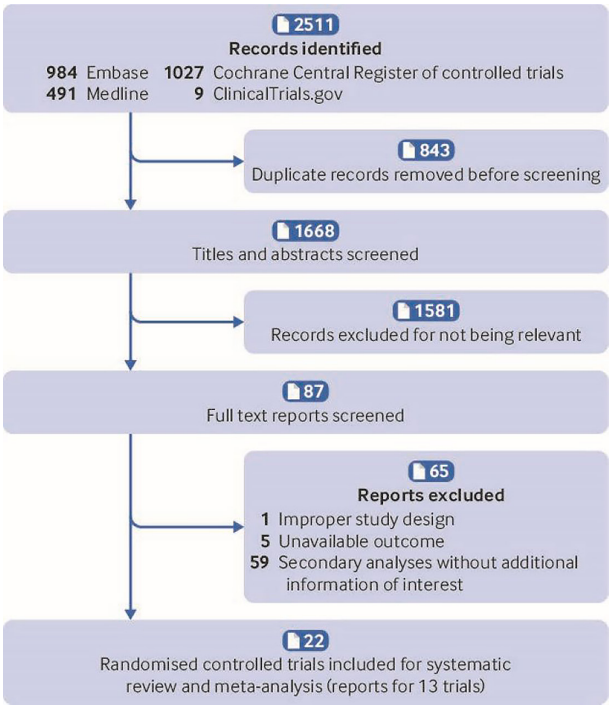

Figure 1 | Flow diagram

thresholds of importance were five per 1000 patients for all cause death, cardiovascular death, and kidney related death; 10 per 1000 patients for kidney failure, non-fatal stroke, lower limb amputation, and ketoacidosis; 20 per 1000 patients for admitted to hospital for heart failure, non-fatal myocardial infarction, and acute kidney injury requiring dialysis; 30 per 1000 patients for bone fracture; 40 per 1000 patients for genital infection; 50 per 1000 patients for symptomatic hypovolaemia. Final assessments of certainty were fully contextualised, considering all outcomes together and aligned with judgements of the guideline panel. Certainty of evidence for each outcome was rated as high, moderate, low, or very low.[25]

Patient and public involvement

The accompanying guideline included three patient partners. They expressed their views on patients' values and preferences and participated in all decisions regarding outcome selection, minimal important difference, and appraising the benefits, harms, and burden of treatments. This study had no public participation. On publication, the study findings will be disseminated to related patients and the public as linked evidence for the paralleled BMJ Rapid Recommendation (https://www.bmj.com/rapid-recommendations) on the use of SGLT-2 inhibitors in people with chronic kidney disease.

Results

Description of included studies

Thirteen randomised controlled trials enrolling 29 614 patients proved eligible, with a median follow-up duration ranging from 24 weeks to 137 weeks (figure 1).[5–7 26–35] A complete list of included and excluded studies from full text screening is provided in online supplemental appendix 6.

The mean age of study participants was 66.2 years (95% CI 64.8 to 67.6). Of 29 614 participants, 61.4% were male, 83.2% had diabetes, and 88.0% received renin-angiotensin-aldosterone system inhibitors. Five types of SGLT-2 inhibitors and one SGLT-1 and SGLT-2 dual inhibitor were investigated: dapagliflozin (n=4), canagliflozin (n=2), empagliflozin (n=2), ertugliflozin (n=1), bexagliflozin (n=1), and sotagliflozin (n=3). Six trials included adults with stage 4 chronic kidney disease (estimated glomerular filtration rate <30 mL/min per 1.73 m²).[6 7 28 30 31 33] Details of eligible studies are summarised in table 1 and in the online supplemental appendix 6.

Risk of bias

Some concerns regarding risk of bias arose in five studies and in 47% of trial-outcome pairs due to early trial termination and measurement of the outcome (online supplemental appendix 7).[5–7 31 35] Of note, four studies that accounted for 83% of all patients involved early termination: CREDENCE, DAPA-CKD, EMPA-KIDNEY trials for efficacy;[5 6 7 31] and SCORED trial due to loss of funding. Sensitivity analyses of excluding trials that stopped early for benefit showed smaller effects for all-cause death; effects for other outcomes were similar to those in the primary analysis. Certainty was already rated down for serious imprecision for all cause death based on wide confidence intervals and small event rates, therefore, we judged that uncertainty related to early termination was already accounted for in the overall moderate certainty evidence and so we did not further rate down the risk of bias. Similarly, given that treatment effect had no evidence of overestimation for other outcomes, we did not rate the risk of bias as high.

Relative and absolute effects of SGLT-2 inhibitors

Pooled relative effects and absolute effect estimates stratified by risk across outcomes are summarised in figure 2 and online supplemental appendix 8.

Mortality

Eleven trials (28 981 participants) reported on all cause death,[5–7 26 28–34] seven (27 429 participants) reported on cardiovascular death,[5–7 31–34] and four (25 898 participants) reported on kidney-related death.[5–7 31]

SGLT-2 inhibitors probably reduced all cause death in individuals with chronic kidney disease at low, moderate, and high risks (all moderate certainty); certainty of an important survival benefit was high for individuals at very high risk (risk ratio 0.85 (95% CI 0.74 to 0.98)). Treatment resulted in little or no effect on cardiovascular death for individuals at low risk (high certainty) and probably little or no effect for

Table 1 | Baseline characteristics of included randomised controlled trials and participants

Characteristic	Measurement
Study settings (of eligible studies)	
Total trials	13
Participants	29 614
Follow-up, weeks, median (range)	52 (24 to 137)
Study characteristics (of participants)	
Age, years, mean (95% CI)*	66.2 (64.8 to 67.6)
Female, No (%)	11 429 (38.6)
Male No (%)	18 185 (61.4)
Diabetes, No (%)	24 647 (83.2)
eGFR, mL/min/1.73 m², mean (95% CI)*	44.7 (40.2 to 49.2)
RAAS inhibitors use, No (%)	26 049 (88.0)

*Pooled mean was estimated using random-effects meta-analyses of single mean.
eGFR, estimated glomerular filtration rate; RAAS, renin-angiotensin-aldosterone system.

those at moderate risk (moderate certainty); certainty of an important risk reduction was moderate for individuals at high or very high risk (0.84 (0.74 to 0.96)). SGLT-2 inhibitors probably had little or no effect on death related to the kidneys across risk strata (0.80 (0.37 to 1.72); moderate certainty).

No subgroup differences were observed based on diabetes status, heart failure status, estimated glomerular filtration rate level, and follow-up duration (online supplemental appendices 9 and 11). Meta-regression findings showed a subgroup effect that SGLT-2 inhibitors may have had a larger relative effect on all cause death in people with higher urinary albumin-to-creatinine ratio, in line with our hypothesis; however, credibility of the subgroup effect was low (online supplemental appendices 10 and 12). No significant difference in effects was observed in sensitivity analyses (online supplemental appendix 13).

Other benefit outcomes

Nine trials involving 28 221 participants reported on kidney failure.[5–7 26 29–33] SGLT-2 inhibitors had little or no effect on kidney failure in individuals at low, moderate, and high risks; individuals at very high risk derived an important reduction in risk (risk ratio 0.68 (95% CI 0.60 to 0.77)) (all high certainty) (figure 2).

Four trials enrolling 16 049 individuals reported on non-fatal stroke and non-fatal myocardial infarction.[5 31–33] SGLT-2 inhibitors probably reduced non-fatal stroke in individuals across risk strata (0.73 (0.57 to 0.94)) (all moderate certainty). Treatment probably had little or no effect on non-fatal myocardial infarction in individuals at low and moderate risk, and probably resulted in important risk reductions in individuals at high and very high risk (0.75 (0.60 to 0.93)) (all moderate certainty).

Six trials enrolling 26 962 individuals reported on admission to hospital for heart failure.[5–7 29–33] SGLT-2 inhibitors had little or no effect in individuals at low, moderate, and high risks (all high certainty), and probably resulted in an important risk reduction in individuals at very high risk (0.68 (0.60 to 0.78)) (moderate certainty).

We did not detect significant effects in subgroup and sensitivity analyses.

Safety outcomes

For all safety outcomes, baseline risks that were stratified were unavailable; absolute effects were therefore estimated across risk strata. Certainty of evidence was downgraded for indirectness in baseline risks to reflect the absence of absolute effect estimates stratified by risk.

Two trials reported on acute kidney injury requiring dialysis,[5 6] 12 reported on bone fracture,[5–7 26 28–35] eight reported on lower limb amputation,[5–7 28 31–33 35] 13 reported on genital infection,[5–7 26–35] six reported on ketoacidosis,[5–7 28 30 31] and 13 reported on symptomatic hypovolaemia.[5–7 26–35] Per 1000 patients over five years, SGLT-2 inhibitors probably had little or no effect on acute kidney injury requiring dialysis (nine fewer patients (95% CI −14 to −1)), fracture (two more (−10 to 15)), lower limb amputation (two more (−4 to 10), genital infection (27 more (17 to 39)), ketoacidosis (four more (1 to 9)), and symptomatic hypovolaemia (32 more (17 to 49)) (low certainty for lower limb amputation; moderate certainty for other outcomes). No subgroup effects were noted (online supplemental appendices 9–11). Sensitivity analyses confirmed the robustness of our findings (online supplemental appendix 13).

Funnel plots, together with statistical tests, did not find evidence of publication bias across outcomes (online supplemental appendix 14).

Discussion

Among people with chronic kidney disease regardless of diabetes status, SGLT-2 inhibitors showed benefits in reducing risks of all cause death, cardiovascular death, kidney failure, non-fatal myocardial infarction, non-fatal stroke, and admission to hospital for heart failure. Little or no effect was observed across all prioritised outcomes of harm, including acute kidney injury requiring dialysis, bone fracture, lower limb amputation, genital infection, ketoacidosis, and symptomatic hypovolaemia. Considerable benefits and small harms support the utility of SGLT-2 inhibitors for individuals with chronic kidney disease in addition to current standard of care.

Using a fully contextualised approach and all available evidence, this systematic review estimated benefits by risk stratification of SGLT-2 inhibitors in people with chronic kidney disease, balanced

Figure 2 | Summary of findings for relative and absolute effects. Risk categories were KDIGO low, moderate, high, and very high risk categories, with baseline risks over five years for each category derived from a UK cohort. Baseline risks across risk categories were obtained from single-group meta-analyses of the control arms in the included studies. Estimates represent risk differences per 1000 patients in five years compared with placebo or standard treatments without sodium-glucose co-transporter-2 inhibitors. Certainty of evidence used GRADE, with the thresholds of importance determined by the guideline panel, details in the methods. Hollow squares in the certainty rating column represent six rating domains listed in order from left to right including risk of bias, inconsistency, indirectness, imprecision, publication bias, and other concerns. Black squares means that the certainty was downgraded because of that domain.*Anticipated absolute effects for patients with chronic kidney disease, by or across KDIGO risk categories were estimated by multiplying the point estimate of the relative risk reduction to the anticipated baseline risks. CI=confidence interval; GRADE=Grading of Recommendations, Assessment, Development, and Evaluation; KDIGO=Kidney Disease Improving Global Outcomes

against risk of potential harms. An international multidisciplinary panel formulated the study question, protocol, and the decision thresholds for each patient important outcome, enhancing its applicability in clinical decision making. Absolute effects of treatment were estimated and stratified using the KDIGO classification with baseline risks informed by a large, population based, observational, cohort study, and GRADE approach was applied to determine certainty of evidence.

Quantitative evidence suggested heterogeneous benefits and harms across different KDIGO risk categories. For instance, individuals at low risk probably derived small but important reductions in their risks of all cause death (0.7%) and non-fatal stroke (1%) with little or no effects across other outcomes of benefit. Individuals at very high risk probably derived incrementally larger benefits across all outcomes of interest, including a 4.8% reduction in all cause death over five years. These benefits are balanced against small increases in risks of genital infection, ketoacidosis, and symptomatic hypovolaemia. Estimates stratified by risk provided by this systematic review facilitated judgements for an international practice guideline and can facilitate shared decision making that is evidence informed and individualised to a given patient's prognosis in terms of sequelae related to the cardiovascular system and kidney.

Our meta-analysis has limitations. Firstly, four large scale kidney outcome trials, which accounted for 83% of study population, were terminated early; we acknowledge the possibility of treatment overestimation with stopping early, which warrants longer term surveillance in real-world practice.[36] Secondly, our study population included a limited number of patients with chronic kidney disease at low risk; relative effect estimates were therefore primarily derived from higher risk individuals. Since we did not identify credible subgroup effects based on albuminuria or estimated glomerular filtration rate, we judged that individuals at low risk were likely to derive similar effects in relative terms to those at higher risk when receiving SGLT-2 inhibitors. Thirdly, 83.2% of included patients had diabetes; the effects of SGLT-2 inhibitors among people with chronic kidney disease who did not have diabetes could therefore be under-represented. Nevertheless, no subgroup effect was found based on diabetes status. Fourthly, the KDIGO 2012 classification system provided a systematic and pragmatic strategy for risk stratification but did not incorporate physiological estimated glomerular filtration rate decline that is associated with ageing,[37] which could lead to a possible overestimation of baseline risks in older individuals and an underestimation of risk in younger individuals. Validated risk calculators are needed to facilitate more accurate risk assessments at the individual level. Lastly, the eligibility criteria excluded people who have received a kidney replacement therapy and those with rare kidney diseases (eg, polycystic kidney disease), which limits the applicability of findings for these groups. Ongoing trials focusing on these groups will provide valuable evidence.[38 39]

Conclusions

In individuals with chronic kidney disease, regardless of diabetes status, SGLT-2 inhibitors improved cardiovascular and kidney outcomes and survival; associated harms were small. Absolute effects were anticipated to vary based on an individual's risk of cardiovascular and kidney-related complications, which might be estimated based on their baseline glomerular function and degree of albuminuria; individual level risk stratification is therefore warranted to inform clinical decision making.

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Contributors XZo and QS contributed equally to this study. SL conceived and designed the study. XZo, QS, AA, BP, XZe, PF, TA, and SL discussed and drafted the study protocol. XZo and YM screened and selected the articles. XZo, QS, YM, and QY extracted the data. XZo, QS, YM, and QY assessed the risk of bias of included trials. XZo and QS analysed the data. XZo and QS rated and revised the GRADE certainty of evidence. XZo, POV, AA, BP, XZe, GHG, XL, CX, PF, HT, TA, and SL interpreted the results. XZo drafted the manuscript. XZo, QS, AA, BP, TA, and SL critically revised the manuscript. All authors contributed to revising the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. POV and GHG supervised the study. SL is the guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. Transparency: The lead author (the guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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