Sodium-glucose cotransporter protein-2 (SGLT-2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists for type 2 diabetes: systematic review and network meta-analysis of randomised controlled trials

Suetonia C Palmer,[1] Britta Tendal,[2] Reem A Mustafa,[3,4] Per Olav Vandvik,[5] Sheyu Li,[6,7] Qiukui Hao,[8] David Tunnicliffe,[9] Marinella Ruospo,[10] Patrizia Natale,[9,10] Valeria Saglimbene,[10] Antonio Nicolucci,[11] David W Johnson,[12] Marcello Tonelli,[13] Maria Chiara Rossi,[11] Sunil V Badve,[14] Yeoungjee Cho,[12] Annie-Claire Nadeau-Fredette,[15] Michael Burke,[16] Labib I Faruque,[17] Anita Lloyd,[17] Nasreen Ahmad,[17] Yuanchen Liu,[17] Sophanny Tiv,[17] Tanya Millard,[2] Lucia Gagliardi,[18,19] Nithin Kolanu,[20] Rahul D Barmanray,[21] Rita McMorrow,[22] Ana Karina Raygoza Cortez,[23] Heath White,[2] Xiangyang Chen,[6] Xu Zhou,[24] Jiali Liu,[25] Andrea Flores Rodríguez,[23] Alejandro Díaz González-Colmenero,[23] Yang Wang,[26] Ling Li,[25] Surya Sutanto,[27] Ricardo Cesar Solis,[23] Fernando Díaz González-Colmenero,[23] René Rodriguez-Gutierrez,[23] Michael Walsh,[28,29] Gordon Guyatt,[4] Giovanni F M Strippoli[9,10]

For numbered affiliations see end of the article.

Correspondence to:
G F M Strippoli
gfmstrippoli@gmail.com
(or @gstrip3 on Twitter;
ORCID 0000-0002-6936-0616)

ABSTRACT

OBJECTIVE
To evaluate sodium-glucose cotransporter-2 (SGLT-2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists in patients with type 2 diabetes at varying cardiovascular and renal risk.

DESIGN
Network meta-analysis.

DATA SOURCES
Medline, Embase, and Cochrane CENTRAL up to 11 August 2020.

ELIGIBILITY CRITERIA FOR SELECTING STUDIES
Randomised controlled trials comparing SGLT-2 inhibitors or GLP-1 receptor agonists with placebo, standard care, or other glucose lowering treatment in adults with type 2 diabetes with follow up of 24 weeks or longer. Studies were screened independently by two reviewers for eligibility, extracted data, and assessed risk of bias.

MAIN OUTCOME MEASURES
Frequentist random effects network meta-analysis was carried out and GRADE (grading of recommendations assessment, development, and evaluation) used to assess evidence certainty. Results included estimated absolute effects of treatment per 1000 patients treated for five years for patients at very low risk (no cardiovascular risk factors), low risk (three or more cardiovascular risk factors), moderate risk (cardiovascular disease), high risk (chronic kidney disease), and very high risk (cardiovascular disease and kidney disease). A guideline panel provided oversight of the systematic review.

RESULTS
764 trials including 421 346 patients proved eligible. All results refer to the addition of SGLT-2 inhibitors and GLP-1 receptor agonists to existing diabetes treatment. Both classes of drugs lowered all cause mortality, cardiovascular mortality, non-fatal myocardial infarction, and kidney failure (high certainty evidence). Notable differences were found between the two agents: SGLT-2 inhibitors reduced mortality and admission to hospital for heart failure more than GLP-1 receptor agonists, and GLP-1 receptor agonists reduced non-fatal stroke more than SGLT-2 inhibitors (which appeared to have no effect). SGLT-2 inhibitors caused genital infection (high certainty), whereas GLP-1 receptor agonists might cause severe gastrointestinal events (low certainty). Low certainty evidence suggested that SGLT-2 inhibitors and GLP-1 receptor agonists might lower body weight. Little or no evidence was found for the effect of SGLT-2 inhibitors or GLP-1 receptor agonists on limb amputation, blindness, eye disease, neuropathic pain, or health related quality of life. The absolute benefits of these drugs vary substantially across patients from low to very

WHAT IS ALREADY KNOWN ON THIS TOPIC

Although trial results conflict, sodium-glucose transporter 2 (SGLT-2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists probably reduce cardiovascular and kidney disease when added to other glucose lowering treatment in adults with type 2 diabetes

Uncertainty remains about the relative and absolute benefits and harms of these drugs across all important outcomes in patients with type 2 diabetes at varying levels of cardiovascular and kidney disease risk

WHAT THIS STUDY ADDS

Benefits shared by SGLT-2 inhibitors and GLP-1 receptor agonists include reductions in all cause and cardiovascular mortality, myocardial infarction, kidney failure, and serious hyperglycaemia (high certainty evidence) and lower body weight (low certainty) without incurring severe hypoglycaemia (high certainty)

The two drug classes appear to have similar relative effects on cardiovascular mortality, myocardial infarction, kidney failure, health related quality of life, and serious hyperglycaemia

Absolute benefits of these drugs vary substantially based on cardiovascular and renal disease risk profiles of patients with type 2 diabetes, as reflected in risk stratified *BMJ* Rapid Recommendations directly informed by this systematic review

high risk of cardiovascular and renal outcomes (eg, SGLT-2 inhibitors resulted in 5 to 48 fewer deaths in 1000 patients over five years; see interactive decision support tool (https://magicevidence.org/match-it/200820dist/#!/) for all outcomes.

CONCLUSIONS
In patients with type 2 diabetes, SGLT-2 inhibitors and GLP-1 receptor agonists reduced cardiovascular and renal outcomes, with notable differences in benefits and harms. Absolute benefits are determined by individual risk profiles of patients, with clear implications for clinical practice, as reflected in the *BMJ* Rapid Recommendations directly informed by this systematic review.

SYSTEMATIC REVIEW REGISTRATION
PROSPERO CRD42019153180.

Introduction

Diabetes affects half a billion people worldwide and accounted for 1.5 million deaths in 2016.[1] Glucose lowering is a mainstay of treatment.[2] In people with type 2 diabetes and higher risks of cardiovascular disease, several large scale randomised controlled trials have investigated sodium-glucose cotransporter-2 (SGLT-2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists and reported reductions in cardiovascular mortality and non-fatal cardiovascular complications with both classes of drug.[3 4] The mortality reductions have not, however, proved consistent across trials, leaving clinicians and patients uncertain of the magnitude of benefits.[5-8]

Recommendations released in 2019 by the American Diabetes Association include using SGLT-2 inhibitors and GLP-1 receptor agonists in the management of diabetes for people with cardiovascular disease or kidney disease who have not reached their glycaemic target goals.[2] European Society of Cardiology guidelines in 2019 recommended SGLT-2 inhibitors and GLP-1 receptor agonists in people with type 2 diabetes and cardiovascular disease or a high risk of cardiovascular disease.[9] National Institute for Health and Care Excellence (NICE) guidance, updated in 2019, suggested a stepped approach to intensification of treatment with diabetes drugs, considering metformin as the first treatment with additions of dual and triple treatment from several drug classes, including SGLT-2 inhibitors.[10]

Several published systematic reviews and meta-analyses have summarised glucose lowering treatments for people with type 2 diabetes, including a network meta-analysis of stepped intensification of treatment added to metformin and sulfonylurea.[11] Results from more recent meta-analyses report reductions in mortality and selected cardiovascular and renal events with both SGLT-2 inhibitors and GLP-1 receptor agonists.[12-15] A network meta-analysis including all available glucose lowering treatments, the full range of important outcomes, GRADE (grading of recommendations assessment, development, and evaluation) certainty ratings, and estimates of absolute benefits and harms in patients with

varying risks of cardiovascular and kidney disease remains unavailable. Moreover, several large scale trials published recently require updated evidence synthesis.[5 7 8 16]

We therefore conducted a systematic review and network meta-analysis evaluating the benefits and harms of SGLT-2 inhibitors and GLP-1 receptor agonists in adults with type 2 diabetes. This review is conducted as part of the *BMJ* Rapid Recommendations project, a collaborative initiative from the MAGIC (Making GRADE the Irresistible Choice) Evidence Ecosystem Foundation (https://magicevidence.org/) and *The BMJ*. The aim of the initiative is to provide trustworthy practice guidelines within months of newly released evidence, underpinned by rigorous evidence summaries. This systematic review is part of a forthcoming *BMJ* Rapid Recommendations cluster and a fuller version on MAGICapp (www.magicapp.org). Although the network meta-analysis includes all classes of diabetes drugs, it focuses on these SGLT-2 inhibitors and GLP-1 receptor agonists added to other diabetes drugs, and in relation to one another.[17]

Methods

Protocol registration
We registered the protocol for this systematic review with PROSPERO (CRD42019153180).

Guideline panel involvement
In accordance with the *BMJ* Rapid Recommendations process, a guideline panel that comprised content experts, diabetologists, nephrologists, internal medicine physicians, primary care physicians, methodologists, and patients provided critical oversight of the review. The panel reviewed the protocol, identified the population, selected and ranked important patient outcomes, and recommended baseline risks on which absolute treatment effects were calculated.

Search strategy
The literature search designed by an information specialist was conducted in Medline, Embase, and the Cochrane Central Register of Controlled Trials from March 2016 to 11 August 2020 without language restriction (appendix 1). The search from a previous network meta-analysis provided records from database inception to March 2016.[11]

Study selection
Two reviewers, working independently, screened citations and evaluated full text records for eligible studies using Covidence systematic review software (Veritas Health Innovation, Melbourne, VIC, Australia; https://www.covidence.org). A third reviewer (BT or SCP) resolved disagreements by consensus.

Parallel group randomised controlled trials were eligible if they compared SGLT-2 inhibitors or GLP-1 receptor agonists with one another or with other glucose lowering treatments, placebo, or standard care in adults with type 2 diabetes. We included

studies reporting outcomes at 24 weeks or longer. Treatment was given either as monotherapy or added to non-randomised background glucose lowering management and other treatments.

Using definitions of outcomes specified in individual randomised controlled trials, the review examined all patient-important outcomes as defined by the guideline panel, regardless of whether evidence was available in the eligible trials: all cause mortality, cardiovascular mortality, non-fatal myocardial infarction, non-fatal stroke, kidney failure, admission to hospital for heart failure, severe hypoglycaemia, blindness, eye disease requiring intervention, health related quality of life, body weight, amputation, neuropathic pain, diabetic ketoacidosis, serious hyperglycaemia, genital infection, Fournier gangrene, severe gastrointestinal events, pancreatic cancer, and pancreatitis. Glycated haemoglobin A1c was not identified as an outcome important to patients by the guideline panel, although it was included in the review because it is prioritised by some decision makers.

Data extraction
For each eligible study, two reviewers independently extracted the following: study characteristics (year of publication, country or countries, funding, duration), population (setting, sample size, patient demographics, coexisting illnesses), description of interventions (drug class, name, dose), and outcomes. Reviewers resolved disagreements by discussion or, if necessary, consultation with a third reviewer.

Risk of bias assessment
Two reviewers independently assessed risk of bias, with adjudication by a third reviewer (SCP) using the Cochrane tool for assessing risk of bias in randomised trials, which includes random sequence generation, allocation concealment, blinding, missing outcome data, and selective reporting of outcomes.[18] Each domain was judged as low, unclear, or high risk of bias. Reviewers considered allocation concealment as low risk if there were no reported methods for allocation concealment and participants and investigators were blind to treatment allocation.

Data synthesis and analysis
For each direct comparison of two treatments, we conducted a frequentist pairwise meta-analysis using a restricted maximum likelihood estimation and reported, with corresponding 95% confidence intervals, odds ratios for dichotomous outcomes, mean differences for continuous outcomes (body weight and glycated haemoglobin A1c), and standardised mean difference for health related quality of life.[19] We assessed statistical heterogeneity using the I^2 statistic and funnel plots for evidence of small study effects in analyses including 10 or more studies.

We conducted network meta-analysis using frequentist methods with restricted maximum likelihood estimation to quantify network heterogeneity, assuming a common heterogeneity estimate within a network. We assessed agreement between direct and indirect estimates in every closed loop of evidence using node splitting approaches, and for the entire network using a design-by-treatment interaction model.[20] We imputed missing standard deviations for continuous variables when absent using standard deviations borrowed from other similar randomised controlled trials.[21 22]

The guideline panel recommended five baseline risk categories to estimate absolute effects of treatment on cardiovascular and kidney outcomes in different categories of patients, reflecting typical clinical scenarios in practice. Patient categories were defined as very low risk (no or few (<3) cardiovascular risk factors), low risk (three or more cardiovascular risk factors), moderate risk (cardiovascular disease), high risk (chronic kidney disease (estimated glomerular filtration rate 45-75 mL/min per 1.73 m^2 with albuminuria >300 mg/g (30 mg/mmol) or estimated glomerular filtration rate 15-45 mL/min per 1.73 m^2)), and very high risk (cardiovascular disease and chronic kidney disease)). The panel calculated absolute treatment effects of the network estimates based on the event rates from the best sources of evidence, including cohort studies, risk prediction equations, or the placebo arm in available trials.[23-28] We estimated baseline absolute risk per 1000 patients treated for five years, extrapolating from shorter term data when necessary and assuming a constant annual risk of the selected outcome for each year up to five years. A single estimate was obtained for all outcomes and treatment comparisons, which was used in combination with the baseline risk estimates to present results as absolute effects. We planned subgroup analysis if sufficient data were available according to trial duration, BMI, presence of high cardiovascular risk, and presence of chronic kidney disease. All pairwise and network meta-analyses were performed with Stata 13 MP (StataCorp, College Station, TX) using published routines.[29]

Assessment of evidence certainty
The GRADE approach provided the methods to assess the certainty of the evidence for direct and network comparisons, using a non-contextualised approach.[30 31] Ratings of evidence certainty for direct estimates included considerations of risk of bias, inconsistency, indirectness, imprecision, and publication bias.

The lower of the ratings from the two direct estimates forming the dominant first order loop provided the starting point for certainty ratings for each indirect estimate, with further downward rating for intransitivity,[32] if present. The estimate that provided the most information—direct or indirect—was the basis for the certainty of the network estimates. If these estimates contributed similar amounts of information, we chose the higher of the two certainty judgments. If evidence of incoherence between direct and indirect estimates existed, the certainty of the network estimate was
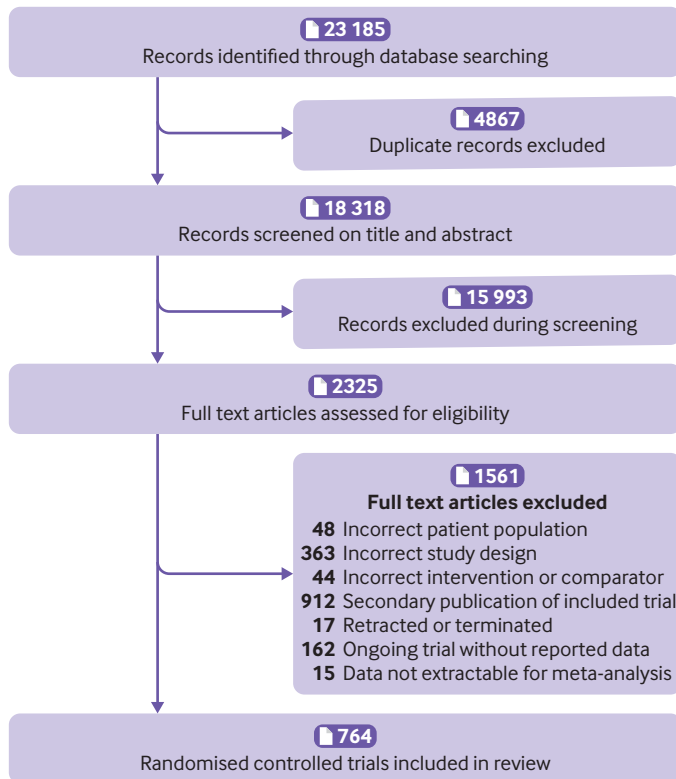
Fig 1 | PRISMA flow diagram of studies included in the review of glucose lowering treatments for type 2 diabetes

rated down, and we used the estimate with the highest certainty—direct or indirect—as the best estimate of the treatment effect. MAGICapp (https://www.magicapp.org/) provided the platform to develop tables of the GRADE summary of findings. We also provide the absolute estimates of effect and associated uncertainties across risk groups, derived from best relative estimates of effect from the network meta-analysis. These results are presented in evidence summaries and decision aids developed in MAGICapp, including an interactive decision support tool for multiple treatment choices (https://magicevidence.org/match-it/200820dist/#!/).

Patient and public involvement

Four patient partners living with type 2 diabetes were included in the guideline panel that oversaw the generation of this paper. Patient partners were recruited from patient advocacy organisations and Cochrane Task Exchange. They were involved as full panel members in modifying the research question and identifying and prioritising patient-important outcomes. There was no public participation in this project.

Results

Description of included studies

The electronic search yielded 23 185 unique records. Screening and full text article analysis identified 764 trials including 421 346 patients (fig 1, appendix 2) comparing 11 glucose lowering drugs, placebo, or standard care. Figure 2 shows the network of treatment comparisons in available trials. The trial sample size ranged from 16 to

17 160. The median trial mean age was 57.1 years, and the median proportion of men was 55.6%. At baseline, the median trial mean glycated haemoglobin A1c was 8.1% and BMI was 30.1. Eligibility criteria included coronary artery disease or macrovascular disease in 35 trials,[3 6 7 33-64] atrial fibrillation in 1 trial,[65] heart failure in 9 trials,[66-74] chronic kidney disease and/or albuminuria in 37 trials,[8 75-110] and high risk of cardiovascular or kidney disease in 10 trials.[4 5 16 111-117] Treatment with SGLT-2 inhibitors or GLP-1 receptor agonists was generally added to background glucose lowering treatment.

Risk of bias

Appendix 3 presents the risk of bias in each trial. The key limitation was low levels of reported blinding for participants, investigators, and outcome assessors. Three hundred and seven (40.2%) of 764 trials were at low risk of bias in random sequence generation and 529 (69.2%) were at low risk of bias in allocation concealment. Four hundred and sixty two trials (60.5%) reported blinding for participants and investigators, and 105 trials (13.7%) reported blinding for outcome assessment. Three hundred and twenty eight trials (42.9%) were adjudicated as being at low risk of attrition bias and 355 trials (46.5%) were at low risk of bias from selective outcome reporting.

Outcomes

Appendix 4 presents the network plot for each outcome. No evidence of global network inconsistency or heterogeneity was found except for health related quality of life (appendix 5), and no serious concerns of incoherence between direct and indirect evidence (appendix 6). Appendix 7 presents network estimates for each drug comparison for all outcomes. The expected absolute differences in treatment with SGLT-2 inhibitors or GLP-1 receptor agonists compared with placebo and each other are shown in table 1, table 2, table 3, table 4, and appendix 8. The interactive decision support tool at https://magicevidence.org/match-it/200820dist/#!/ shows absolute estimates of effect for key outcomes in patients with type 2 diabetes, from very low to very high risk of cardiovascular and renal outcomes.

All cause and cardiovascular mortality

Two hundred and thirty eight trials including 290 662 patients reported all cause mortality. SGLT-2 inhibitors lowered all cause mortality compared with placebo (odds ratio 0.77 (95% confidence interval 0.71 to 0.83); 5 fewer per 1000 in five years for very low risk patients (moderate certainty); 15 fewer for low risk patients (high certainty); 25 fewer for moderate risk patients (high certainty); 34 fewer for high risk patients (high certainty); and 48 fewer for very high risk patients (high certainty); table 4). GLP-1 receptor agonists lowered all cause mortality compared with placebo (0.88 (0.83 to 0.94); 2, 8, 13, 17, and 24 fewer per 1000 in five years for very low, low, moderate, high, and very high risk patients respectively, moderate to high certainty; table 4).

SGLT-2 inhibitors reduced all cause mortality compared with GLP-1 receptor agonists (0.88 (0.79 to 0.97); 2, 7, 12, 16, and 23 fewer per 1000 in five years for
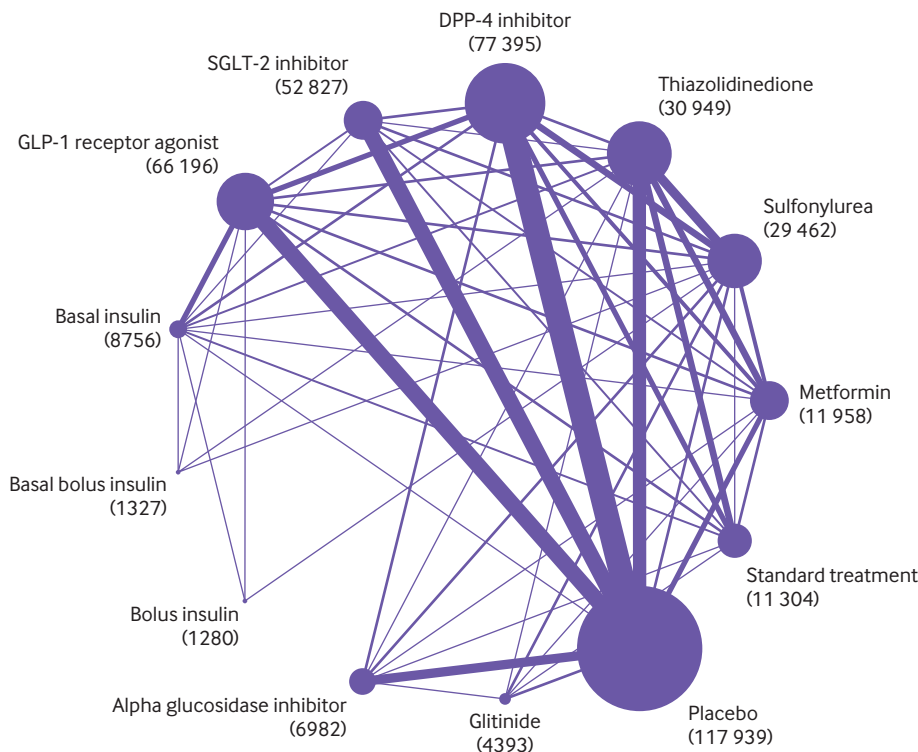
Fig 2 | Network plot of trials evaluating glucose lowering treatments for type 2 diabetes. Network shows the number of participants assigned to each glucose lowering class with the size of each circle proportional to the number of randomly assigned participants in the treatment comparisons (sample size for the specific treatment shown in brackets). Line widths are proportional to the number of trials comparing the corresponding pair of treatments. The most frequent drug comparison was DPP-4 inhibitors compared with placebo. DPP-4=dipeptidyl peptidase-4 inhibitors; GLP-1=glucagon-like peptide-1; SGLP-1=sodium-glucose cotransporter-2

very low, low, moderate, high, and very high risk patients respectively, moderate to high certainty; table 3).

One hundred and thirty five trials including 226 701 patients reported cardiovascular mortality. SGLT-2 inhibitors lowered cardiovascular mortality compared with placebo (0.84 (0.76 to 0.92); 2, 7, 12, 16, and 24 fewer per 1000 in five years for very low, low, moderate, high, and very high risk patients respectively, moderate to high certainty; table 1), as did GLP-1 receptor agonists (0.88 (0.80 to 0.96); 2,

Table 1 | Summary of anticipated absolute differences comparing sodium-glucose cotransporter-2 inhibitor treatment with placebo treatment per 1000 patients with diabetes type 2 and with very low to very high cardiovascular risk, treated for five years

Risk*	All cause mortality	Cardiovascular mortality	Non-fatal myocardial infarction	Non-fatal stroke	Kidney failure	Hospital admission for heart failure	Diabetic ketoacidosis	Genital infection	Body weight
Very low	5 fewer (6 fewer to 3 fewer) ⊕⊕⊕	2 fewer (3 fewer to 1 fewer) ⊕⊕⊕	4 fewer (6 fewer to 1 fewer) ⊕⊕⊕	0 more (3 fewer to 4 more) ⊕⊕⊕	1 fewer (1 fewer to 0) ⊕⊕⊕	2 fewer (2 fewer to 1 fewer) ⊕⊕⊕			
Low	15 fewer (19 fewer to 11 fewer) ⊕⊕⊕⊕	7 fewer (11 fewer to 4 fewer) ⊕⊕⊕⊕	7 fewer (12 fewer to 2 fewer) ⊕⊕⊕⊕	1 more (6 fewer to 8 more) ⊕⊕⊕⊕	3 fewer (4 fewer to 1 fewer) ⊕⊕⊕⊕	9 fewer (11 fewer to 7 fewer) ⊕⊕⊕⊕			
Moderate	25 fewer (32 fewer to 18 fewer) ⊕⊕⊕⊕	12 fewer (18 fewer to 6 fewer) ⊕⊕⊕⊕	13 fewer (21 fewer to 3 fewer) ⊕⊕⊕⊕	1 more (11 fewer to 13 more) ⊕⊕⊕⊕	6 fewer (9 fewer to 2 fewer) ⊕⊕⊕⊕	23 fewer (28 fewer to 17 fewer) ⊕⊕⊕⊕	0 (1 fewer to 2 more) ⊕⊕⊕	143 more (119 more to 170 more) ⊕⊕⊕⊕	1.92 kg lower (2.23 lower to 1.62 lower) over 6 months ⊕⊕
High	34 fewer (43 fewer to 25 fewer) ⊕⊕⊕⊕	16 fewer (25 fewer to 8 fewer) ⊕⊕⊕⊕	14 fewer (23 fewer to 3 fewer) ⊕⊕⊕⊕	1 more (12 fewer to 15 more) ⊕⊕⊕⊕	25 fewer (37 fewer to 9 fewer) ⊕⊕⊕⊕	29 fewer (36 fewer to 22 fewer) ⊕⊕⊕⊕			
Very high	48 fewer (61 fewer to 35 fewer) ⊕⊕⊕⊕	24 fewer (36 fewer to 12 fewer) ⊕⊕⊕⊕	21 fewer (34 fewer to 5 fewer) ⊕⊕⊕⊕	2 more (17 fewer to 21 more) ⊕⊕⊕⊕	38 fewer (58 fewer to 14 fewer) ⊕⊕⊕⊕	58 fewer (73 fewer to 44 fewer) ⊕⊕⊕⊕			

*Risk categories represent the following patient populations: very low=no or less than three cardiovascular risk factors; low=three or more cardiovascular risk factors; moderate=cardiovascular disease; high=chronic kidney disease (reduced glomerular filtration rate or macroalbuminuria); very high=cardiovascular disease and chronic kidney disease.
Certainty of the evidence for each estimate is shown: high certainty ⊕⊕⊕⊕; moderate certainty ⊕⊕⊕; low certainty ⊕⊕; very low certainty ⊕.

Table 2 | Summary of anticipated absolute differences comparing glucagon-like peptide-1 receptor agonist treatment with placebo treatment per 1000 patients with diabetes type 2 and with very low to very high cardiovascular risk, treated for five years

Risk*	All cause mortality	Cardiovascular mortality	Non-fatal myocardial infarction	Non-fatal stroke	Kidney failure	Hospital admission for heart failure	Severe gastrointestinal events	Body weight
Very low	2 fewer (3 fewer to 1 fewer) ⊕⊕⊕	2 fewer (3 fewer to 1 fewer) ⊕⊕⊕	2 fewer (4 fewer to 0) ⊕⊕⊕	5 fewer (7 fewer to 2 fewer) ⊕⊕⊕	0 (1 fewer to 0) ⊕⊕⊕	0 (1 fewer to 0) ⊕⊕⊕		
Low cardiovascular risk factors	8 fewer (11 fewer to 4 fewer) ⊕⊕⊕⊕	5 fewer (9 fewer to 2 fewer) ⊕⊕⊕⊕	4 fewer (8 fewer to 1 fewer) ⊕⊕⊕⊕	9 fewer (13 fewer to 4 fewer) ⊕⊕⊕⊕	2 fewer (1 fewer to 3 fewer) ⊕⊕⊕⊕	2 fewer (4 fewer to 1 more) ⊕⊕⊕⊕	58 more (9 more to 142 more) ⊕⊕	145 kg lower (1.72 lower to 1.18 lower) over 6 months ⊕⊕
Moderate	13 fewer (18 fewer to 6 fewer) ⊕⊕⊕⊕	9 fewer (15 fewer to 1 fewer) ⊕⊕⊕⊕	8 fewer (15 fewer to 1 fewer) ⊕⊕⊕⊕	16 fewer (24 fewer to 7 fewer) ⊕⊕⊕⊕	4 fewer (7 fewer to 2 fewer) ⊕⊕⊕⊕	4 fewer (11 fewer to 2 more) ⊕⊕⊕⊕		
High	17 fewer (25 fewer to 9 fewer) ⊕⊕⊕⊕	12 fewer (20 fewer to 4 fewer) ⊕⊕⊕⊕	9 fewer (16 fewer to 1 fewer) ⊕⊕⊕⊕	17 fewer (26 fewer to 7 fewer) ⊕⊕⊕⊕	19 fewer (28 fewer to 7 fewer) ⊕⊕⊕⊕	6 fewer (14 fewer to 3 more) ⊕⊕⊕⊕		
Very high	24 fewer (35 fewer to 12 fewer) ⊕⊕⊕⊕	18 fewer (30 fewer to 6 fewer) ⊕⊕⊕⊕	13 fewer (24 fewer to 2 fewer) ⊕⊕⊕⊕	25 fewer (39 fewer to 11 fewer) ⊕⊕⊕⊕	29 fewer (44 fewer to 10 fewer) ⊕⊕⊕⊕	11 fewer (28 fewer to 5 more) ⊕⊕⊕⊕		

*Risk categories represent the following patient populations: very low=no or less than three cardiovascular risk factors; low=three or more cardiovascular risk factors; moderate=cardiovascular disease; high=chronic kidney disease (reduced glomerular filtration rate or macroalbuminuria); very high=cardiovascular disease and chronic kidney disease.
Certainty of the evidence for each estimate is shown: high certainty ⊕⊕⊕⊕; moderate certainty ⊕⊕⊕; low certainty ⊕⊕; very low certainty ⊕.

5, 9, 12, and 18 fewer per 1000 in five years for very low, low, moderate, high, and very high risk patients respectively, moderate to high certainty; table 2). SGLT-2 inhibitors and GLP-1 receptor agonists did not have different effects on cardiovascular mortality (0.96 (0.84 to 1.09, moderate to high certainty; appendix 8).

Non-fatal myocardial infarction
Two hundred and eight trials including 265 921 patients reported non-fatal myocardial infarction. SGLT-2 inhibitors lowered odds of non-fatal myocardial infarction compared with placebo (odds ratio 0.87 (95% confidence interval 0.79 to 0.97); 4, 7, 13, 14, and 21 fewer per 1000 in five years for very

low, low, moderate, high, and very high risk patients respectively, moderate to high certainty; appendix 8), as did GLP-1 receptor agonists (0.92 (0.85 to 0.99); 2, 4, 8, 9, 13 fewer per 1000 in five years for very low, low, moderate, high, and very high risk patients respectively, moderate to high certainty; appendix 8). SGLT-2 inhibitors and GLP-1 receptor agonists did not have different effects on non-fatal myocardial infarction (0.95 (0.84 to 1.08); moderate to high certainty; appendix 8).

Non-fatal stroke
One hundred and seventy six trials including 261 434 patients reported non-fatal stroke. SGLT-2 inhibitors

Table 3 | Summary of anticipated absolute differences comparing sodium-glucose cotransporter-2 inhibitor treatment with glucagon-like peptide-1 receptor agonist treatment per 1000 patients with diabetes type 2 and with very low to very high cardiovascular risk, treated for five years

Risk*	All cause mortality	Cardiovascular mortality	Non-fatal myocardial infarction	Non-fatal stroke	Kidney failure	Hospital admission for heart failure	Body weight	Diabetic ketoacidosis	Serious hyperglycaemia	Genital infection
Very low	2 fewer (4 fewer to 1 fewer) ⊕⊕⊕	0 fewer (2 fewer to 1 more) ⊕⊕⊕	1 fewer (4 fewer to 2 more) ⊕⊕⊕	5 more (1 more to 10 more) ⊕⊕⊕	0 (1 fewer to 0) ⊕⊕	1 fewer (2 fewer to 1 fewer) ⊕⊕⊕				
Low	7 fewer (12 fewer to 2 fewer) ⊕⊕⊕⊕	2 fewer (6 fewer to 4 more) ⊕⊕⊕⊕	3 fewer (8 fewer to 4 more) ⊕⊕⊕⊕	9 more (1 more to 19 more) ⊕⊕⊕⊕	1 fewer (2 fewer to 2 more) ⊕⊕⊕	7 fewer (10 fewer to 4 fewer) ⊕⊕⊕⊕	0.47 kg lower (0.09 lower to 0.85 lower) over 6 months ⊕⊕⊕	1 more (0 to 3 more) ⊕⊕⊕	5 more (2 fewer to 19 more) ⊕⊕⊕	158 more (64 more to 299 more) ⊕⊕⊕⊕
Moderate	12 fewer (21 fewer to 3 fewer) ⊕⊕⊕⊕	3 fewer (11 fewer to 6 more) ⊕⊕⊕⊕	5 fewer (15 fewer to 7 more) ⊕⊕⊕⊕	16 more (2 more to 33 more) ⊕⊕⊕⊕	1 fewer (5 fewer to 3 more) ⊕⊕⊕	18 fewer (25 fewer to 11 fewer) ⊕⊕⊕⊕				
High	16 fewer (28 fewer to 4 fewer) ⊕⊕⊕⊕	4 fewer (15 fewer to 8 more) ⊕⊕⊕⊕	5 fewer (16 fewer to 8 more) ⊕⊕⊕⊕	18 more (3 more to 36 more) ⊕⊕⊕⊕	6 fewer (21 fewer to 13 more) ⊕⊕⊕	24 fewer (32 fewer to 13 fewer) ⊕⊕⊕⊕				
Very high	23 fewer (40 fewer to 6 fewer) ⊕⊕⊕⊕	5 fewer (22 fewer to 12 more) ⊕⊕⊕⊕	7 fewer (24 fewer to 11 more) ⊕⊕⊕⊕	27 more (4 more to 53 more) ⊕⊕⊕⊕	10 fewer (34 fewer to 20 more) ⊕⊕⊕	48 fewer (66 fewer to 27 fewer) ⊕⊕⊕⊕				

*Risk categories represent the following patient populations: very low=no or less than three cardiovascular risk factors; low=three or more cardiovascular risk factors; moderate=cardiovascular disease; high=chronic kidney disease (reduced glomerular filtration rate or macroalbuminuria); very high=cardiovascular disease and chronic kidney disease.
Certainty of the evidence for each estimate is shown: high certainty ⊕⊕⊕⊕; moderate certainty ⊕⊕⊕; low certainty ⊕⊕; very low certainty ⊕.

Table 4 | GRADE summary of findings to illustrate absolute effects based on cardiovascular and renal risk, for all cause mortality for sodium-glucose cotransporter-2 (SGLT-2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists compared with placebo or each other

Comparison	Relative effect (odds ratio (95% CI))	Anticipated absolute effects over five years			Anticipated absolute effects (95% CI) over five years	Certainty in treatment effects (GRADE)	Plain text summary
		Baseline risk*	Risk with control	Risk with intervention			
SGLT-2 inhibitor v placebo	0.77 (0.71 to 0.83)	Very low	Placebo: 20 per 1000	SGLT-2 inhibitor: 15 per 1000	5 fewer per 1000 (from 3 fewer to 6 fewer)	Moderate due to indirectness	SGLT-2 inhibitor treatment probably reduces all cause mortality in people with diabetes and few or no cardiovascular risk factors
		Low	Placebo: 70 per 1000	SGLT-2 inhibitor: 55 per 1000	15 fewer per 1000 (from 11 fewer to 19 fewer	High	SGLT-2 inhibitor treatment reduces all cause mortality in people with diabetes and cardiovascular risk factors
		Moderate	Placebo: 120 per 1000	SGLT-2 inhibitor: 95 per 1000	25 fewer per 1000 (from 18 fewer to 32 fewer)	High	SGLT-2 inhibitor treatment reduces all cause mortality in people with diabetes and established cardiovascular disease
		High	Placebo: 170 per 1000	SGLT-2 inhibitor: 136 per 1000	34 fewer per 1000 (from 25 fewer to 43 fewer)	High	SGLT-2 inhibitor treatment reduces all cause mortality in people with diabetes and chronic kidney disease
		Very high	Placebo: 265 per 1000	SGLT-2 inhibitor: 217 per 1000	48 fewer per 1000 (from 35 fewer to 61 fewer)	High	SGLT-2 inhibitor treatment reduces all cause mortality in people with diabetes and established cardiovascular disease and chronic kidney disease
GLP-1 receptor agonist v placebo	0.88 (0.83 to 0.94)	Very low	Placebo: 20 per 1000	GLP-1 receptor agonist: 18 per 1000	2 fewer per 1000 (from 1 fewer to 3 fewer)	Moderate due to indirectness	GLP-1 receptor agonist treatment probably reduces all cause mortality in people with diabetes and few or no cardiovascular risk factors
		Low	Placebo: 70 per 1000	GLP-1 receptor agonist: 62 per 1000	8 fewer per 1000 (from 4 fewer to 11 fewer)	High	GLP-1 receptor agonist treatment reduces all cause mortality in people with diabetes and cardiovascular risk factors
		Moderate	Placebo: 120 per 1000	GLP-1 receptor agonist: 107 per 1000	13 fewer per 1000 (from 6 fewer to 18 fewer)	High	GLP-1 receptor agonist treatment reduces all cause mortality in people with diabetes and established cardiovascular disease
		High	Placebo: 170 per 1000	GLP-1 receptor agonist: 153 per 1000	17 fewer per 1000 (from 9 fewer to 25 fewer)	High	GLP-1 receptor agonist treatment reduces all cause mortality in people with diabetes and chronic kidney disease
		Very high	Placebo: 265 per 1000	GLP-1 receptor agonist: 241 per 1000	24 fewer per 1000 (from 12 fewer to 35 fewer)	High	GLP-1 receptor agonist treatment reduces all cause mortality in people with diabetes and established cardiovascular disease and chronic kidney disease
SGLT-2 inhibitor v GLP-1 receptor agonist	0.88 (0.79 to 0.98)	Very low	GLP-1 receptor agonist: 18 per 1000	SGLT-2 inhibitor: 16 per 1000	2 fewer per 1000 (from 1 fewer to 4 fewer)	Moderate due to indirectness	SGLT-2 inhibitor treatment probably reduces all cause mortality compared with GLP-1 receptor agonist treatment in people with diabetes and few or no cardiovascular risk factors
		Low	GLP-1 receptor agonist: 62 per 1000	SGLT-2 inhibitor: 55 per 1000	7 fewer per 1000 (from 2 fewer to 12 fewer)	High	SGLT-2 inhibitor treatment reduces all cause mortality compared with GLP-1 receptor agonist treatment in people with diabetes and cardiovascular risk factors
		Moderate	GLP-1 receptor agonist: 107 per 1000	SGLT-2 inhibitor: 95 per 1000	12 fewer per 1000 (from 3 fewer to 21 fewer)	High	SGLT-2 inhibitor treatment reduces all cause mortality compared with GLP-1 receptor agonist treatment in people with diabetes and established cardiovascular disease
		High	GLP-1 receptor agonist: 153 per 1000	SGLT-2 inhibitor: 137 per 1000	16 fewer per 1000 (from 4 fewer to 28 fewer)	High	SGLT-2 inhibitor treatment reduces all cause mortality compared with GLP-1 receptor agonist treatment in people with diabetes and chronic kidney disease
		Very high	GLP-1 receptor agonist: 241 per 1000	SGLT-2 inhibitor: 218 per 1000	23 fewer per 1000 (from 6 fewer to 40 fewer)	High	SGLT-2 inhibitor treatment reduces all-cause mortality compared with GLP-1 receptor agonist treatment in people with diabetes and established cardiovascular disease and chronic kidney disease

GRADE=grading of recommendations assessment, development, and evaluation.
*Risk categories represent the following patient populations: very low=no or less than three cardiovascular risk factors; low=three or more cardiovascular risk factors; moderate=cardiovascular disease; high=chronic kidney disease (reduced glomerular filtration rate or macroalbuminuria); very high=cardiovascular disease and chronic kidney disease.
The point estimate of the absolute effect for GLP-1 receptor agonist treatment, obtained from GLP-1 receptor agonist treatment versus placebo, was used to calculate the absolute effect for SGLT-2 inhibitors versus GLP-1 receptor agonists.

had little or no effect on non-fatal stroke (odds ratio 1.01 (95% confidence interval 0.89 to 1.14); moderate to high certainty; appendix 8). GLP-1 receptor agonists reduced non-fatal stroke (0.84 (0.76 to 0.93); 5, 9, 16, 17, and 25 fewer per 1000 in five years for very low, low, moderate, high, and very high risk patients respectively, moderate to high certainty; appendix 8). SGLT-2 inhibitors had higher odds of non-fatal stroke than GLP-1 receptor agonists (1.20 (1.03 to 1.41); moderate to high certainty; appendix 8).

Kidney failure
Thirty three trials including 98 284 patients reported kidney failure, defined generally as estimated glomerular filtration rate below 15 ml/min per 1.73 m^2 or start of kidney replacement treatment. SGLT-2 inhibitors reduced kidney failure (odds ratio 0.71 (95% confidence interval 0.57 to 0.89); 1,3, 6, 25, and 38 fewer per 1000 in five years for very low, low, moderate, high, and very high risk patients respectively, moderate to high certainty; appendix 8). GLP-1 receptor agonists also reduced kidney failure (0.78 (0.67 to 0.92); 0, 2, 4, 19, and 29 fewer per 1000 in five years for very low, low, moderate, high, and very high risk patients respectively, moderate to high certainty; appendix 8). SGLT-2 inhibitors and GLP-1 receptor agonists probably did not have different effects on kidney failure (0.91 (0.69 to 1.20); low to moderate certainty).

Admission to hospital for heart failure
One hundred and forty nine trials including 242 361 patients reported admission to hospital for heart failure. SGLT-2 inhibitors reduced admission for heart failure (odds ratio 0.70 (95% confidence interval 0.63 to 0.77); 2, 9, 23, 29, and 58 fewer per 1000 in five years for very low, low, moderate, high, and very high risk patients respectively, moderate to high certainty; appendix 8). GLP-1 receptor agonists had little or no effect on hospitalisation for heart failure (0.94 (0.85 to 1.03), moderate to high certainty; appendix 8). SGLT-2 inhibitors reduced hospitalisation for heart failure compared with GLP-1 receptor agonists (0.74 (0.65 to 0.85); 1, 7, 18, 24, and 48 fewer per 1000 in five years for very low, low, moderate, high, and very high risk patients respectively, moderate to high certainty; table 3).

Blindness and eye disease requiring intervention
Seven trials including 68 221 patients reported blindness. The results of the network meta-analysis were uninformative as blindness was rarely reported and the confidence intervals for estimated treatment effects were very wide (appendix 7). The outcome of eye disease requiring intervention was not specifically reported in any trial.

Health related quality of life
Twenty five trials including 11 912 patients reported health related quality of life during a median follow-up of six months. The reported instruments included the Diabetes Treatment Satisfaction Questionnaire, the Short Form 12 and 36, the EuroQoL five dimensions (EQ-5D), the Diabetes Quality of Life, Treatment Satisfaction Status Scale, and the Impact of Weight on Quality of Life. SGLT-2 inhibitors had uncertain effects on health related quality of life (standardised mean difference 0.14 (95% confidence interval −0.08 to 0.36); low certainty; appendix 8). GLP-1 receptor agonists might increase health related quality of life (0.13 (0.03 to 0.23); low certainty; appendix 8). No evidence was found that SGLT-2 inhibitors and GLP-1 receptor agonists had different effects on health related quality of life (0.01 (−0.19 to 0.20); low certainty; appendix 8).

Body weight
Four hundred and sixty nine trials including 226 361 patients reported body weight during a median follow-up of six months. SGLT-2 inhibitor treatment and GLP-1 receptor agonist treatment might lower body weight (mean difference for SGLT-2 inhibitors −1.92 kg (95% confidence interval −2.23 to −1.62); low certainty; mean difference for GLP-1 receptor agonists −1.45 kg (−1.72 to −1.18); low certainty; appendix 8). SGLT-2 inhibitors appeared to lower body weight to a greater extent than GLP-1 receptor agonists (−0.47 kg (−0.85 to −0.09); moderate certainty).

Glycated haemoglobin A1c
Six hundred and four trials including 242 745 patients reported glycated haemoglobin A1c during a median follow-up of six months. SGLT-2 inhibitors (mean difference −0.60% (95% confidence interval −0.67 to −0.54); low certainty) and GLP-1 receptor agonists (−0.89% (−0.95 to −0.82); low certainty) might lower glycated haemoglobin A1c levels more than placebo (low certainty). GLP-1 receptor agonists reduced glycated haemoglobin A1c levels to a greater extent than SGLT-2 inhibitors (mean difference −0.28% (95% CI −0.37 to −0.19); high certainty).

Other outcomes
GLP-1 receptor agonists reduced serious hyperglycaemia with moderate to high certainty (15 fewer events in 1000 patients treated with GLP-1 receptor agonists over five years). Results showed the effects of treatment on amputation or neuropathic pain were very uncertain (appendix 8).

Harms
No difference in the odds of serious hypoglycaemia was found in a comparison of SGLT-2 inhibitor or GLP-1 receptor agonist treatment with placebo or with each other in high or moderate certainty evidence (appendix 8). SGLT-2 inhibitor treatment and GLP-1 receptor agonist treatment probably did not increase diabetic ketoacidosis compared with placebo or each other (moderate certainty). SGLT-2 inhibitors increased genital infection compared with placebo and GLP-1 receptor agonists (high certainty). The effects of treatments on Fournier gangrene were uncertain. GLP-1 receptor agonists might incur severe

gastrointestinal events (low certainty). An increase in pancreatic cancer or pancreatitis is probably not likely with SGLT-2 inhibitor or GLP-1 receptor agonist treatment compared with placebo (low to moderate certainty), and there might be no difference between SGLT-2 inhibitor and GLP-1 receptor agonist treatment for pancreatic cancer (low certainty). SGLT-2 inhibitor treatment might incur a lower risk of pancreatitis than GLP-1 receptor agonist treatment (low certainty).

No evidence was found that treatment effects differed according to trial level characteristics, including trial duration, BMI, cardiovascular risk, and presence of chronic kidney disease (appendix 9).

Discussion

Principal findings

This network meta-analysis provides high certainty evidence that SGLT-2 inhibitors and GLP-1 receptor agonists, when added to other diabetes treatment, reduce mortality, non-fatal myocardial infarction, kidney failure, and serious hyperglycaemia. In the absence of head-to-head trials, we also found high certainty evidence for notable differences between SGLT-2 inhibitors and GLP-1 receptor agonists; SGLT-2 inhibitors reduced all cause mortality and admission to hospital for heart failure more than GLP-1 receptor agonists, whereas GLP-1 receptor agonists reduced non-fatal stroke more than SGLT-2 inhibitors (which appeared to have no effect). Differential effects of SGLT-2 inhibitors and GLP-1 receptor agonists on other patient important outcomes included lower body weight and increased quality of life, albeit with small absolute differences. Harms also differed. SGLT-2 inhibitors caused genital infection, and GLP-1 receptor agonists might increase severe gastrointestinal events. Importantly, the absolute benefits for cardiovascular and renal outcomes varied substantially for patients, depending on their absolute cardiovascular risk (very low to very high; https://magicevidence.org/match-it/200820dist/#!/) Taken together, the results have clear implications for clinical practice, as reflected in the *BMJ* Rapid Recommendations directly informed by our systematic review.

Strength and limitations of this study

The strengths of the review include a sensitive search to identify eligible trials, and independent study identification, selection, data extraction, and adjudication of risk of bias by two reviewers. The review used the GRADE approach to report the certainty of available evidence and reported estimated absolute risks for all outcomes, including patients with varying risks of cardiovascular and kidney disease. Limitations include the heterogeneity in clinical settings of the included trials, although the consistency of results across studies diminishes this concern. Some outcomes resulted in imprecise estimates of effects and low certainty evidence.

Clinical uncertainties

SGLT-2 inhibitors failed to reduce non-fatal stroke in the same way that it reduced other cardiovascular endpoints, a finding not scientifically intuitive. Trials generally did not include patients with lowest cardiovascular risk. Accordingly, the certainty of evidence was graded down for the lowest risk patients owing to indirectness. The panel agreed that a non-contextualised approach was appropriate to assess imprecision in estimates of effects to inform judgments about the certainty of evidence in the network meta-analysis. We therefore did not adjudicate whether the range of treatment effects for each outcome was trivial, small, moderate, or large; assess critical outcomes simultaneously; or make inferences about their value relative to each other.[31] The related *BMJ* Rapid Recommendation will adjudicate the importance of the absolute effects of treatment and rate certainty accordingly. This approach might lower the adjudicated evidence certainty for several outcomes that inform the *BMJ* Rapid Recommendations. Whether SGLT-2 inhibitors and GLP-1 receptor agonists given together provide additional benefits compared with each treatment alone is not answered by this review. Notably, the effects of treatment on glycated haemoglobin A1c and body weight were provided in trials with an average follow up of six months. Possibly, the relative effects of the SGLT-2 inhibitor and GLP-1 receptor agonist treatment on these outcomes might have been different in shorter duration trials than in the longer therapeutic evaluations of cardiovascular outcomes.

Comparisons with other studies

This systematic review included substantially more trials—including large and recently published trials—and patients than previously reported reviews and is based on priority setting and received oversight by a panel with a range of clinical and lived experiences. SGLT-2 inhibitors and GLP-1 receptor agonists had similar treatment effects on mortality as observed by a previous network meta-analysis published in 2016, although precision in the treatment estimates has increased substantially.[11] The results provide evidence to support guideline recommendations made in 2019 that patients at highest risk of cardiovascular disease and kidney disease are likely to have important benefits on risks of cardiovascular events and heart failure with SGLT-2 inhibitors.[2 9] This network meta-analysis aims to provide a broader representation of both relative and absolute estimates of a wide range of important clinical outcomes.

The analysis is consistent with large scale observational analyses of SGLT-2 inhibitor treatment in a range of countries and settings, which suggest beneficial effects on a range of clinical outcomes, including reduced mortality and heart failure in people with diabetes at low cardiovascular risk and those with atherosclerotic cardiovascular disease.[118 119] The effects of treatment in the available randomised trials in our analyses are smaller than seen with observational data, as the trial data enable analyses that reduce the risks of confounding by treatment indication; in other words, in real world datasets, people who receive drug treatment might be healthier or have

other characteristics that lead to better outcomes than people who are not prescribed treatment. The present review can discern important differences between the effect of SGLT-2 inhibitors and GLP-1 receptor agonists on mortality and heart failure, not identified in large scale non-randomised studies.[120]

Policy implications

This systematic review of 764 clinical trials provides detailed information for decision makers about the benefits and harms of SGLT-2 inhibitors and GLP-1 receptor agonists on important outcomes in adults with type 2 diabetes. It includes trials with publicly available information up to August 2020. A core finding suggests that there is high certainty that SGLT-2 inhibitors reduce all cause and cardiovascular mortality, non-fatal myocardial infarction, kidney failure, and admission to hospital for heart failure. GLP-1 receptor agonist treatment reduces all cause and cardiovascular mortality, non-fatal myocardial infarction, non-fatal stroke, and kidney failure. SGLT-2 inhibitor treatment reduces all cause mortality and admission to hospital for heart failure to a greater extent than GLP-1 receptor agonist treatment, whereas GLP-1 receptor agonist treatment reduces non-fatal stroke more than SGLT-2 inhibitors. The effect of SGLT-2 inhibitors and GLP-1 receptor agonists on many other important patient outcomes is uncertain. Glycated haemoglobin A1c was not chosen as an important outcome in the review by the oversight panel, which included patients and clinicians, but it was reported as it is considered by some decision makers to be a measure of glycaemic control and indicative of a more immediate measure of diabetes control.

Conclusions

Trials of SGLT-2 inhibitors in people with existing cardiovascular disease and chronic kidney disease with or without diabetes are emerging or ongoing,[7 6 9 121] indicating that SGLT-2 treatment decreases heart failure in the absence of type 2 diabetes. The findings of the Dapagliflozin and Prevention of Adverse outcomes in Chronic Kidney Disease (DAPA-CKD) randomised controlled trial are awaited to identify whether dapagliflozin decreases kidney and cardiovascular events in people regardless of the presence of diabetes.[121]

In conclusion, this network meta-analysis provides evidence of the absolute benefits and harms of SGLT-2 inhibitors and GLP-1 receptor agonists. The balance of benefits and harms depends on individual risk profiles of patients, and thus the results support a risk stratified approach for provision of SGLT-2 inhibitors and GLP-1 receptor agonists to patients with type 2 diabetes. Accordingly, the associated *BMJ* Rapid Recommendations will provide risk stratified recommendations and highlight the need for shared decision making to allow patients and clinicians to make well informed decisions together.

These data provide direct evidence for the absolute benefits and harms of SGLT-2 inhibitors and GLP-1 receptor agonists. The findings of this research paper raise questions about how they should be used in clinical practice. In the linked article, readers will find recommendations on SGLT-2 inhibitors and GLP-1 receptor agonists based on data from this paper. To do this a guideline panel has considered how direct this evidence is and using GRADE methodology has integrated this with, for example, the values and preferences of patients and resource implications. To read more about the guidelines please see the guideline article in this package.

AUTHOR AFFILIATIONS
[1]Department of Medicine, University of Otago, Christchurch, New Zealand

[2]School of Public Health and Preventive Medicine, Monash University, Melbourne, VIC, Australia

[3]Department of Internal Medicine, Division of Nephrology and Hypertension, University of Kansas, Kansas City, KS, USA

[4]Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, ON, Canada

[5]Institute of Health and Society, University of Oslo, Oslo, Norway

[6]Department of Endocrinology and Metabolism, West China Hospital, Sichuan University, Chengdu, China

[7]Division of Population Health and Genomics, Ninewells Hospital, University of Dundee, Dundee, UK

[8]Centre for Gerontology and Geriatrics, West China Hospital, Sichuan University, Chengdu, China

[9]Sydney School of Public Health, University of Sydney, Sydney, NSW, Australia

[10]Department of Emergency and Organ Transplantation, University of Bari, Piazza Giulio CESARE, 70124 Bari, Italy

[11]Centre for Outcomes Research and Clinical Epidemiology (CORESEARCH), Pescara, Italy

[12]Department of Nephrology, Division of Medicine, University of Queensland at Princess Alexandra Hospital, Woolloongabba, QLD, Australia

[13]Cumming School of Medicine, University of Calgary, Calgary, AB, Canada

[14]George Institute for Global Health, Sydney, NSW, Australia

[15]Division of Nephrology, Hôpital Maisonneuve-Rosemont, Montréal, QC, Canada

[16]Mater Private Clinic, Brisbane, QLD, Australia

[17]Department of Nephrology, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, AB, Canada

[18]Endocrine and Diabetes Unit, Queen Elizabeth Hospital, Woodville, SA, Australia

[19]Endocrine and Metabolic Unit, Royal Adelaide Hospital, Adelaide, SA, Australia

[20]Garvan Institute of Medical Research, Sydney, NSW, Australia

[21]Department of Medicine, University of Melbourne, Melbourne, VIC, Australia

[22]Department of General Practice and Primary Health Care, University of Melbourne, Melbourne, VIC, Australia

[23]Plataforma INVEST Medicina UANL-KER Unit Mayo Clinic (KER Unit Mexico), Universidad Autonoma de Nuevo Leon, Monterrey, Mexico

[24]Evidence-based Medicine Research Centre, Jiangxi University of Traditional Chinese Medicine, Nanchang, China

[25]Chinese Evidence-based Medicine Centre, Cochrane China Centre

[26]West China School of Medicine, Sichuan University, Chengdu, China

[27]Faculty of Medicine and Health, Charles Perkins Centre, University of Sydney, Sydney, NSW, Australia

[28]Department of Medicine, McMaster University, Hamilton, ON, Canada

[29]Population Health Research Institute, Hamilton Health Sciences, McMaster University, Hamilton, ON, Canada

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Web appendix: Supplementary material