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.

WEB METHODS

WEB REFERENCES

WEBTABLES

- Webtable 1: Definition of kidney disease progression by trial
- Webtable 2: Sources of analysis data
- Webtable 3: Risk of bias assessments
- Webtable 4: Additional baseline characteristics of participants in included trials

WEBFIGURES

Webfigure 1: Study selection

Webfigure 2: Effect of SGLT2 inhibition on KIDNEY FAILURE, by diabetes status

- Webfigure 3: Effect of SGLT2 inhibitors on KIDNEY DISEASE, by diabetes status and uACR
- Webfigure 4: Effect of SGLT2 inhibitors on KIDNEY DISEASE outcomes, by diabetes status
- Webfigure 5: Effect of SGLT2 inhibitors on KIDNEY DISEASE PROGRESSION, by different glomerular diseases
- Webfigure 6: Effect of SGLT2 inhibition on CARDIOVASCULAR DEATH or HOSPITALISATION FOR HEART FAILURE, by diabetes status
- Webfigure 7: Effect of SGLT2 inhibitors on CARDIOVASCULAR and NON-CARDIOVASCULAR DEATH, by diabetes status

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

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

Webfigure 10: Effect of SGLT2 inhibitors on ADDITIONAL SAFETY outcomes

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).

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 (excluding crossover trials)
- 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 terms and 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 cat 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.

		Co	mponents &	k definition	s used in this meta-analysis					
Trial	Sustained 250% eGFR decline Kidney replacement therapy Sustained eGFR <15 (or <10) Renal death				Definition of sustained	Definitions used by individual trials in their previous publications				
DECLARE-TIMI 58	~	~	~	~	As confirmed by two tests at the central laboratory ≥4 weeks apart	Sustained \geq 40% eGFR decline to <60 mL/min/1.73 m ² or ESKD (defined as dialysis \geq 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	~	~	Sustained for \geq 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	~	~	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	~	~	Measured at two consecutive scheduled study follow-up visits (≥ 1 month apart), or at last available visit	Sustained ≥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 \geq 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 ≥50% eGFR decline, ESKD (defined as maintenance dialysis ≥90 days or kidney transplantation), a sustained eGFR <10 mL/min/1.73m ² or renal death				

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. The terms 'renal death' and 'renal replacement therapy' have previously been used in trials but are superseded by the terms 'death from kidney failure' and 'kidney replacement therapy' used in this analysis. * 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%)	√ 	,		
	Any death, CV death; CV death/HHF		\checkmark		
0	Non-CV death		\checkmark		
	AKI, amputation, ketoacidosis		\checkmark	\checkmark	Rates estimated from numbers of events. AKI: defined by MedDRA Preferred Term for AKI (serious and non-serious; unadjudicated).
Trial DECLARE- TIMI 58 CANVAS Program VERTIS CV EMPA-REG OUTCOME DAPA-HF EMPEROR- REDUCED	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.
	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.
	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			· · · · · ·
	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.
DAPA-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	√			y
	AKI, amputation, ketoacidosis	\checkmark	\checkmark	\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
EMPEROR-	Non-CV death	\checkmark			
PRESERVED	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. Page 10
	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. Hypoglycaemia includes non-severe hypoglycaemia.

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	· · ·			Ridney function assessed at fandomisation, and then 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	~		•	AKI: defined by MedDRA Preferred Term for AKI (serious and non-serious; unadjudicated).
	UTI, mycotic genital infections, hypoglycaemia,	•			Risk ratios and rates estimated from numbers of events. UTI: includes serious adverse events only.
DELIVER SOLOIST-WHF CREDENCE	fractures			\checkmark	Fracture and mycotic genital infections not reported.
	Kidney disease progression (≥50%)	NA	NA	NA	The due and myothe gental meetions not reported.
	Any death, CV death; CV death/HHF	INA		INA	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-WHE					Rates & risk ratios estimated from numbers of events. AKI: defined by MedDRA Preferred Term for
SOLOIS1-WIII	AKI, amputation, ketoacidosis		\checkmark	\checkmark	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		
	Non-CV death			\checkmark	Calculated indirectly from any death & CV death data.
CREDENCE	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 minica to schous.
	Kidney failure	NA	NA	NA	
	Any death, CV death; CV death/HHF	1471	1171	 ✓	CV death/HHF: Rates estimated from numbers of events.
	Non-CV death			✓	Rates & risk ratio estimated from numbers of events.
SCORED	AKI, amputation, ketoacidosis			~	AKI: event numbers estimated; defined by narrow SMQ for <i>acute renal failure</i> (serious and non-seriou 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.
Trial DELIVER SOLOIST-WHF CREDENCE SCORED DAPA-CKD EMPA-KIDNEY Rates	Kidney disease progression (≥50%)		\checkmark		
SCORED	Kidney failure		· · · · · · · · · · · · · · · · · · ·		
	Any death, CV death; CV death/HHF		 ✓		
	Non-CV death		•	\checkmark	Calculated indirectly from any death & CV death data.
DAPA-CKD	AKI, amputation, ketoacidosis		√		AKI: ascertained from outcome "abrupt decline in kidney function" (defined as a doubling of creatinin
					compared with most recent results; adjudicated).
	UTI, mycotic genital infections, hypoglycaemia,			\checkmark	Risk ratios and rates estimated from numbers of events. UTI and mycotic genital infections: includes
	fractures	,			serious adverse events only.
	Kidney disease progression (≥50%)	<u>√</u>			
	Kidney failure				
	Any death; CV death; CV death/HHF				
EMPA-KIDNEY	Non-CV death				1979 11 11 . 1 . 1 . 1 . 1 . 1 . 1 . 1 . 1
	AKI, amputation, ketoacidosis	\checkmark			AKI: adjudicated serious AKI based on standard definition of Serious Adverse Event.
	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.

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.

Webtable 3: Risk of bias assessments

Webtable 3: Risk	of bias assessmer	nts	/	opiestion process Deviation	ons from the north of the strength of the stre	outcome data	rement of the one Selection	of the sult
Study ID	Intervention	Comparator	Randi	omis. Deviati	on internet	oute Measure Out	ret. come Selection	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:

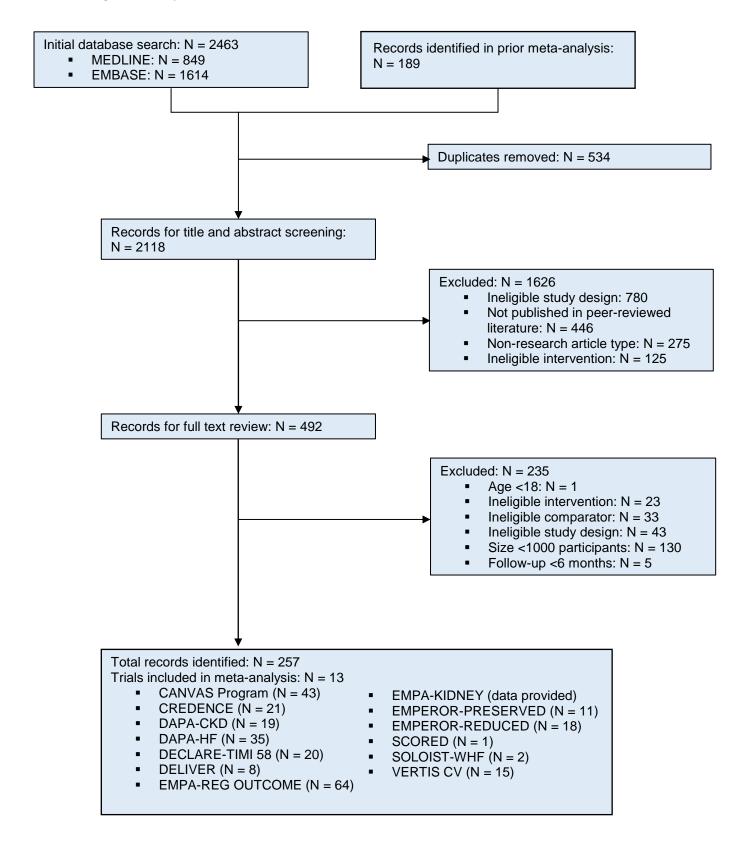
+	Low risk of bias
!	Some concerns
-	High risk of bias

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 (80.0)†	
VERTIS CV	8246	64.4 (8.1)	2477 (30.0)	6686 (81.1) †	
EMPA-REG OUTCOME	7020	63.1 (8.7)	2004 (28.5)	5666 (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 (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 4: Additional baseline characteristics of participants in 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.

Webfigure 1: Study selection



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

-	Mean baseline eGFR (mL/min/1.73m²)		Events/participants)	Relative risk	Trend across trials sorted
(mL/min/1.7			Placebo	SGLT2il	Placeb	0	(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					n = 0.49
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			$\langle \rangle$	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 1.25 1.5	
						SGLT2i better	Placebo 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), chronic 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

Median Number of Number of Rate per 1000 Rate per 1000 baseline uACR Relative risk events/ Relative risk events/ patient years patient years (95% CI) (95% CI) (mg/g) participants participants SGLT2i Placebo SGLT2i Placebo Diabetes 0.66 (0.39, 1.11) **CANVAS** Program 12 80/5795 81/4347 3.6 5.8 0.61 (0.45, 0.83) 30/5790 28/4344 1.6 2.5 13 0.55 (0.39, 0.76) 4.9 0.69 (0.55, 0.87) **DECLARE-TIMI 58** 56/8582 102/8578 1.6 3.0 125/8574 175/8569 3.5 0.51 (0.35, 0.76) 0.41 (0.27, 0.63) EMPA-REG OUTCOME 18 51/4645 47/2323 4.0 7.6 45/4687 37/2333 2.5 6.2 0.76 (0.49, 1.19) VERTIS CV 19 49/5499 32/2747 2.6 3.4 42/5493 22/2745 2.5 2.7 0.95 (0.57, 1.59) 30 0.82 (0.53, 1.27) 60/1466 28 0.69 (0.50, 0.97) EMPEROR-PRESERVED 38/1466 44/1472 15 18 84/1472 20 0.52 (0.26, 1.03) 0.77 (0.46, 1.28) EMPEROR-REDUCED 35 13/927 23/929 13 24 26/927 33/929 21 27 SCORED 74 0.71 (0.46, 1.08) 16 1.04 (0.81, 1.35) 37/5292 52/5292 5.0 7.0 116/5291 111/5286 16 EMPA-KIDNEY 263 108/1525 175/1515 36 59 0.55 (0.44, 0.71) 73/1525 81/1515 24 27 0.88 (0.64, 1.20) 0.64 (0.52, 0.79) 0.85 (0.64, 1.13) CREDENCE 927 153/2202 230/2199 27 41 86/2200 98/2197 17 20 DAPA-CKD 1017 103/1455 173/1451 35 60 0.57 (0.45, 0.73) 48/1455 69/1451 15 22 0.66 (0.46, 0.96) 0.73 (0.39, 1.34) 0.79 (0.50, 1.25) DAPA-HF 18/1075 24/1064 12 16 31/1073 39/1063 19 24 SOLOIST-WHF NA/NA 25/605 55 59 0.94 (0.55, 1.59) NA/NA 27/611 DELIVER 33/1578 37/1572 9.5 11 0.87 (0.54, 1.39) 59/1578 52/1572 17 15 \rightarrow 1.13 (0.78, 1.63) \diamond 0.62 (0.56, 0.68) 0.79 (0.72, 0.88) Subtotal: DIABETES 739/40041 1020/33489 766/40664 856/34087 \diamond No diabetes 0.50 (0.17, 1.48) 0.56 (0.32, 0.98) EMPEROR-REDUCED 15 5/936 10/938 5.2 10 20/936 34/938 16 28 0.68 (0.33, 1.40) 0.80 (0.52, 1.23) EMPEROR-PRESERVED 16 12/1531 18/1519 4.5 6.9 37/1531 47/1519 12 15 0.74 (0.59, 0.95) 0.63 (0.41, 0.97) EMPA-KIDNEY 380 119/1779 157/1790 35 47 34/1779 54/1790 10 16 DAPA-CKD 861 29 53 0.51 (0.34, 0.75) 0.75 (0.39, 1.43) 39/697 70/701 16/697 21/701 11 15 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 (0.34, 1.08) \rightarrow 1.01 (0.51, 1.97) 0.64 (0.41, 1.02) DFI IVFR 17/1551 5.0 4.9 30/1551 17/1557 47/1558 8.8 14 Subtotal: NO DIABETES 202/7792 287/7812 \diamond 0.69 (0.57, 0.82) 155/7789 233/7811 \diamond 0.66 (0.54, 0.81) TOTAL: OVERALL 941/47833 1307/41301 0.63 (0.58, 0.69) 921/48453 1089/41898 0.77 (0.70, 0.84) ۲ 0.25 0.5 0.75 1 1.5 0.25 0.5 0.75 1 15 SGLT2i better SGLT2i better Placebo better Placebo better Trend across trials sorted by uACR: Trend across trials sorted by uACR: Diabetes p=1.00; Diabetes p=0.05; No diabetes p=0.47; No diabetes p=0.75; Heterogeneity by diabetes status: p=0.31 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

			KIDNEY DISEASE PROGRESSION					ACUTE KIDNEY INJURY			
	Mean baseline eGFR	Events/pa	articipants		Relative risk	Events/pa	rticipants		Relative risk		
	(mL/min/1.73m ²)	SGLT2i	Placebo		(95% CI)	SGLT2i	Placebo		(95% CI)		
Diabetes											
High atherosclerotic CV risk tria	ls 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	-	0.83 (0.68, 1.02)		
Chronic kidney disease trials	45	401/10474	630/10457		0.60 (0.53, 0.68)	323/10471	359/10449		0.88 (0.76, 1.02)		
Subtotal: DIABETES	67	739/40041	1020/33489	\diamond	0.62 (0.56, 0.68)	766/40664	856/34087	\$	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	2345		
			S	GLT2i better Placebo I					cebo better		
			Heter	ogeneity by diabetes sta	tus: p=0.31		Heterogen	eity by diabete	s status: p=0.12		

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/participants		Rate pe patient		Relative I	
	(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			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	<u> </u>	.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			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			0.60 (0.46, 0	.78)
						0.25 0.5 0.75 1 1.5 SGLT2i better Placebo 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		Events/p	Rate po patien	er 1000 t years		Relative risk			
(mL/min/1.73	3m²)	SGLT2i	Placebo	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	_ i		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	#	+	0.78 (0.60, 1.03)	
Subtotal: DIABETES	67	3056/40691	3233/34113			\$		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)	ρ=0.20
DAPA-CKD	42	15/697	19/701	11	13 🗲	į	\rightarrow	0.79 (0.40, 1.55)	
EMPA-KIDNEY	39	35/1779	34/1790	10	9.9		$\blacksquare \rightarrow$	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		0.5 S0	0.75 GLT2i better	1 1.25 1.5 Placebo bett		

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

			•/						non	0/11/2			
baseline e		Events/pa	articipants		er 1000 t years		Relative risk	Events/p	oarticipants	Rate per period	er 1000 t years		Relative risk
(mL/min/1.7	3m²)	SGLT2i	Placebo	SGLT2	i Placebo		(95% CI)	SGLT2i	Placebo	SGLT2	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	_ im	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		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		→ 0.79 (0.39, 1.57)
SCORED	44	155/5292	170/5292	22	24		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	.	• 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		- 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		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		→ 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			\diamond	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	0.5 0.75 1	1.5				0.25	0.5 0.75 1	1.5
							lacebo better						Placebo better
					Trend	across trials sorted by	eGFR:				Trend a	cross trials sorted b	y eGFR:
						Diabetes p=0.44; No diabetes p=0.74;					I	Diabetes p=0.52; No diabetes p=0.66	;
					Heteroger	eity by diabetes sta	tus: p=0.68			н	eterogene	eity by diabetes sta	atus: 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

Aver baseline e	GFR	Events/pa	rticipants	Rate per patient				Relative risk trials	
(mL/min/1.73	3m²)	SGLT2i	Placebo	SGLT2i	Placebo			(95% CI) b	y 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 bette		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		Events/pa	articipants	Rate per			Relative risk	Trend across trials sorted	
(mL/min/1.73	3m²)	SGLT2i	Placebo	bo 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		<u> </u> ∔∎→	1.32 (0.56, 3.16)	
EMPEROR-REDUCED	61	12/927	9/926	9.4	7.0		<u> </u> ∔∎→	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		\mapsto	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 🗲 -		$ \longrightarrow$	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 ←		$ \longrightarrow$	0.50 (0.04, 5.46)	p=0.23
DAPA-CKD	42	0/696	1/699	0.0	0.6 ←	e	\rightarrow	0.50 (0.02, 14.94)	
EMPA-KIDNEY	39	5/1779	2/1790	1.5	0.6		$ \longrightarrow$	2.59 (0.50, 13.36)	
Subtotal: NO DIABETES	56	12/7788	13/7807					0.98 (0.43, 2.25)	
TOTAL: OVERALL	65	692/48449	473/41889				•	1.15 (1.02, 1.30)	
TOTAL: OVERALL	64	552/42659	426/37545			•		1.06 (0.93, 1.21)	
(excluding CANVAS)*					0.25 S	0.5 0.75 GLT2i better		bo better	

Heterogeneity by diabetes 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. CI = 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

ba	Mean seline eGFR	Events/pa	rticipants		Relative risk
	L/min/1.73m²) SGLT2i Place		Placebo		(95% CI)
Urinary tract infections					
High atherosclerotic CV risk trials	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 infections					
High atherosclerotic CV risk trials	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 trials	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 trials	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 trials	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	¢	1.07 (0.99, 1.14)
				0.25 0.5 1 2 SGLT2i better Placeb	3 4 5 oo better

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.