THE LANCET

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: The Nuffield Department of Population Health Renal Studies Group and the SGLT2 inhibitor Meta-Analysis Cardio-Renal Trialists' Consortium. Impact of diabetes on the effects of sodium glucose co-transporter-2 inhibitors on kidney outcomes: collaborative meta-analysis of large placebo-controlled trials. *Lancet* 2022; published online Nov 6. https://doi.org/10.1016/S0140-6736(22)02074-8.

WEB MATERIALS

IMPACT OF DIABETES ON THE EFFECTS OF SODIUM GLUCOSE CO-TRANSPORTER-2 (SGLT2) INHIBITORS ON KIDNEY OUTCOMES:

COLLABORATIVE META-ANALYSIS OF LARGE PLACEBO-CONTROLLED TRIALS

This supplemental material has been provided by the authors

to give readers additional information about their work.

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LIST OF COLLABORATORS

WEB METHODS

Literature search methods

This systematic review is an update of a previous systematic review and meta-analysis (PROSPERO ID: CRD42021240468) (1). The present review was registered on PROSPERO ahead of the updated database search (PROSPERO ID: CRD42022351618). The subsequent systematic search of MEDLINE and EMBASE databases was undertaken on 5th September 2022, limited to studies added to the database after 29th August 2021 (the date of completion of the previously published meta-analysis literature search). The search strategy utilised was identical to that of the prior systematic review and meta-analysis (with the exception of limits applied to dates) including the use of validated filters for randomised controlled trials (see below for full list of search terms). No language restriction was applied. Identified records were downloaded to a dedicated database, and titles and abstracts were screened for relevance and duplicates by a single study author (AJR), together with studies identified during the previous systematic review. Further full text screening was undertaken using a previously piloted spreadsheet against pre-specified inclusion criteria to identify studies for inclusion. The final database included primary trial publications and subsidiary peer-reviewed publications.

The inclusion criteria for this study included those of the previous meta-analysis, with an additional requirement (pre-specified in the PROSPERO-registered protocol) that studies should have a duration of greater than 6 months. The final inclusion criteria were as follows:

- Parallel-group randomised controlled trial in adults
- Randomisation of ≥1000 participants to an SGLT2 inhibitor (including combined SGLT1/2 inhibitors) versus placebo (required ≥500 participants in each group)
- Duration ≥ 6 months (additional inclusion criterion for updated systematic review)
- Reporting any of the pre-specified main efficacy outcomes and any of the pre-specified safety outcomes

Where relevant, multiple reports from the same study were collated using the study acronym or National Clinical Trials (NCT) database reference number.

Outcomes

Pre-specified outcomes analysed in the present study comprised the following:

 Kidney disease progression based on at least a 50% sustained decline in estimated glomerular filtration rate from baseline (Webtable 1)

- Acute kidney injury
- Hospitalisation for heart failure or cardiovascular death
- Cardiovascular death
- Any death
- Non-cardiovascular death
- Ketoacidosis
- Lower limb amputation

Outcomes were analysed separately by diabetes status.

Safety analyses evaluated in the previous meta-analysis were additionally analysed:

- Urinary tract infections
- Mycotic genital infections
- Fournier's gangrene
- Severe hypoglycaemia
- Bone fracture

Data extraction

For each identified trial, relevant results were identified from primary or subsidiary peer-reviewed publications and transcribed to dedicated spreadsheets by two authors (KJM, AJR), with discrepancies resolved by consensus discussion. Where potentially relevant data from identified trials were not available in the peer-reviewed literature, trial authors were contacted to request additional data.

For each trial, extracted data included main eligibility criteria; follow-up duration; relevant participant characteristics on the trial level (including proportion of patients with type 2 diabetes or heart failure, and average kidney function); number of events and participants for each arm in reported comparisons; event rate per 1000 patient-years in each arm; and hazard ratio and 95% confidence intervals for relevant comparisons, if reported. Where possible, data were extracted separately for patients with and without type 2 diabetes and, where reported, stratified by presumed primary kidney disease and glomerular disease (for chronic kidney disease [CKD] trials only). Trials were classified according to their primary inclusion criteria into three populations: type 2 diabetes at high risk of cardiovascular disease, stable heart failure (i.e. not in receipt of intravenous diuretic therapy), and CKD.

Risk of bias assessment

Risk of bias was assessed using Version 2 of the Cochrane risk-of-bias tool for randomized trials (ROB2) by two authors (KJM, AJR), independently and in duplicate.

Search Strategy

MEDLINE Search strategy

| 1 | randomized controlled trial.pt. |
|----|---|
| 2 | controlled clinical trial.pt. |
| 3 | randomized.ab. |
| 4 | placebo.ab. |
| 5 | clinical trials as topic.sh. |
| 6 | randomly.ab. |
| 7 | trial.ti. |
| 8 | 1 or 2 or 3 or 4 or 5 or 6 or 7 |
| 9 | exp animals/ not humans.sh. |
| 10 | 8 not 9 |
| 11 | exp Sodium-Glucose Transporter 2 Inhibitors/ |
| 12 | sglt2.tw. |
| 13 | sglt-2.tw. |
| 14 | exp Sodium-Glucose Transporter 2/ |
| 15 | sodium-glucose transporter\$.tw. |
| 16 | sodium-glucose co-transporter\$.tw. |
| 17 | sodium-glucose cotransporter\$.tw. |
| | (canagliflozin\$ or dapagliflozin\$ or empagliflozin\$ or ertugliflozin\$ or ipragliflozin\$ or luseogliflozin\$ or |
| 18 | remogliflozin\$ or sergliflozin\$ or sotagliflozin\$ or tofogliflozin\$).tw. |
| 19 | 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 |
| 20 | 10 and 19 |

EMBASE Search strategy

- 1 Randomized controlled trial/
- 2 Controlled clinical study/
- 3 random\$.ti,ab.
- 4 randomization/
- 5 intermethod comparison/
- 6 placebo.ti,ab.
- 7 (compare or compared or comparison).ti.

((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or

- 8 comparison)).ab.
- 9 (open adj label).ti,ab.
- 10 ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab.
- 11 double blind procedure/
- 12 parallel group\$1.ti,ab.
- 13 (crossover or cross over).ti,ab.

((assign\$ or match or matched or allocation) adj5 (alternate or group\$1 or intervention\$1 or patient\$1 or

- 14 subject\$1 or participant\$1)).ti,ab.
- 15 (assigned or allocated).ti,ab.
- 16 (controlled adj7 (study or design or trial)).ti,ab.
- 17 (volunteer or volunteers).ti,ab.
- 18 human experiment/
- 19 trial.ti.
- 20 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 (random\$ adj sampl\$ adj7 ("cross section\$" or questionnaire\$1 or survey\$ or database\$1)).ti,ab. not
- 21 (comparative study/ or controlled study/ or randomi?ed controlled.ti,ab. or randomly assigned.ti,ab.) Cross-sectional study/ not (randomized controlled trial/ or controlled clinical study/ or controlled study/ or
- 22 randomi?ed controlled.ti,ab. or control group\$1.ti,ab.)
- 23 (((case adj control\$) and random\$) not randomi?ed controlled).ti,ab.
- 24 (Systematic review not (trial or study)).ti.
- 25 (nonrandom\$ not random\$).ti,ab.
- 26 "Random field\$".ti,ab.
- 27 (random cluster adj3 sampl\$).ti,ab.
- 28 (review.ab. and review.pt.) not trial.ti.
- 29 "we searched".ab. and (review.ti. or review.pt.)
- 30 "update review".ab.
- 31 (databases adj4 searched).ab.

(rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset\$1).ti.

- 32 and animal experiment/
- 33 Animal experiment/ not (human experiment/ or human/)

34 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33

- 35 20 not 34
- 36 exp Sodium-Glucose Transporter 2 Inhibitors/
- 37 sglt2.tw.
- 38 sglt-2.tw.
- 39 exp Sodium-Glucose Transporter 2/
- 40 sodium-glucose transporter\$.tw.
- 41 sodium-glucose co-transporter\$.tw.
- 42 sodium-glucose cotransporter\$.tw.(canagliflozin\$ or dapagliflozin\$ or empagliflozin\$ or ertugliflozin\$ or ipragliflozin\$ or luseogliflozin\$ or
- 43 remogliflozin\$ or sergliflozin\$ or sotagliflozin\$ or tofogliflozin\$).tw.
- 44 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43

Searches were limited to dates ranging from 29th August 2021 to the date of the search.

Data from eligible trials not included in meta-analyses

Two randomised trials were identified in the prior systematic review but not included in meta-analysis due to short follow-up duration (<6 months) and study populations not consistent with the pre-defined populations (type 2 diabetes with high atherosclerotic cardiovascular disease risk, heart failure, and CKD) in the previous meta-analysis. Data from these trials are summarised here.

InTandem3* (2) enrolled a population with type 1 diabetes and therefore did not fit into one of the 3 pre-defined patient groups. Follow-up was also only 24 weeks precluding the reporting of a large number of relevant outcomes. Outcomes relevant to this meta-analysis are summarised in the table below:

| | Sotagliflozin (n=699) | Placebo (n=703) |
|---|--------------------------|--------------------------|
| | Participants with events | Participants with events |
| Hospitalisation for heart failure or cardiovascular death | 0 | 0 |
| "Renal event" | 5 | 3 |
| Ketoacidosis | 21 | 4 |
| Amputation | 0 | 0 |
| Any death | 1 | 0 |

* 24 week trial in a population with type 1 diabetes with primary outcome of: glycated haemoglobin level <7.0% at week 24, with no episodes of severe hypoglycaemia or diabetic ketoacidosis after randomisation. Kidney disease progression and acute kidney injury events data not available.

The Dapagliflozin in Respiratory Failure in Patients With COVID-19 (DARE-19) trial (3) was identified by the systematic review but not included in meta-analysis given the study population (hospitalised patients with COVID-19) and very short treatment and follow-up duration (30 days), limiting reporting of most relevant outcomes. Reported outcomes relevant to this meta-analysis are summarised below:

| | Dapagliflozin (n=625) | Placebo (n=625) |
|-----------------------|--------------------------|--------------------------|
| | Participants with events | Participants with events |
| Any death | 41 | 54 |
| Acute kidney injury | 21 | 34 |
| Diabetic ketoacidosis | 2 | 0 |

WEB REFERENCES

1. Staplin N, Roddick AJ, Emberson J, Reith C, Riding A, Wonnacott A, et al. Net effects of sodiumglucose co-transporter-2 inhibition in different patient groups: a meta-analysis of large placebo-controlled randomized trials. eClinicalMedicine. 2021;41.

 Garg SK, Henry RR, Banks P, Buse JB, Davies MJ, Fulcher GR, et al. Effects of Sotagliflozin Added to Insulin in Patients with Type 1 Diabetes. New England Journal of Medicine. 2017;377(24):2337-48.
Kosiborod MN, Esterline R, Furtado RHM, Oscarsson J, Gasparyan SB, Koch GG, et al. Dapagliflozin in patients with cardiometabolic risk factors hospitalised with COVID-19 (DARE-19): a randomised, doubleblind, placebo-controlled, phase 3 trial. Lancet Diabetes Endocrinol. 2021;9(9):586-94.

| | | Cor | mponents 8 | k definition | s used in this meta-analysis | | | | | | |
|-----------------------|--|--------------|--|--------------|---|---|--|--|--|--|--|
| Trial | Sustained Sustained decline Kidney replacement therapy Sustained | | Sustained eGFR <15 (or <10) Renal death | | Definition of sustained | Definitions originally applied by individual trials | | | | | |
| DECLARE-TIMI 58 | ~ | \checkmark | \checkmark | \checkmark | As confirmed by two tests at the central laboratory ≥ 4 weeks apart | Sustained ≥40% eGFR decline to <60 mL/min/1.73 m ² or ESKD (defined as dialysis ≥90 days, kidney transplantation, or sustained eGFR <15 mL/min/1.73 m ²) or renal death | | | | | |
| CANVAS Program | ~ | \checkmark | \checkmark | ~ | Two consecutive measurements ≥30 days apart unless identified on the last available measurement | Sustained 50% eGFR decline or ESKD (defined as maintenance dialysis \geq 30 days, kidney transplantation, sustained eGFR <15 mL/min/1.73 m ²) or renal death | | | | | |
| VERTIS CV | ~ | \checkmark | \checkmark | ~ | Subsequent value that also met the cut-off criterion >30 days later | Pre-specified secondary: Doubling of serum creatinine, dialysis*/kidney transplantation or renal death Pre-specified exploratory: Sustained ≥40% decline in eGFR, chronic* dialysis/kidney transplantation or renal death | | | | | |
| EMPA-REG OUTCOME | ~ | \checkmark | \checkmark | ~ | Sustained for ≥28 days according to central laboratory assessment | Pre-specified: Sustained \geq 40% eGFR decline or ESKD (defined as "sustained continuous" [*] dialysis/ kidney transplantation or sustained eGFR <15 mL/min/1.73 m ²) or <i>hospitalisation for heart failure or cardiac</i> or renal <i>death</i> . Post-hoc: Sustained \geq 40%; (also published for \geq 30%, \geq 50% and \geq 57%) eGFR decline or RRT initiation or renal death. | | | | | |
| DAPA-HF | ~ | \checkmark | \checkmark | ~ | Defined as lasting ≥28 days | Sustained \geq 50% eGFR decline, ESKD (defined as chronic [*] dialysis, kidney transplantation or sustained eGFR <15 mL/min/1.73 m ²) or renal death | | | | | |
| EMPEROR- REDUCED | ~ | \checkmark | \checkmark | \checkmark | Sustained for ≥30 days according to central laboratory assessment or if the last measurement meets criteria and death occurred within 60 days | Sustained \geq 40% eGFR decline or ESKD (defined as chronic* dialysis/ kidney transplantation or sustained eGFR <15 for patients with baseline eGFR \geq 30, or sustained eGFR <10 for patients with baseline eGFR <30 mL/min/1.73 m ²) | | | | | |
| EMPEROR- PRESERVED | ~ | \checkmark | \checkmark | ~ | Sustained for ≥30 days according to central laboratory assessment or if the last measurement meets criteria and death occurred within 60 days | Sustained \geq 40% eGFR decline or ESKD (defined as chronic* dialysis/ kidney transplantation or sustained eGFR <15 for patients with baseline eGFR \geq 30 or sustained eGFR<10 for patients with baseline eGFR<30 mL/min/1.73 m ²) | | | | | |
| DELIVER | \checkmark | \checkmark | \checkmark | \checkmark | Measured at two consecutive scheduled study follow-up visits (≥ 1 month apart), or at last available visit | Sustained \geq 50% eGFR decline, ESKD (defined from adverse event reports), sustained eGFR <15 mL/min/1.73 m ² , or renal death | | | | | |
| SOLOIST-WHF | | | | | | Not available | | | | | |
| CREDENCE | ~ | \checkmark | \checkmark | ~ | Sustained for ≥30 days according to central laboratory assessment | Primary: Sustained doubling of serum creatinine, ESKD (defined as maintenance dialysis \geq 30 days, kidney transplantation or sustained eGFR <15 mL/min/1.73 m ²) or renal or <i>cardiovascular death</i> Secondary: Sustained doubling of serum creatinine, ESKD or renal death | | | | | |
| SCORED | ~ | \checkmark | \checkmark | х | Sustained for ≥30 days | Sustained \geq 50% eGFR decline, long-term* dialysis, kidney transplantation or sustained eGFR <15 mL/min/1.73 m ² | | | | | |
| DAPA-CKD | ~ | \checkmark | \checkmark | \checkmark | Two consecutive central laboratory eGFR values ≥28 days apart | Sustained \geq 50% eGFR decline, ESKD (defined as maintenance dialysis \geq 28 days, kidney transplantation or sustained eGFR <15 mL/min/1.73 m ²) or renal death | | | | | |
| EMPA-KIDNEY | ~ | \checkmark | \checkmark | ~ | (a) measured at two consecutive scheduled study follow-up visits; or (b) last available measurement | Sustained ≥40% eGFR decline, ESKD (defined as maintenance dialysis ≥90 days or kidney transplantation), sustained eGFR <10 mL/min/1.73m ² or renal death side of the table, with a record of original trial or post-hoc versions of the outcome | | | | | |

Kidney disease progression definitions used for meta-analysis are provided in the left side of the table, with a record of original trial or post-hoc versions of the outcome provided in the final column on the right. * Duration undefined. eGFR=estimated glomerular filtration rate; ESKD=end-stage kidney disease. RRT=renal replacement therapy.

Webtable 2: Sources of analysis data in 13 included trials

| Trial | Outcome | Provided after request | Published (required format) | Published (estimated indirectly) | Comment |
|---------------------|---|------------------------------|---------------------------------------|--|---|
| | Kidney disease progression (≥50%) | \checkmark | · · · · · · · · · · · · · · · · · · · | • / | |
| | Any death, CV death; CV death/HHF | | \checkmark | | |
| ECLARE- | Non-CV death | | \checkmark | | |
| TIMI 58 | AKI, amputation, ketoacidosis | | \checkmark | \checkmark | Rates estimated from numbers of events. AKI: defined by MedDRA Preferred Term for AKI (serious and non-serious; unadjudicated). |
| | UTI, mycotic genital infections, hypoglycaemia, fractures | | | \checkmark | Rates estimated from number of events. Serious UTI not reported. |
| | Kidney disease progression (≥50%) | | \checkmark | | Event numbers by arm estimated from reported event rates, total events and hazard ratios. |
| | Any death, CV death; CV death/HHF | | \checkmark | \checkmark | Event numbers by arm estimated from reported event rates, total events and hazard ratios. |
| CANVAS | Non-CV death | | | \checkmark | Calculated indirectly from any death & CV death data. |
| rogram | AKI, amputation, ketoacidosis | | \checkmark | \checkmark | Risk ratio estimated from rates. Event numbers by arm estimated from reported event rates, total events and hazard ratios. AKI: defined by MedDRA Preferred Term for AKI (serious only; unadjudicated). |
| | UTI, mycotic genital infections, hypoglycaemia, fractures | | | \checkmark | Risk ratio estimated from rates. Data for UTI and mycotic genital infections extracted from previous meta-analysis. Hypoglycaemia not included. Serious UTI not reported. |
| | Kidney disease progression (≥50%) | \checkmark | | | |
| | Any death, CV death; CV death/HHF | | \checkmark | | |
| | Non-CV death | | | \checkmark | Calculated indirectly from any death & CV death data. |
| ERTIS CV | AKI, amputation, ketoacidosis | | \checkmark | \checkmark | Rates & risk ratios estimated from event numbers. AKI: defined by MedDRA Preferred Term for AKI (serious only; unadjudicated). |
| | UTI, mycotic genital infections, hypoglycaemia, fractures | | | \checkmark | Risk ratios and rates estimated from numbers of events. UTI and serious UTI reported separately.Mycotic genital infections: results for male and female infections combined by inverse-variance meta-analysis. |
| | Kidney disease progression (≥50%) | \checkmark | | | |
| EMPA-REG OUTCOME | Any death, CV death; CV death/HHF | | \checkmark | | CV death definition excluded stroke. |
| | Non-CV death | | • | ✓ | Calculated indirectly from any death & CV death data. |
| | AKI, amputation, ketoacidosis | | \checkmark | √ | Amputation: published in required format. AKI & ketoacidosis: rates & risk ratios estimated from numbers of events. AKI: defined by MedDRA Preferred Term for AKI (serious and non-serious; unadjudicated). |
| | UTI, mycotic genital infections, hypoglycaemia, fractures | | | \checkmark | Risk ratios and rates estimated from numbers of events. UTI and serious UTI reported separately. |
| | Kidney disease progression (≥50%) | | \checkmark | | |
| | Any death, CV death; CV death/HHF | | \checkmark | | CV death/HHF: used analyses excluding urgent HF visits. |
| | Non-CV death | | | \checkmark | Calculated indirectly from any death & CV death data. |
| APA-HF | AKI, amputation, ketoacidosis | \checkmark | \checkmark | \checkmark | AKI: provided as defined by MedDRA Preferred Term for AKI (serious and non-serious; unadjudicated). Amputation: Rates estimated from numbers of events. Ketoacidosis: Rates & risk ratios estimated from numbers of events. |
| | UTI, mycotic genital infections, hypoglycaemia, fractures | | | \checkmark | Risk ratios and rates estimated from numbers of events. UTI and mycotic genital infections not reported. |
| | Kidney disease progression (≥50%) | \checkmark | | | |
| | Any death, CV death; CV death/HHF | | \checkmark | \checkmark | Any death: calculated indirectly rom CV and non-CV death |
| | Non-CV death | \checkmark | | | |
| MPEROR- EDUCED | AKI, amputation, ketoacidosis | √ | ~ | \checkmark | AKI: provided as defined by MedDRA Preferred Term for AKI (serious and non-serious; unadjudicated). Amputation: Risk ratios estimated from numbers of events. Ketoacidosis: zero events occurred in either treatment arm. |
| | UTI, mycotic genital infections, hypoglycaemia, fractures | | | \checkmark | Risk ratios and rates estimated from numbers of events. UTI and serious UTI reported separately. Genital infections presented overall. |
| | Kidney disease progression (≥50%) | \checkmark | | | |
| | Any death, CV death; CV death/HHF | | \checkmark | | CV death/HHF: rates estimated from numbers of events |
| MDEDOD | Non-CV death | \checkmark | | | |
| MPEROR- RESERVED | AKI, amputation, ketoacidosis | \checkmark | \checkmark | \checkmark | AKI: provided as defined by MedDRA Preferred Term for AKI (serious and non-serious; unadjudicated). Amputation & ketoacidosis: Rates & risk ratios estimated from numbers of events. |
| | UTI, mycotic genital infections, hypoglycaemia, | | | ✓ | Risk ratios and rates estimated from numbers of events. UTI and serious UTI reported separately. Page 10 |

| Trial | Outcome | Provided after request | Published (required format) | Published (estimated indirectly) | Comment |
|-------------|---|------------------------------|-----------------------------------|--|--|
| | Kidney disease progression (≥50%) | \checkmark | | | Kidney function assessed at randomisation, and then at 1, 4, 12, 24 and 36 months. |
| | Any death; CV death; CV death/HHF | ~ | | | Reney function assessed a function, and tion at 1, 4, 12, 24 and 50 months. |
| | Non-CV death | | | \checkmark | Calculated indirectly from provided any death & CV death data. |
| DELIVER | AKI, amputation, ketoacidosis | \checkmark | | | AKI: defined by MedDRA Preferred Term for AKI (serious and non-serious; unadjudicated). |
| | UTI, mycotic genital infections, hypoglycaemia, | | | \checkmark | Risk ratios and rates estimated from numbers of events. UTI: includes serious adverse events only. |
| | fractures | | | v | Fracture and mycotic genital infections not reported. |
| | Kidney disease progression (≥50%) | NA | NA | NA | |
| | Any death, CV death; CV death/HHF | | \checkmark | | CV death/HHF: Number of events & rates estimated. Used analyses excluding urgent HF visits. |
| | Non-CV death | | | \checkmark | Calculated indirectly from any death & CV death data. |
| SOLOIST-WHF | AKI, amputation, ketoacidosis | | \checkmark | \checkmark | Rates & risk ratios estimated from numbers of events. AKI: defined by MedDRA Preferred Term for AKI (treatment-emergent, serious and non-serious; unadjudicated). |
| | UTI, mycotic genital infections, hypoglycaemia, fractures | | | \checkmark | Risk ratios and rates estimated from numbers of events. Serious UTI not reported. Mycotic genital infections: results for male and female infections combined by inverse-variance meta-analysis. |
| | Kidney disease progression (≥50%) | \checkmark | | | |
| | Kidney failure | | \checkmark | | |
| | Any death, CV death; CV death/HHF | | \checkmark | | |
| CREDENCE | Non-CV death | | | \checkmark | Calculated indirectly from any death & CV death data. |
| | AKI, amputation, ketoacidosis | | \checkmark | | AKI: defined by MedDRA Preferred Term for AKI (serious and non-serious; unadjudicated). |
| | UTI, mycotic genital infections, hypoglycaemia, fractures | | | \checkmark | Risk ratios and rates estimated from numbers of events. Serious UTI not reported. Mycotic genital infections: results for male and female infections combined by inverse-variance meta-analysis. Hypoglycaemia not limited to serious. |
| | Kidney disease progression (≥50%) | | \checkmark | | nypogiyeachila not inined to schous. |
| | Kidney failure | NA | NA | NA | |
| | Any death, CV death; CV death/HHF | | | ✓ | CV death/HHF: Rates estimated from numbers of events. |
| CODED | Non-CV death | | | \checkmark | Rates & risk ratio estimated from numbers of events. |
| SCORED | AKI, amputation, ketoacidosis | | | \checkmark | AKI: event numbers estimated; defined by narrow SMQ for <i>acute renal failure</i> (serious and non-serious unadjudicated). Amputation & ketoacidosis: rates & risk ratios estimated from numbers of events. |
| | UTI, mycotic genital infections, hypoglycaemia, fractures | | | \checkmark | Risk ratios and rates estimated from numbers of events. Serious UTI not reported. |
| | Kidney disease progression (≥50%) | | \checkmark | | |
| | Kidney failure | | \checkmark | | |
| | Any death, CV death; CV death/HHF | | \checkmark | | |
| DAPA-CKD | Non-CV death | | | ~ | Calculated indirectly from any death & CV death data. |
| | AKI, amputation, ketoacidosis | | \checkmark | | AKI: ascertained from outcome "abrupt decline in kidney function" (defined as a doubling of creatinine compared with most recent results; adjudicated). |
| | UTI, mycotic genital infections, hypoglycaemia, fractures | | | \checkmark | Risk ratios and rates estimated from numbers of events. UTI and mycotic genital infections: includes serious adverse events only. |
| | Kidney disease progression (≥50%) | \checkmark | | | All data were previously unpublished and provided directly. |
| | Kidney failure | \checkmark | | | All data were previously unpublished and provided directly. |
| | Any death; CV death; CV death/HHF | \checkmark | | | All data were previously unpublished and provided directly. |
| | Non-CV death | \checkmark | | | All data were previously unpublished and provided directly. |
| EMPA-KIDNEY | AKI, amputation, ketoacidosis | \checkmark | | | All data were previously unpublished and provided directly. AKI: adjudicated serious AKI based on standard definition of Serious Adverse Event. |
| | UTI, mycotic genital infections, hypoglycaemia, fractures | ~ | | | All data were previously unpublished and provided directly. Risk ratios and rates estimated from numbers of events. UTI and mycotic genital infections: includes serious adverse events only. |

Rates estimated as events per 1000 patient-years. Serious UTI includes events defined as serious as per ICH GCP criteria or events defined as complicated in primary trial publications. Kidney failure outcome applies only to CKD trials. Abbreviations: AKI = acute kidney injury; CV = cardiovascular; HHF = hospitalisation for heart failure; MedDRA = Medical Dictionary for Regulatory Activities; NA = not available from SOLOIST-WHF as data not collected; SMQ = Standardised MedDRA Query; UTI = urinary tract infection.

| Patient group | | | Female sex, | RAS inhibitor, N (%) | | | |
|------------------------------------|-------|-------------------------|-------------|----------------------|--------------------|--|--|
| Trial acronym | Ν | Mean (SD) age, years* | N (%) | ACE inhibitor | ARB | | |
| Type 2 diabetes at high ASCVD risk | | | | | | | |
| DECLARE-TIMI 58 | 17160 | 63.9 (6.8)* | 6422 (37.4) | 13950 (| (81.3)† | | |
| CANVAS Program | 10142 | 63.3 (8.3) | 3633 (35.8) | 8116 (8 | 80.0)† | | |
| VERTIS CV | 8246 | 64.4 (8.1) | 2477 (30.0) | 6686 (8 | 81.1) † | | |
| EMPA-REG OUTCOME | 7020 | 63.1 (8.7) | 2004 (28.5) | 5666 (8 | 80.7) † | | |
| Heart failure | | | | | | | |
| DAPA-HF | 4744 | 66.3 (10.9) | 1109 (23.4) | 2661 (56.0) | 1307 (27.6) | | |
| EMPEROR-REDUCED | 3730 | 66.8 (11.0) | 893 (23.9) | 1703 (45.7) | 908 (24.3) | | |
| EMPEROR-PRESERVED | 5988 | 71.8 (9.5) | 2676 (44.7) | 2409 (40.2) | 2316 (38.7) | | |
| DELIVER | 6263 | 71.6 (9.6) | 2747 (43.9) | 2295 (36.6) | 2272 (36.3) | | |
| SOLOIST-WHF | 1222 | 69.7 (9.3) [§] | 412 (33.7) | 495 (40.5) | 515 (42.1) | | |
| Chronic kidney disease | | | | | | | |
| CREDENCE | 4401 | 63.0 (9.2) | 1494 (33.9) | 4395 (9 | 99.9) [†] | | |
| SCORED | 10584 | 68.7 (8.1) [§] | 4754 (44.9) | 4048 (38.2) | 5181 (49.0) | | |
| DAPA-CKD | 4304 | 61.9 (12.1) | 1425 (33.1) | 1354 (31.5) | 2870 (66.7) | | |
| EMPA-KIDNEY | 6609 | 63.9 (13.9) | 2192 (33.2) | 2211 (33.5) | 3411 (51.6) | | |

Webtable 3: Additional baseline characteristics of participants in 13 included trials

*Mean (SD) age calculated for overall cohort where reported only by treatment arm. [†]Not presented separately. [§]Mean (SD) estimated from median (IQR) reported by treatment arm. RAS = renin angiotensin system; ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker.

Webtable 4: Risk of bias assessments

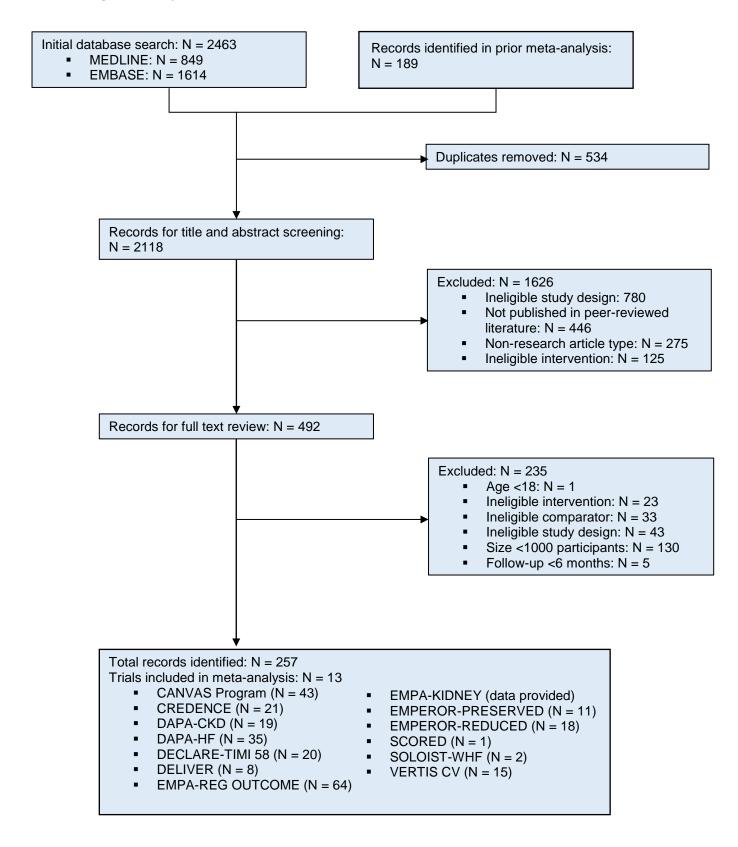
| Webtable 4: Risk | of bias assessmer | nts | | opistion process Derive | ons from the notion | us une data | rement of the one Selection | of the suit |
|-----------------------|-------------------|------------|------|----------------------------|---------------------|--------------|--------------------------------|--------------|
| Study ID | Intervention | Comparator | Rand | omist Deviati | ons from the nior | outcome data | rent Selection rep | not the suit |
| DECLARE-TIMI 58 | Dapagliflozin | Placebo | + | + | + | + | + | |
| CANVAS Program | Canagliflozin | Placebo | + | + | + | + | + | |
| VERTIS CV | Ertugliflozin | Placebo | + | + | + | + | + | |
| EMPA-REG OUTCOME | Empagliflozin | Placebo | + | + | + | + | + | |
| DAPA-HF | Dapagliflozin | Placebo | + | + | + | + | + | |
| DELIVER | Dapagliflozin | Placebo | + | + | + | + | + | |
| EMPEROR- REDUCED | Empagliflozin | Placebo | + | + | + | + | + | |
| EMPEROR- PRESERVED | Empagliflozin | Placebo | + | + | + | + | + | |
| CREDENCE | Canagliflozin | Placebo | + | + | + | + | + | |
| SOLOIST-WHF | Sotagliflozin | Placebo | + | + | + | + | + | |
| SCORED | Sotagliflozin | Placebo | + | + | + | + | + | |
| DAPA-CKD | Dapagliflozin | Placebo | + | + | + | + | + | |
| EMPA-KIDNEY | Empagliflozin | Placebo | + | + | + | + | + | |

Risk of bias of included trials as assessed using Version 2 of the Cochrane Risk-of-Bias tool for randomised trials (ROB2).

Key:

| + | Low risk of bias |
|---|-------------------|
| ! | Some concerns |
| - | High risk of bias |

Webfigure 1: Study selection



Multiple records were identified for many of the included trials. The breakdown of the 257 identified records by trial is listed in the final stage of the chart.

Webfigure 2: Effect of SGLT2 inhibition on KIDNEY FAILURE, by diabetes status (CKD trials only)

| N baseline e | Mean GFR | Events/pa | articipants | Rate pe patient | | | Relative risk | Trend across trials sorted |
|-----------------------|-------------|-----------|-------------|--------------------|----|-------------------------------|---------------------------|-------------------------------|
| (mL/min/1.73n | | SGLT2i | Placebo | SGLT2i | | | (95% CI) | by eGFR |
| Diabetes | | | | | | | | |
| CREDENCE | 56 | 116/2202 | 165/2199 | 20 | 29 | | 0.68 (0.54, 0.86) | |
| SCORED | 44 | NA/NA | NA/NA | | | | | |
| DAPA-CKD | 44 | 77/1455 | 109/1451 | 26 | 37 | | 0.69 (0.51, 0.92) | p=0.48 |
| EMPA-KIDNEY | 36 | 74/1525 | 116/1515 | 24 | 39 | | 0.59 (0.44, 0.79) | |
| Subtotal: DIABETES | 47 | 267/5182 | 390/5165 | | | \langle | 0.66 (0.56, 0.77) | |
| No diabetes | | | | | | | | |
| DAPA-CKD | 42 | 32/697 | 52/701 | 24 | 39 | ←■───── | 0.56 (0.36, 0.87) | |
| EMPA-KIDNEY | 39 | 83/1779 | 105/1790 | 25 | 31 | | - 0.80 (0.60, 1.07) | p=0.19 |
| Subtotal: NO DIABETES | 40 | 115/2476 | 157/2491 | | | | 0.72 (0.56, 0.91) | |
| TOTAL: OVERALL | 45 | 382/7658 | 547/7656 | | | • | 0.67 (0.59, 0.77) | |
| | | | | | | 0.5 0.75 1 SGLT2i better P | 1.25 1.5 lacebo better | |

Heterogeneity by diabetes status: p=0.54

Kidney failure defined as composite of sustained eGFR<15 mL/min/1.73m² (or eGFR <10 mL/min/1.73m² in EMPA-KIDNEY), maintenance dialysis, or kidney transplantation. Data for kidney failure not available for SCORED. CI = confidence interval. eGFR = estimated glomerular filtration rate. SGLT2i = sodium-glucose co-transporter-2 inhibitor.

Webfigure 3: Effect of SGLT2 inhibitors on KIDNEY DISEASE outcomes, by diabetes status and uACR

| | | | KIDN | | ISEAS | E PROGRESSION | | | | A | | NET INJU | Rĭ | |
|-----------------------|--|-------------------------------|------------|-------|------------------------------|---|---------------------------|-----------|--|-------|-------------------------------------|---|--------------------------------|---------------------|
| baseline uAC | R | nber of events/ cipants | | patie | per 10 ent yea 2i Plac | rs | Relative risk (95% Cl) | р | Number of events/ articipants | patie | per 1000 ent years 2i Placebo | | | ive risk 95% CI) |
| Diabetes | | | | | | | | | | | | | | |
| CANVAS Program 1 | 2 | 80/5795 | 81/4347 | 3.6 | 5.8 | — — —————————————————————————————————— | 0.61 (0.45, 0.83) | 30/5790 | 28/4344 | 1.6 | 2.5 — | | 0.66 (0.3 | 9, 1.11) |
| DECLARE-TIMI 58 1 | 3 | 56/8582 | 102/8578 | 1.6 | 3.0 | | 0.55 (0.39, 0.76) | 125/8574 | 175/8569 | 3.5 | 4.9 | - B - | 0.69 (0.5 | 5, 0.87) |
| EMPA-REG OUTCOME 1 | 8 | 51/4645 | 47/2323 | 4.0 | 7.6 | ∎ ∔ | 0.51 (0.35, 0.76) | 45/4687 | 37/2333 | 2.5 | 6.2 | - | 0.41 (0.2 | 27, 0.63) |
| VERTIS CV 1 | 9 | 49/5499 | 32/2747 | 2.6 | 3.4 | | 0.76 (0.49, 1.19) | 42/5493 | 22/2745 | 2.5 | 2.7 | | → 0.95 (0.5 | 7, 1.59) |
| EMPEROR-PRESERVED 3 | 0 3 | 38/1466 | 44/1472 | 15 | 18 | | 0.82 (0.53, 1.27) | 60/1466 | 84/1472 | 20 | 28 - | | 0.69 (0.5 | 0, 0.97) |
| EMPEROR-REDUCED 3 | 5 | 13/927 | 23/929 | 13 | 24 | _ | 0.52 (0.26, 1.03) | 26/927 | 33/929 | 21 | 27 — | | 0.77 (0.4 | 6, 1.28) |
| SCORED 7 | 4 : | 37/5292 | 52/5292 | 5.0 | 7.0 | | 0.71 (0.46, 1.08) | 116/5291 | 111/5286 | 16 | 16 | | - 1.04 (0.8 | 31, 1.35) |
| EMPA-KIDNEY 26 | 3 1 | 08/1525 | 175/1515 | 36 | 59 | — — — | 0.55 (0.44, 0.71) | 73/1525 | 81/1515 | 24 | 27 | | 0.88 (0.6 | 4, 1.20) |
| CREDENCE 92 | 7 1 | 53/2202 | 230/2199 | 27 | 41 | #∎ | 0.64 (0.52, 0.79) | 86/2200 | 98/2197 | 17 | 20 | | 0.85 (0.6 | 4, 1.13) |
| DAPA-CKD 101 | 7 1 | 03/1455 | 173/1451 | 35 | 60 | ∎ | 0.57 (0.45, 0.73) | 48/1455 | 69/1451 | 15 | 22 — | | 0.66 (0.4 | 6, 0.96) |
| DAPA-HF | | 18/1075 | 24/1064 | 12 | 16 | | 0.73 (0.39, 1.34) | 31/1073 | 39/1063 | 19 | 24 - | | 0.79 (0.5 | 0, 1.25) |
| SOLOIST-WHF | | NA/NA | NA/NA | | | | | 25/605 | 27/611 | 55 | 59 | | → 0.94 (0.5 | 5, 1.59) |
| DELIVER | ; | 33/1578 | 37/1572 | 9.5 | 11 | ➡ | 0.87 (0.54, 1.39) | 59/1578 | 52/1572 | 17 | 15 | | → 1.13 (0.7 | 8, 1.63) |
| Subtotal: DIABETES | 73 | 9/40041 | 1020/33489 | | | \diamond | 0.62 (0.56, 0.68) | 766/40664 | 856/34087 | | | \diamond | 0.79 (0.7 | 2, 0.88) |
| No diabetes | | | | | | | | | | | | | | |
| EMPEROR-REDUCED 1 | 5 | 5/936 | 10/938 | 5.2 | 10 | ← ■ | - 0.50 (0.17, 1.48) | 20/936 | 34/938 | 16 | 28 | | 0.56 (0.3 | 2, 0.98) |
| EMPEROR-PRESERVED 1 | 6 | 12/1531 | 18/1519 | 4.5 | 6.9 | - | 0.68 (0.33, 1.40) | 37/1531 | 47/1519 | 12 | 15 · | | 0.80 (0.5 | 2, 1.23) |
| EMPA-KIDNEY 38 | 0 1 | 19/1779 | 157/1790 | 35 | 47 | — ₩ — | 0.74 (0.59, 0.95) | 34/1779 | 54/1790 | 10 | 16 — | | 0.63 (0.4 | 1, 0.97) |
| DAPA-CKD 86 | 1 | 39/697 | 70/701 | 29 | 53 | | 0.51 (0.34, 0.75) | 16/697 | 21/701 | 11 | 15 — | | - 0.75 (0.3 | 9, 1.43) |
| DAPA-HF | | 10/1298 | 15/1307 | 5.0 | 8.0 | | - 0.67 (0.30, 1.49) | 18/1295 | 30/1305 | 9.9 | 16 | | 0.60 (0.3 | 4, 1.08) |
| DELIVER | | 17/1551 | 17/1557 | 5.0 | 4.9 | | > 1.01 (0.51, 1.97) | 30/1551 | 47/1558 | 8.8 | 14 — | - | 0.64 (0.4 | 1, 1.02) |
| Subtotal: NO DIABETES | 2 | 02/7792 | 287/7812 | | | \diamond | 0.69 (0.57, 0.82) | 155/7789 | 233/7811 | | | $\dot{\diamond}$ | 0.66 (0.5 | 4, 0.81) |
| TOTAL: OVERALL | 94 | 1/47833 | 1307/41301 | | | • | 0.63 (0.58, 0.69) | 921/48453 | 1089/41898 | | | • | 0.77 (0.7 | 0, 0.84) |
| | | | 1 | | Diabete | | 1.5 cebo better | | | | SGLT2i rend across t Diabo | 5 0.75 1 better Pla trials sorted by etes p=0.05; betes p=0.75; | 1.5 acebo better / uACR: | |
| | Heterogeneity by diabetes status: p=0. | | | | | | | | Heterogeneity by diabetes status: p=0.12 | | | | | |

KIDNEY DISEASE PROGRESSION

ACUTE KIDNEY INJURY

Kidney disease progression: analyses are based upon ≥50% decline in eGFR in all presented trials (see Webtable 1 for outcome definition details). Acute kidney injury definitions for each trial are provided in Webtable 2. Trials that did not report baseline uACR are excluded from the trend test. CI = confidence interval. eGFR = estimated glomerular filtration rate. SGLT2i = sodium-glucose co -transporter-2 inhibitor.

Webfigure 4: Effect of SGLT2 inhibitors on KIDNEY DISEASE outcomes, by diabetes status

| | | | RIDINE | DISEASE PRO | GRESSION | | ACUTE KIDNET INJUKT | | | | |
|------------------------------------|--|-----------|-------------|---------------------|-------------------|-----------|---------------------|------------------|-------------------|--|--|
| | Mean baseline eGFR (mL/min/1.73m²) | Events/pa | articipants | | Relative risk | Events/pa | rticipants | | Relative risk | | |
| | | SGLT2i | Placebo | | (95% CI) | SGLT2i | Placebo | | (95% CI) | | |
| Diabetes | | | | | | | | | | | |
| High atherosclerotic CV risk trial | s 80 | 236/24521 | 262/17995 | _ ≣ | 0.59 (0.49, 0.71) | 242/24544 | 262/17991 | | 0.65 (0.55, 0.78) | | |
| Stable heart failure trials | 61 | 102/5046 | 128/5037 | ÷ | 0.77 (0.59, 1.00) | 176/5044 | 208/5036 | - i | 0.83 (0.68, 1.02) | | |
| Chronic kidney disease trials | 45 | 401/10474 | 630/10457 | i | 0.60 (0.53, 0.68) | 323/10471 | 359/10449 | | 0.88 (0.76, 1.02) | | |
| Subtotal: DIABETES | 67 | 739/40041 | 1020/33489 | \$ | 0.62 (0.56, 0.68) | 766/40664 | 856/34087 | \diamond | 0.79 (0.72, 0.88) | | |
| No diabetes | | | | | | | | | | | |
| Stable heart failure trials | 64 | 44/5316 | 60/5321 | → ∎-∔ | 0.74 (0.50, 1.10) | 105/5313 | 158/5320 | - - | 0.66 (0.52, 0.85) | | |
| Chronic kidney disease trials | 40 | 158/2476 | 227/2491 | - # - | 0.67 (0.55, 0.83) | 50/2476 | 75/2491 | | 0.67 (0.46, 0.95) | | |
| Subtotal: NO DIABETES | 56 | 202/7792 | 287/7812 | \diamond | 0.69 (0.57, 0.82) | 155/7789 | 233/7811 | \diamond | 0.66 (0.54, 0.81) | | |
| TOTAL: OVERALL | 65 | 941/47833 | 1307/41301 | • | 0.63 (0.58, 0.69) | 921/48453 | 1089/41898 | • | 0.77 (0.70, 0.84) | | |
| | | | 0 | .25 0.5 1 2 | 3 4 5 | | 0.25 | 0.5 1 2 | 2 3 4 5 | | |
| | | | | | bo better | | | | ebo better | | |
| | | | Heterog | geneity by diabetes | status: p=0.31 | | Heterogen | eity by diabetes | s status: p=0.12 | | |

KIDNEY DISEASE PROGRESSION

ACUTE KIDNEY INJURY

Kidney disease progression: analyses are based upon a sustained ≥50% decline in eGFR from randomisation, end-stage kidney disease or death from kidney failure in all presented trials (see Webtable 1 for outcome definition details). Acute kidney injury definitions for each trial are provided in Webtable 2. Data from SOLOIST-WHF excluded from the stable heart failure trials group as it included patients with acute decompensated heart failure. CI = confidence interval. eGFR = estimated glomerular filtration rate. SGLT2i = sodium-glucose co-transporter-2 inhibitor.

Webfigure 5: Effect of SGLT2 inhibitors on KIDNEY DISEASE PROGRESSION, by different glomerular diseases

| | Average baseline eGFR | Events/pa | rticipants | Rate per patient | | | Relative risk |
|---------------------|--------------------------|-----------|------------|------------------|---------|--------|-------------------------|
| | (mL/min/1.73m²) | SGLT2i | Placebo | SGLT2i | Placebo | | (95% CI) |
| IgA nephropathy | | | | | | | |
| DAPA-CKD | 44 | 5/137 | 20/133 | 21 | 88 | ← | 0.24 (0.09, 0.65) |
| EMPA-KIDNEY | 43 | 32/413 | 48/404 | 43 | 65 | | 0.56 (0.36, 0.89) |
| Subtotal | 43 | 37/550 | 68/537 | | | \sim | 0.49 (0.32, 0.74) |
| Focal segmental glo | merulosclerosis | | | | | | |
| DAPA-CKD | 42 | 4/53 | 7/62 | 37 | 57 | ← ■ | → 0.52 (0.15, 1.83) |
| EMPA-KIDNEY | 41 | 9/98 | 8/97 | 46 | 43 | | → 1.24 (0.47, 3.25) |
| Subtotal | 41 | 13/151 | 15/159 | | | | = 0.89 (0.42, 1.92) |
| Other glomeronephr | itis | | | | | | |
| DAPA-CKD | 43 | 12/153 | 19/157 | 33 | 50 | | 0.65 (0.33, 1.29) |
| EMPA-KIDNEY | 42 | 28/342 | 39/315 | 44 | 68 | | 0.70 (0.43, 1.15) |
| Subtotal | 42 | 40/495 | 58/472 | | | \sim | 0.68 (0.46, 1.02) |
| ANY GLOMERULAR | DISEASE | | | | | | |
| DAPA-CKD | 43 | 21/343 | 46/352 | 33 | 70 | | 0.43 (0.26, 0.72) |
| EMPA-KIDNEY | 42 | 69/853 | 95/816 | 44 | 64 | | 0.68 (0.50, 0.93) |
| TOTAL | 42 | 90/1196 | 141/1168 | | | \sim | 0.60 (0.46, 0.78) |
| | | | | | | | ⊐ 1.5 cebo better |

Heterogeneity across three subtypes of glomerular disease: p=0.30

Based on investigator-reported primary kidney diagnoses. CI = confidence interval. eGFR = estimated glomerular filtration rate. SGLT2i = sodium-glucose co-transporter-2 inhibitor.

Webfigure 6: Effect of SGLT2 inhibition on CARDIOVASCULAR DEATH or HOSPITALISATION FOR HEART FAILURE, by diabetes status

| Average baseline eGFR (mL/min/1.73m²) | | Events/p | Rate pe patient | er 1000 t years | | Relative risk | Trend across trials sorted | | |
|---|----|---------------|--------------------|--------------------|---------|----------------------|-------------------------------|-------------------|---------|
| | | SGLT2i Placeb | | SGLT2i | Placebo | (95% CI) | | | by eGFR |
| Diabetes | | | | | | | | | |
| DECLARE-TIMI 58 | 85 | 417/8582 | 496/8578 | 12 | 15 | | | 0.83 (0.73, 0.95) | |
| CANVAS Program | 77 | 364/5795 | 288/4347 | 16 | 21 | | | 0.78 (0.67, 0.91) | |
| VERTIS CV | 76 | 444/5499 | 250/2747 | 23 | 27 | | + | 0.88 (0.75, 1.03) | |
| EMPA-REG OUTCOME | 74 | 265/4687 | 198/2333 | 20 | 30 | — — — | | 0.66 (0.55, 0.79) | |
| DAPA-HF | 63 | 213/1075 | 268/1064 | 144 | 191 | # | | 0.75 (0.63, 0.90) | |
| EMPEROR-REDUCED | 61 | 200/927 | 265/929 | 177 | 246 | | | 0.72 (0.60, 0.87) | |
| EMPEROR-PRESERVED | 60 | 239/1466 | 291/1472 | 83 | 102 | — İ | | 0.79 (0.67, 0.94) | p=0.22 |
| DELIVER | 60 | 271/1578 | 330/1572 | 83 | 104 | | | 0.80 (0.68, 0.93) | |
| CREDENCE | 56 | 179/2202 | 253/2199 | 32 | 45 | | | 0.69 (0.57, 0.83) | |
| SOLOIST-WHF | 51 | NA/608 | NA/614 | - | - | — — | | 0.71 (0.56, 0.89) | |
| SCORED | 44 | 283/5292 | 357/5292 | 41 | 52 | — — | | 0.77 (0.66, 0.91) | |
| DAPA-CKD | 44 | 85/1455 | 119/1451 | 27 | 38 - | | | 0.70 (0.53, 0.92) | |
| EMPA-KIDNEY | 36 | 96/1525 | 118/1515 | 32 | 40 | i | ÷ | 0.78 (0.60, 1.03) | |
| Subtotal: DIABETES | 67 | 3056/40691 | 3233/34113 | | | \diamond | | 0.77 (0.73, 0.81) | |
| No diabetes | | | | | | | | | |
| DAPA-HF | 68 | 169/1298 | 227/1307 | 91 | 124 | — — | | 0.73 (0.60, 0.89) | |
| EMPEROR-REDUCED | 63 | 161/936 | 197/938 | 139 | 176 | | | 0.78 (0.64, 0.97) | |
| DELIVER | 63 | 204/1551 | 246/1558 | 62 | 76 | | | 0.82 (0.68, 0.99) | p=0.28 |
| EMPEROR-PRESERVED | 62 | 176/1531 | 220/1519 | 56 | 72 | # | | 0.78 (0.64, 0.95) | p=0.20 |
| DAPA-CKD | 42 | 15/697 | 19/701 | 11 | 13 🗲 | | \rightarrow | 0.79 (0.40, 1.55) | |
| EMPA-KIDNEY | 39 | 35/1779 | 34/1790 | 10 | 9.9 | | ■ → | 1.04 (0.65, 1.67) | |
| Subtotal: NO DIABETES | 56 | 760/7792 | 943/7813 | | | \diamond | | 0.79 (0.72, 0.87) | |
| TOTAL: OVERALL | 65 | 3816/48483 | 4176/41926 | | · | • | | 0.77 (0.74, 0.81) | |
| | | | | | 0.5 | 0.10 | 1 1.25 1.5 | | |
| | | | | | SC | GLT2i better | Placebo bett | er | |

Heterogeneity by diabetes status: p=0.67

Excludes urgent heart failure visits. EMPA-REG OUTCOME cardiovascular death definition excluded stroke. CI = confidence interval. eGFR = estimated glomerular filtration rate. SGLT2i = sodium-glucose co-transporter-2 inhibitor.

Webfigure 7: Effect of SGLT2 inhibitors on CARDIOVASCULAR and NON-CARDIOVASCULAR DEATH, by diabetes status

| | | | | | | | | | - | | | | | |
|-----------------------|------|------------|-------------|------------------|--------------------|---|---------------------|------------|-------------|------------------|-----------|---|---------------|-------------------|
| baseline e | | Events/pa | articipants | Rate per patient | er 1000 t years | | Relative risk | Events/pa | articipants | Rate per patient | | | | Relative risk |
| (mL/min/1.73 | 3m²) | SGLT2i | Placebo | SGLT2i | Placebo | | (95% CI) | SGLT2i | Placebo | SGLT2i | Placebo | | | (95% CI) |
| Diabetes | | | | | | . | | | | | | | | |
| DECLARE-TIMI 58 | 85 | 245/8582 | 249/8578 | 6.8 | 6.9 | - # - | • 0.98 (0.82, 1.17) | 211/8582 | 238/8578 | 5.9 | 6.6 | | - | 0.88 (0.73, 1.06) |
| CANVAS Program | 77 | 268/5795 | 185/4347 | 12 | 13 | ₩ | 0.87 (0.72, 1.06) | 132/5795 | 96/4347 | 5.7 | 6.7 | | _ | 0.87 (0.67, 1.13) |
| VERTIS CV | 76 | 341/5499 | 184/2747 | 18 | 19 | - | 0.92 (0.77, 1.11) | 132/5493 | 70/2745 | 6 | 7 | | | 0.94 (0.71, 1.25) |
| EMPA-REG OUTCOME | 74 | 172/4687 | 137/2333 | 12 | 20 | _∎_ | 0.62 (0.49, 0.77) | 97/4687 | 57/2333 | 7 | 8.4 | | | 0.85 (0.61, 1.17) |
| DAPA-HF | 63 | 121/1075 | 148/1064 | 77 | 97 | | 0.79 (0.63, 1.01) | 22/1075 | 30/1064 | 14 | 20 | | | 0.73 (0.42, 1.25) |
| EMPEROR-REDUCED | 61 | 104/927 | 113/929 | 84 | 91 | | - 0.92 (0.71, 1.20) | 38/927 | 36/929 | 31 | 29 | | ↦ | 1.03 (0.65, 1.62) |
| EMPEROR-PRESERVED | 60 | 120/1466 | 123/1472 | 39 | 39 | - # | - 0.99 (0.77, 1.27) | 114/1466 | 103/1472 | 37 | 33 | - | - | 1.12 (0.86, 1.47) |
| DELIVER | 60 | 123/1578 | 143/1572 | 35 | 41 | - ∔ | 0.85 (0.67, 1.08) | 143/1578 | 147/1572 | 41 | 42 | | - | 0.97 (0.78, 1.21) |
| CREDENCE | 56 | 110/2202 | 140/2199 | 19 | 24 | B | 0.78 (0.61, 1.00) | 58/2202 | 61/2199 | 10 | 11 | | | 0.94 (0.66, 1.35) |
| SOLOIST-WHF | 51 | 51/608 | 58/614 | 106 | 125 | # | - 0.84 (0.58, 1.22) | 14/608 | 18/614 | 29 | 38 | | \rightarrow | 0.79 (0.39, 1.57) |
| SCORED | 44 | 155/5292 | 170/5292 | 22 | 24 | - im | 0.90 (0.73, 1.12) | 85/5292 | 67/5292 | 13 | 11 | - | -∎> | 1.20 (0.89, 1.62) |
| DAPA-CKD | 44 | 56/1455 | 66/1451 | 17 | 21 | ė +_ | - 0.85 (0.59, 1.21) | 28/1455 | 47/1451 | 8 | 13 | _ | | 0.59 (0.37, 0.94) |
| EMPA-KIDNEY | 36 | 42/1525 | 58/1515 | 14 | 19 | ∎∔∔ | 0.71 (0.48, 1.06) | 59/1525 | 65/1515 | 19 | 21 | | | 0.87 (0.61, 1.25) |
| Subtotal: DIABETES | 67 | 1908/40691 | 1774/34113 | | | \diamond | 0.86 (0.80, 0.92) | 1133/40685 | 1035/34111 | | | \diamond | | 0.93 (0.85, 1.01) |
| No diabetes | | | | | | | | | | | | | | |
| DAPA-HF | 68 | 106/1298 | 125/1307 | 55 | 65 | - # + | 0.85 (0.66, 1.10) | 27/1298 | 26/1307 | 14 | 13 | | ↦ | 1.05 (0.61, 1.78) |
| EMPEROR-REDUCED | 63 | 83/936 | 89/938 | 67 | 72 | i | - 0.92 (0.68, 1.24) | 24/936 | 28/938 | 19 | 23 | | | 0.78 (0.45, 1.35) |
| DELIVER | 63 | 108/1551 | 117/1558 | 31 | 34 | i= | - 0.93 (0.72, 1.21) | 123/1551 | 117/1558 | 36 | 34 | | | 1.06 (0.83, 1.35) |
| EMPEROR-PRESERVED | 62 | 99/1531 | 121/1519 | 30 | 37 | - | 0.82 (0.63, 1.07) | 89/1531 | 80/1519 | 27 | 25 | _ | ∎→ | 1.13 (0.83, 1.53) |
| DAPA-CKD | 42 | 9/697 | 14/701 | 6.0 | 10 | | — 0.65 (0.28, 1.49) | 8/697 | 19/701 | 4.8 | 11 ← | _ | | 0.42 (0.19, 0.96) |
| EMPA-KIDNEY | 39 | 17/1779 | 11/1790 | 5.0 | 3.2 | | → 1.54 (0.72, 3.28) | 30/1779 | 33/1790 | 8.8 | 9.6 | | \rightarrow | 0.92 (0.56, 1.50) |
| Subtotal: NO DIABETES | 56 | 422/7792 | 477/7813 | | | \diamond | 0.88 (0.78, 1.01) | 301/7792 | 303/7813 | | | < | > | 1.00 (0.85, 1.17) |
| TOTAL: OVERALL | 65 | 2330/48483 | 2251/41926 | | | • | 0.86 (0.81, 0.92) | 1434/48477 | 1338/41924 | | | • | | 0.94 (0.88, 1.02) |
| | | | | | 0.25 | i 0.5 0.75 1 | 1.5 | | | | 0.25 | 0.5 0.75 1 | 1. | 5 |
| | | | | | | | Placebo better | | | | | SGLT2i better | | ebo better |
| | | | | | Trend | across trials sorted b Diabetes p=0.44; No diabetes p=0.74; | | | | | | cross trials sorted Diabetes p=0.52 No diabetes p=0.6 | 2; | FR: |
| | | | | ł | leteroge | neity by diabetes sta | atus: p=0.68 | | | н | eterogene | eity by diabetes s | status | : p=0.43 |

Webtable 2 provides details of when relative risks were estimated from numbers of events. CI = confidence interval. eGFR = estimated glomerular filtration rate. SGLT2i = sodium-glucose co-transporter-2 inhibitor.

Webfigure 8: Effect of SGLT2 inhibitors on KETOACIDOSIS, by diabetes status

| baseline | | Events/pa | rticipants | Rate per patient | | | Relative risk | Trend across trials sorted |
|-----------------------|----|----------------|------------|------------------|---------|-------------|-----------------------------|-------------------------------|
| (mL/min/1.73m²) | | SGLT2i Placebo | | SGLT2i | Placebo | | (95% CI) | by eGFR |
| Diabetes | | | | | | | | |
| DECLARE-TIMI 58 | 85 | 27/8574 | 12/8569 | 0.7 | 0.3 | | 2.18 (1.10, 4.30) | |
| CANVAS Program | 77 | 13/5795 | 5/4347 | 0.6 | 0.3 | _ | 2.33 (0.76, 7.17) | |
| VERTIS CV | 76 | 19/5493 | 2/2745 | 1.2 | 0.2 | | 4.75 (1.11, 20.37) | |
| EMPA-REG OUTCOME | 74 | 4/4687 | 1/2333 | 0.3 | 0.1 ← | | → 1.99 (0.22, 17.80) | |
| DAPA-HF | 63 | 3/1073 | 0/1063 | 1.9 | 0.0 - | | > 5.94 (0.30, 118.53) | |
| EMPEROR-REDUCED | 61 | 0/927 | 0/926 | 0.0 | 0.0 | | | |
| EMPEROR-PRESERVED | 60 | 4/1465 | 5/1471 | 1.2 | 1.5 ← | | 0.80 (0.22, 2.99) | p=0.69 |
| DELIVER | 60 | 2/1578 | 0/1572 | 0.6 | 0.0 ← | | > 3.98 (0.18, 88.30) | |
| CREDENCE | 56 | 11/2200 | 1/2197 | 2.2 | 0.2 | | → 10.80 (1.39, 83.65) | |
| SOLOIST-WHF | 51 | 2/605 | 4/611 | 4.4 | 8.7 ← | | 0.50 (0.09, 2.75) | |
| SCORED | 44 | 30/5291 | 14/5286 | 4.3 | 2.0 | | 2.14 (1.14, 4.03) | |
| DAPA-CKD | 44 | 0/1453 | 2/1450 | 0.0 | 0.6 ← | | → 0.25 (0.01, 5.53) | |
| EMPA-KIDNEY | 36 | 5/1525 | 1/1515 | 1.6 | 0.3 | | 5.27 (0.61, 45.22) | |
| Subtotal: DIABETES | 67 | 120/40666 | 47/34085 | | | | 2.12 (1.49, 3.04) | |
| No diabetes | | | | | | | | |
| DAPA-HF | 68 | 0/1295 | 0/1305 | | | | | |
| EMPEROR-REDUCED | 63 | 0/936 | 0/937 | | | | | |
| DELIVER | 63 | 0/1551 | 0/1558 | | | | | |
| EMPEROR-PRESERVED | 62 | 0/1531 | 0/1518 | | | | | |
| DAPA-CKD | 42 | 0/696 | 0/699 | | | | | |
| EMPA-KIDNEY | 39 | 1/1779 | 0/1790 | | | | | |
| Subtotal: NO DIABETES | 56 | 1/15592 | | | | | | |
| | | | | | 0.25 | 0.5 | 1 2 3 4 | |
| | | | | | | .T2i better | Placebo better | |

Webtable 2 provides details of when relative risks were estimated from numbers of events. CI = confidence interval. eGFR = estimated glomerular filtration rate. SGLT2i = sodium-glucose co-transporter-2 inhibitor.

Webfigure 9: Effect of SGLT2 inhibitors on LOWER LIMB AMPUTATION, by diabetes status

| Average baseline eGFR (mL/min/1.73m²) | | Events/p | articipants | Rate per patient | | | Relative risk | Trend across trials sorted | |
|---|----|-----------|-------------|------------------|-------------|--------------|---------------|-------------------------------|---------|
| | | SGLT2i | Placebo | SGLT2i | Placebo | | | (95% CI) | by eGFR |
| Diabetes | | | | | | | | | |
| DECLARE-TIMI 58 | 85 | 123/8574 | 113/8569 | 3.4 | 3.1 | - | - | 1.09 (0.84, 1.40) | |
| CANVAS Program | 77 | 140/5790 | 47/4344 | 6.3 | 3.4 | | | 1.97 (1.41, 2.75) | |
| VERTIS CV | 76 | 111/5493 | 45/2745 | 6.7 | 5.5 | - | | 1.23 (0.87, 1.74) | |
| EMPA-REG OUTCOME | 74 | 88/4687 | 43/2333 | 6.5 | 6.5 | | . | 1.00 (0.70, 1.44) | |
| DAPA-HF | 63 | 12/1073 | 9/1063 | 7.5 | 5.6 | | ╡╡᠊ | 1.32 (0.56, 3.16) | |
| EMPEROR-REDUCED | 61 | 12/927 | 9/926 | 9.4 | 7.0 | | ╡╡┱ | 1.33 (0.56, 3.15) | |
| EMPEROR-PRESERVED | 60 | 15/1465 | 21/1471 | 4.7 | 6.5 | | | 0.72 (0.37, 1.39) | p=0.13 |
| DELIVER | 60 | 15/1578 | 21/1572 | 4.3 | 6.1 - | | | 0.70 (0.36, 1.36) | |
| CREDENCE | 56 | 70/2200 | 63/2197 | 12 | 11 | | - | 1.11 (0.79, 1.56) | |
| SOLOIST-WHF | 51 | 4/605 | 1/611 | 8.8 | 2.2 | | \rightarrow | 4.04 (0.45, 36.04) | |
| SCORED | 44 | 32/5291 | 33/5286 | 4.5 | 4.7 | | | 0.97 (0.60, 1.57) | |
| DAPA-CKD | 44 | 35/1453 | 38/1450 | 10 | 11 | | | 0.92 (0.57, 1.46) | |
| EMPA-KIDNEY | 36 | 23/1525 | 17/1515 | 7.6 | 5.6 | | ┼╼─> | 1.30 (0.69, 2.43) | |
| Subtotal: DIABETES | 67 | 680/40661 | 460/34082 | | | | Ś | 1.15 (1.02, 1.30) | |
| No diabetes | | | | | | | | | |
| DAPA-HF | 68 | 1/1295 | 3/1305 | 0.5 | 1.5 ← | | \rightarrow | 0.34 (0.03, 3.23) | |
| EMPEROR-REDUCED | 63 | 1/936 | 1/937 | 0.8 | 0.8 ← | | \rightarrow | 1.00 (0.06, 15.98) | |
| DELIVER | 63 | 4/1551 | 4/1558 | 1.2 | 1.2 — | | \rightarrow | 1.00 (0.25, 3.98) | p=0.23 |
| EMPEROR-PRESERVED | 62 | 1/1531 | 2/1518 | 0.3 | 0.6 ← | | \rightarrow | 0.50 (0.04, 5.46) | p=0.23 |
| DAPA-CKD | 42 | 0/696 | 1/699 | 0.0 | 0.6 ← | | \rightarrow | 0.50 (0.02, 14.94) | |
| EMPA-KIDNEY | 39 | 5/1779 | 2/1790 | 1.5 | 0.6 | | \rightarrow | 2.59 (0.50, 13.36) | |
| Subtotal: NO DIABETES | 56 | 12/7788 | 13/7807 | | | | \rightarrow | 0.98 (0.43, 2.25) | |
| TOTAL: OVERALL | 65 | 692/48449 | 473/41889 | | | | • | 1.15 (1.02, 1.30) | |
| TOTAL: OVERALL (excluding CANVAS)* | 64 | 552/42659 | 426/37545 | | | | ▶ | 1.06 (0.93, 1.21) | |
| (Excluding CANVAS) | | | | | 0.25 | 0.5 0.75 | 1 1.5 2 | ! | |
| | | | | | | GLT2i better | | oo better | |
| | | | | | Heterogenei | ity by diabe | tes status: | p=0.71 | |

Webtable 2 provides details of when relative risks were estimated from numbers of events. *The hypothesis that SGLT2 inhibition might increase the risk of lower limb amputation was first raised by results from the CANVAS trial. The subtotal excluding CANVAS therefore reflects the combined results from the independent set of hypothesis-testing trials. Cl = confidence interval. eGFR = estimated glomerular filtration rate. SGLT2 i sodium-glucose co-transporter-2 inhibitor.

Webfigure 10: Effect of SGLT2 inhibitors on ADDITIONAL SAFETY outcomes

| | Mean baseline eGFR | Events/pa | articipants | | Relative risk |
|-----------------------------------|-----------------------|----------------------|-----------------------|---------------------------------------|--|
| | mL/min/1.73m²) | L/min/1.73m²) SGLT2i | | | (95% CI) |
| Urinary tract infections | | | | | |
| High atherosclerotic CV risk tria | als 80 | 1938/24549 | 975/17994 | | 1.05 (0.97, 1.13) |
| Stable heart failure trials | 61 | 418/7985 | 358/7979 | i i i i i i i i i i i i i i i i i i i | 1.17 (1.02, 1.34) |
| Chronic kidney disease trials | 44 | 936/12944 | 878/12937 | | 1.09 (0.93, 1.27) |
| TOTAL: OVERALL | 65 | 3344/46083 | 2255/39521 | \$ | 1.08 (1.02, 1.15) |
| Serious urinary tract infectior | ns | | | | |
| High atherosclerotic CV risk tria | als 75 | 119/10180 | 63/5078 | | 0.94 (0.69, 1.27) |
| Stable heart failure trials | 61 | 106/7985 | 92/7979 | ∎ | 1.15 (0.87, 1.52) |
| Chronic kidney disease trials | 39 | 81/5453 | 72/5454 | _ | 1.10 (0.80, 1.52) |
| TOTAL: OVERALL | 61 | 306/23618 | 227/18511 | \diamond | 1.07 (0.90, 1.27) |
| Mycotic genital infections | | | | | |
| High atherosclerotic CV risk tria | als 80 | 1258/24549 | 208/17994 | | · - 3.88 (3.32, 4.53) |
| Stable heart failure trials | 61 | 98/4859 | 34/4852 | | 2.87 (1.95, 4.24) |
| Chronic kidney disease trials | 44 | 179/12944 | 59/12937 | | 2.98 (2.22, 3.99) |
| TOTAL: OVERALL | 65 | 1540/42957 | 302/36394 | | 3.57 (3.14, 4.06) |
| Severe hypoglycaemia | | | | | |
| High atherosclerotic CV risk tria | als 80 | 405/18754 | 281/13647 | - | 0.83 (0.71, 0.96) |
| Stable heart failure trials | 62 | 89/10353 | 96/10351 | | 0.93 (0.70, 1.23) |
| Chronic kidney disease trials | 44 | 369/12944 | 400/12937 | | 0.91 (0.79, 1.05) |
| TOTAL: OVERALL | 64 | 872/42656 | 779/37546 | \diamond | 0.89 (0.80, 0.98) |
| Bone fracture | | | | | |
| High atherosclerotic CV risk tria | als 80 | 1151/24549 | 811/17994 | | 1.07 (0.98, 1.17) |
| Stable heart failure trials | 63 | 228/7227 | 218/7220 | - - | 1.04 (0.87, 1.25) |
| Chronic kidney disease trials | 44 | 396/12944 | 377/12937 | + | 1.05 (0.91, 1.21) |
| TOTAL: OVERALL | 65 | 1787/45325 | 1415/38762 | \diamond | 1.07 (0.99, 1.14) |
| 63 44 3 | 3 | 228/7227 96/12944 | 218/7220 377/12937 | | 1.04 (0.87, 1.25) 1.05 (0.91, 1.21) 1.07 (0.99, 1.14) |

Analyses are limited to previously published reports and therefore not all outcomes are available for all trials (see Webtable 2 for detail by outcome and definition of serious urinary tract infections by trial). Data from SOLOIST-WHF included in totals but excluded from the stable heart failure trials group as it included patients with acute decompensated heart failure. There were insufficient cases of Fournier's gangrene to present a reliable estimate of risk (11 events vs 14 events in SGLT2i and placebo arms, respectively). Data extracted from previous meta-analysis (eClinicalMedicine 2021;41:101163), with additional data from DELIVER and EMPA-KIDNEY trials. CI = confidence interval. eGFR = estimated glomerular filtration rate. SGLT2i = sodium-glucose co-transporter-2 inhibitor.

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