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

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$.tw.
18	(canagliflozin$ or dapagliflozin$ or empagliflozin$ or ertugliflozin$ or ipragliflozin$ or luseogliflozin$ or 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.
8	((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or 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$1.ti,ab.
13	(crossover or cross over).ti,ab.
14	((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab.
15	(assigned or allocated).ti,ab.
16	(controlled adj7 (study or design or trial)).ti,ab.
17	(volunteer or volunteers).ti,ab.
18	human experiment/
19	trial.ti.
20	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21	(random$ adj sampl$ adj7 ("cross section$" or questionnaire$1 or survey$ or database$1)).ti,ab. not (comparative study/ or controlled study/ or randomi?ed controlled.ti,ab. or randomly assigned.ti,ab.)
22	Cross-sectional study/ not (randomized controlled trial/ or controlled clinical study/ or controlled study/ or 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.
32	(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. 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$.tw.
43	(canagliflozin$ or dapagliflozin$ or empagliflozin$ or ertugliflozin$ or ipragliflozin$ or luseogliflozin$ or 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 sodium-glucose co-transporter-2 inhibition in different patient groups: a meta-analysis of large placebo-controlled randomized trials. eClinicalMedicine. 2021;41.
2. 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.
3. 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, double-blind, placebo-controlled, phase 3 trial. Lancet Diabetes Endocrinol. 2021;9(9):586-94.

Webtable 1: Definition of kidney disease progression by trial

Trial	Components & definitions used in this meta-analysis					Definitions used by individual trials in their previous publications
	Sustained ≥50% eGFR decline	Kidney replacement therapy	Sustained eGFR <15 (or <10)	Renal death	Definition of sustained	
DECLARE-TIMI 58	✓	✓	✓	✓	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	✓	✓	✓	✓	Two consecutive measurements ≥30 days apart unless identified on the last available measurement	Sustained 50% eGFR decline or ESKD (defined as maintenance dialysis ≥30 days, kidney transplantation, sustained eGFR <15 mL/min/1.73 m^2) or renal death
VERTIS CV	✓	✓	✓	✓	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	✓	✓	✓	✓	Sustained for ≥28 days according to central laboratory assessment	Pre-specified: Sustained ≥40% eGFR decline or ESKD (defined as "sustained continuous"* dialysis/ kidney transplantation or sustained eGFR <15 mL/min/1.73 m^2) or *hospitalisation for heart failure or cardiac* or renal *death*. Post-hoc: Sustained ≥40%; (also published for ≥30%, ≥50% and ≥57%) eGFR decline or RRT initiation or renal death.
DAPA-HF	✓	✓	✓	✓	Defined as lasting ≥28 days	Sustained ≥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	✓	✓	✓	✓	Sustained for ≥30 days according to central laboratory assessment or if the last measurement meets criteria and death occurred within 60 days	Sustained ≥40% eGFR decline or ESKD (defined as chronic* dialysis/ kidney transplantation or sustained eGFR <15 for patients with baseline eGFR ≥30, or sustained eGFR <10 for patients with baseline eGFR <30 mL/min/1.73 m^2)
EMPEROR-PRESERVED	✓	✓	✓	✓	Sustained for ≥30 days according to central laboratory assessment or if the last measurement meets criteria and death occurred within 60 days	Sustained ≥40% eGFR decline or ESKD (defined as chronic* dialysis/ kidney transplantation or sustained eGFR <15 for patients with baseline eGFR≥30 or sustained eGFR<10 for patients with baseline eGFR<30 mL/min/1.73 m^2)
DELIVER	✓	✓	✓	✓	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	✓	✓	✓	✓	Sustained for ≥30 days according to central laboratory assessment	Primary: Sustained doubling of serum creatinine, ESKD (defined as maintenance dialysis ≥30 days, kidney transplantation or sustained eGFR <15 mL/min/1.73 m^2) or renal or *cardiovascular death* Secondary: Sustained doubling of serum creatinine, ESKD or renal death
SCORED	✓	✓	✓	X	Sustained for ≥30 days	Sustained ≥50% eGFR decline, long-term* dialysis, kidney transplantation or sustained eGFR <15 mL/min/1.73 m^2
DAPA-CKD	✓	✓	✓	✓	Two consecutive central laboratory eGFR values ≥28 days apart	Sustained ≥50% eGFR decline, ESKD (defined as maintenance dialysis ≥28 days, kidney transplantation or sustained eGFR <15 mL/min/1.73 m^2) or renal death
EMPA-KIDNEY	✓	✓	✓	✓	(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
DECLARE-TIMI 58	Kidney disease progression (≥50%)	✓			
	Any death, CV death; CV death/HHF		✓		
	Non-CV death		✓		
	AKI, amputation, ketoacidosis		✓	✓	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			✓	Rates estimated from number of events. Serious UTI not reported.
CANVAS Program	Kidney disease progression (≥50%)		✓		Event numbers by arm estimated from reported event rates, total events and hazard ratios.
	Any death, CV death; CV death/HHF		✓	✓	Event numbers by arm estimated from reported event rates, total events and hazard ratios.
	Non-CV death			✓	Calculated indirectly from any death & CV death data.
	AKI, amputation, ketoacidosis		✓	✓	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			✓	Risk ratio estimated from rates. Data for UTI and mycotic genital infections extracted from previous meta-analysis. Hypoglycaemia not included. Serious UTI not reported.
VERTIS CV	Kidney disease progression (≥50%)	✓			
	Any death, CV death; CV death/HHF		✓		
	Non-CV death			✓	Calculated indirectly from any death & CV death data.
	AKI, amputation, ketoacidosis		✓	✓	Rates & risk ratios estimated from event numbers. AKI: defined by MedDRA Preferred Term for AKI (serious only; unadjudicated).
	UTI, mycotic genital infections, hypoglycaemia, fractures			✓	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.
EMPA-REG OUTCOME	Kidney disease progression (≥50%)	✓			
	Any death, CV death; CV death/HHF		✓		CV death definition excluded stroke.
	Non-CV death			✓	Calculated indirectly from any death & CV death data.
	AKI, amputation, ketoacidosis		✓	✓	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			✓	Risk ratios and rates estimated from numbers of events. UTI and serious UTI reported separately.
DAPA-HF	Kidney disease progression (≥50%)		✓		
	Any death, CV death; CV death/HHF		✓		CV death/HHF: used analyses excluding urgent HF visits.
	Non-CV death			✓	Calculated indirectly from any death & CV death data.
	AKI, amputation, ketoacidosis	✓	✓	✓	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			✓	Risk ratios and rates estimated from numbers of events. UTI and mycotic genital infections not reported.
EMPEROR-REDUCED	Kidney disease progression (≥50%)	✓			
	Any death, CV death; CV death/HHF		✓	✓	Any death: calculated indirectly rom CV and non-CV death
	Non-CV death	✓			
	AKI, amputation, ketoacidosis	✓	✓	✓	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			✓	Risk ratios and rates estimated from numbers of events. UTI and serious UTI reported separately. Genital infections presented overall.
EMPEROR-PRESERVED	Kidney disease progression (≥50%)	✓			
	Any death, CV death; CV death/HHF		✓		CV death/HHF: rates estimated from numbers of events
	Non-CV death	✓			
	AKI, amputation, ketoacidosis	✓	✓	✓	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, fractures			✓	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
DELIVER	Kidney disease progression (≥50%)	✓			Kidney function assessed at randomisation, and then at 1, 4, 12, 24 and 36 months.
	Any death; CV death; CV death/HHF	✓			
	Non-CV death			✓	Calculated indirectly from provided any death & CV death data.
	AKI, amputation, ketoacidosis	✓			AKI: defined by MedDRA Preferred Term for AKI (serious and non-serious; unadjudicated).
	UTI, mycotic genital infections, hypoglycaemia, fractures			✓	Risk ratios and rates estimated from numbers of events. UTI: includes serious adverse events only. Fracture and mycotic genital infections not reported.
SOLOIST-WHF	Kidney disease progression (≥50%)	NA	NA	NA	
	Any death, CV death; CV death/HHF		✓		CV death/HHF: Number of events & rates estimated. Used analyses excluding urgent HF visits.
	Non-CV death			✓	Calculated indirectly from any death & CV death data.
	AKI, amputation, ketoacidosis		✓	✓	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			✓	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.
CREDENCE	Kidney disease progression (≥50%)	✓			
	Kidney failure		✓		
	Any death, CV death; CV death/HHF		✓		
	Non-CV death			✓	Calculated indirectly from any death & CV death data.
	AKI, amputation, ketoacidosis		✓		AKI: defined by MedDRA Preferred Term for AKI (serious and non-serious; unadjudicated).
	UTI, mycotic genital infections, hypoglycaemia, fractures			✓	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.
SCORED	Kidney disease progression (≥50%)		✓		
	Kidney failure	NA	NA	NA	
	Any death, CV death; CV death/HHF			✓	CV death/HHF: Rates estimated from numbers of events.
	Non-CV death			✓	Rates & risk ratio estimated from numbers of events.
	AKI, amputation, ketoacidosis			✓	AKI: event numbers estimated; defined by narrow SMQ for *acute renal failure* (serious and non-serious, unadjudicated). Amputation & ketoacidosis: rates & risk ratios estimated from numbers of events.
	UTI, mycotic genital infections, hypoglycaemia, fractures			✓	Risk ratios and rates estimated from numbers of events. Serious UTI not reported.
DAPA-CKD	Kidney disease progression (≥50%)		✓		
	Kidney failure		✓		
	Any death, CV death; CV death/HHF		✓		
	Non-CV death			✓	Calculated indirectly from any death & CV death data.
	AKI, amputation, ketoacidosis		✓		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			✓	Risk ratios and rates estimated from numbers of events. UTI and mycotic genital infections: includes serious adverse events only.
EMPA-KIDNEY	Kidney disease progression (≥50%)	✓			
	Kidney failure	✓			
	Any death; CV death; CV death/HHF	✓			
	Non-CV death	✓			
	AKI, amputation, ketoacidosis	✓			AKI: adjudicated serious AKI based on standard definition of Serious Adverse Event.
	UTI, mycotic genital infections, hypoglycaemia, fractures	✓			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

Study ID	Intervention	Comparator	Randomisation process	Deviations from the intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result
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:

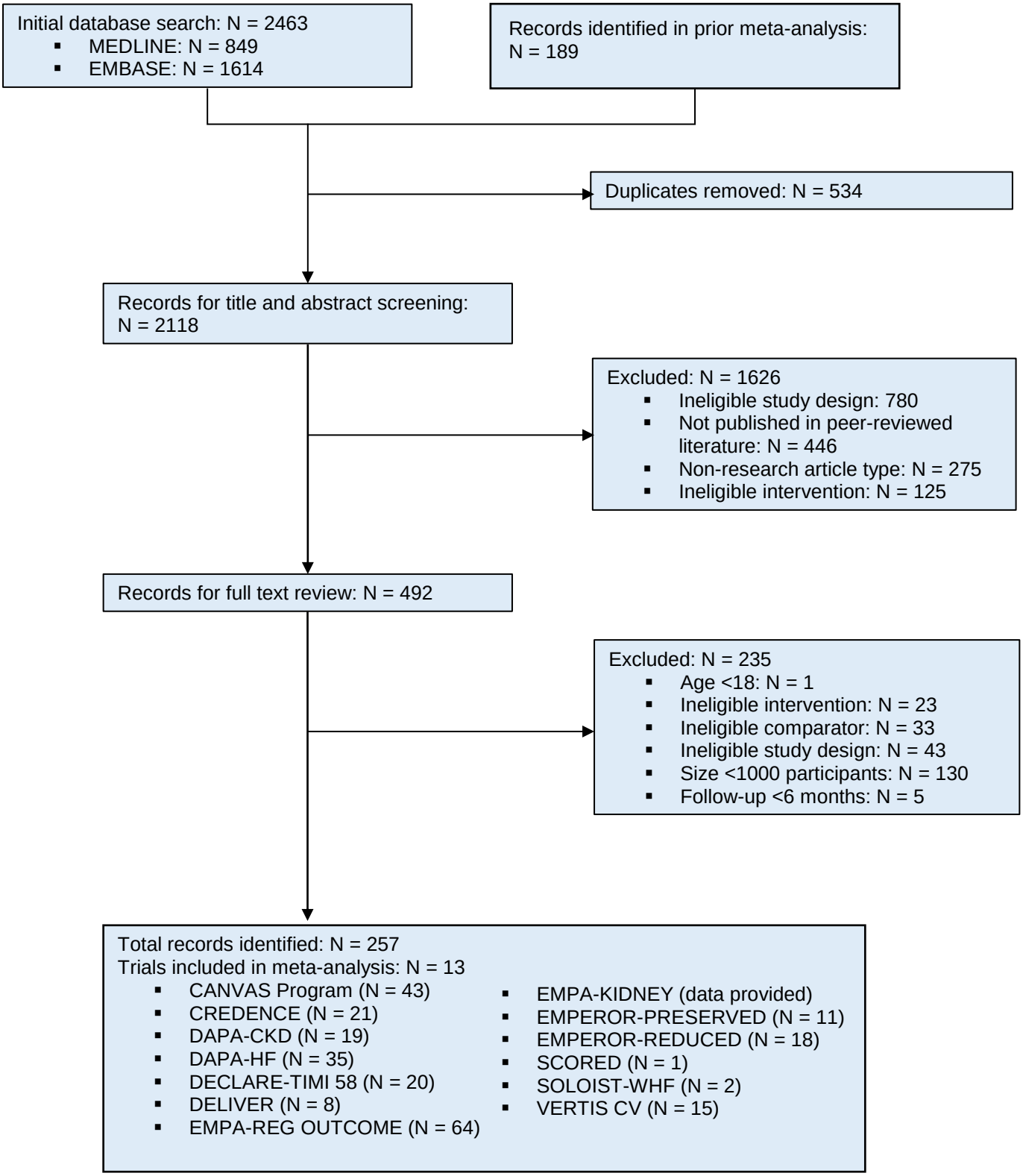
+	Low risk of bias
!	Some concerns
-	High risk of bias

Webtable 4: Additional baseline characteristics of participants in included trials

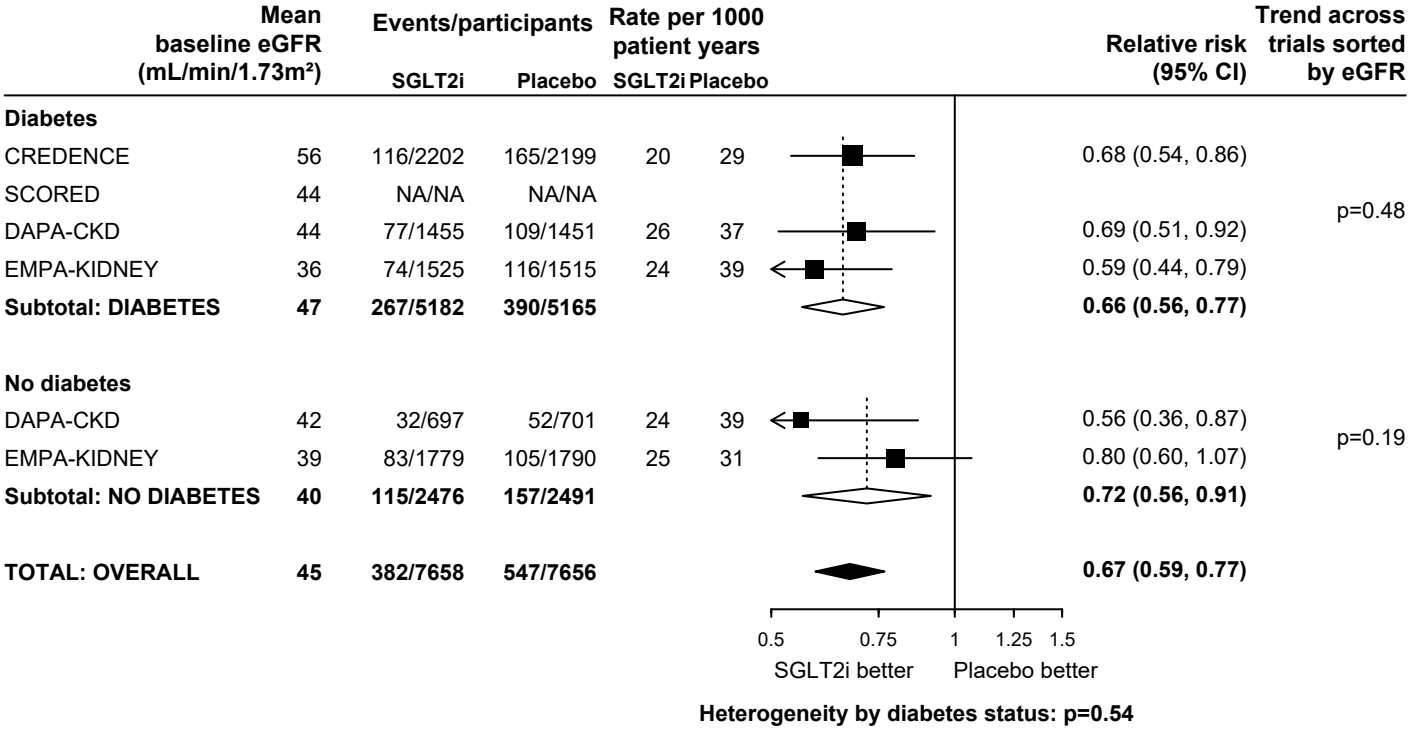
Patient group Trial acronym	**N**	**Mean (SD) age, years***	**Female sex, N (%)**	**RAS inhibitor, N (%)**	
				ACE inhibitor	**ARB**
Type 2 diabetes at high ASCVD risk					
DECLARE-TIMI 58	17160	63.9 (6.8)*	6422 (37.4)	13950 (81.3) [†]	
CANVAS Program	10142	63.3 (8.3)	3633 (35.8)	8116 (80.0) [†]	
VERTIS 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)

*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

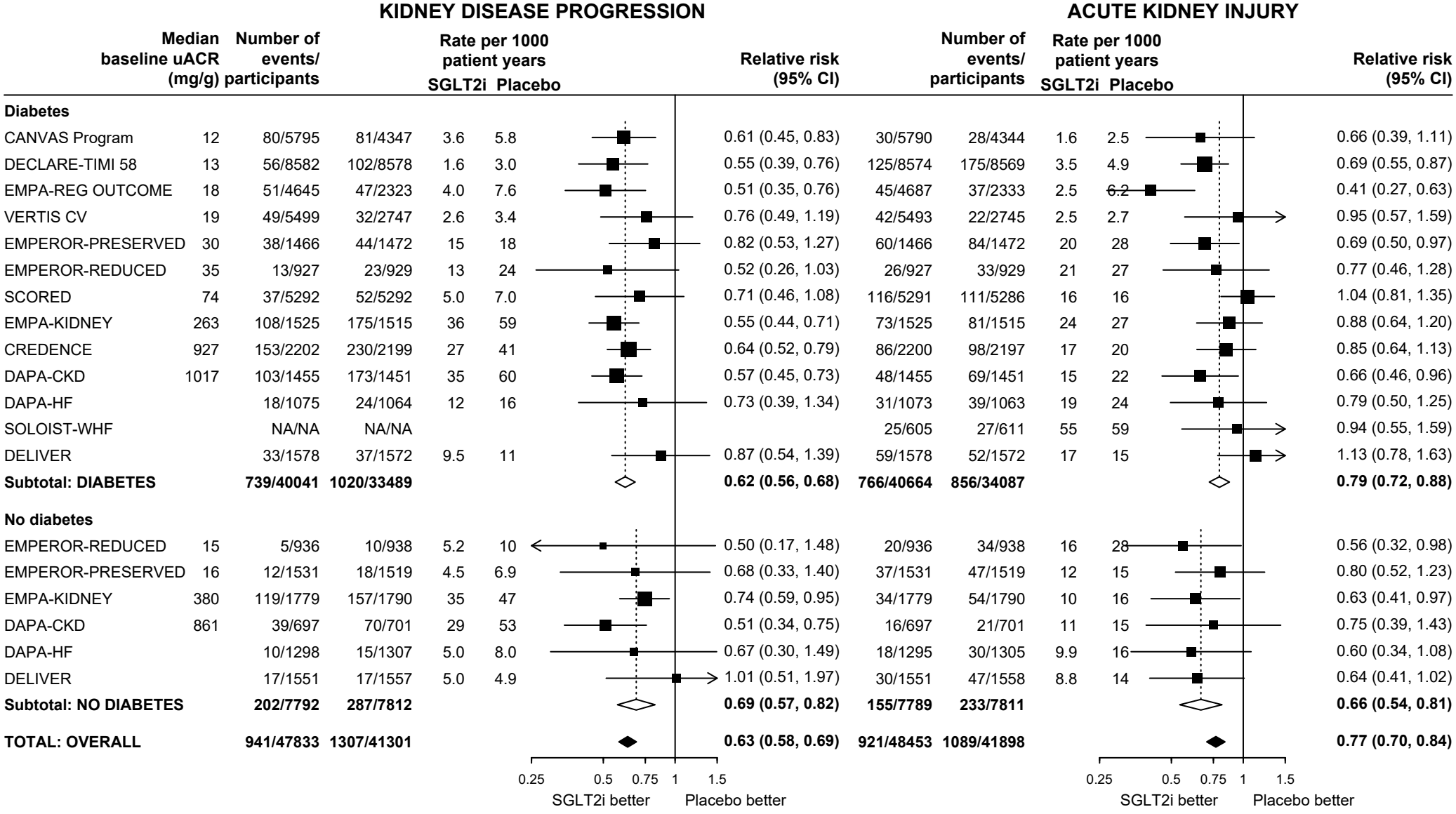


Webfigure 2: Effect of SGLT2 inhibition on KIDNEY FAILURE, by diabetes status (CKD trials only)



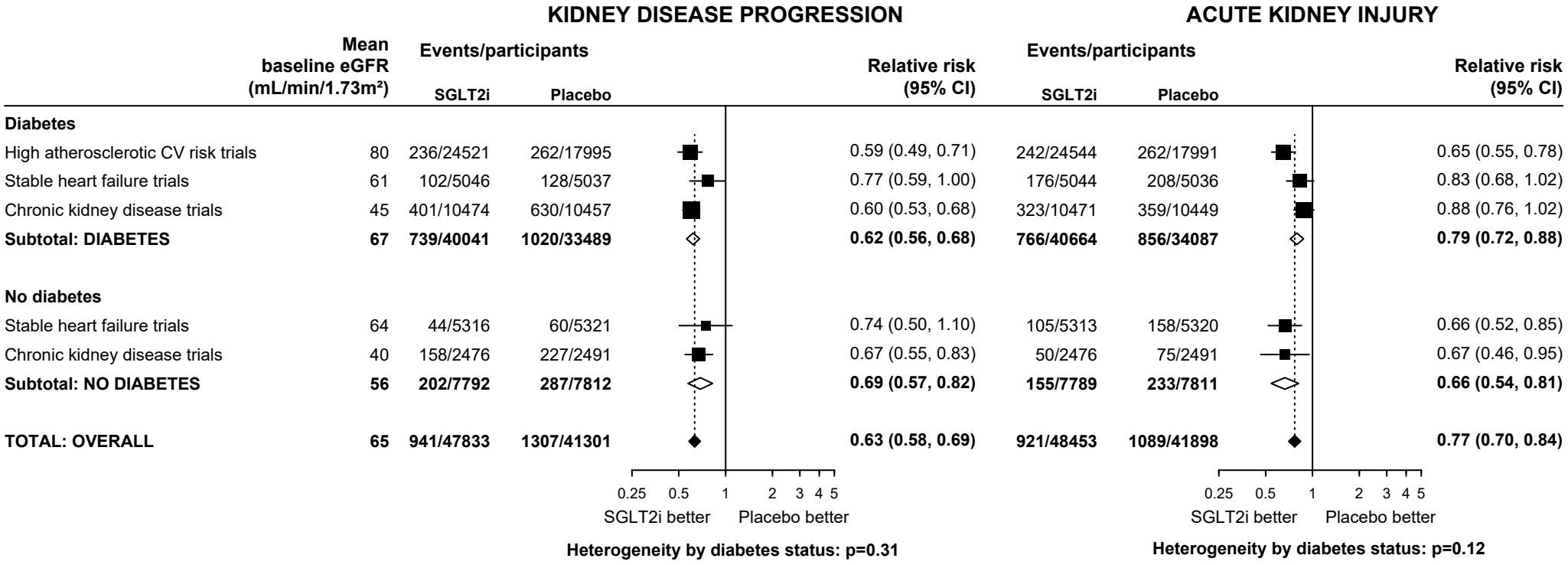
Kidney failure defined as composite of sustained eGFR<15 mL/min/1.73m² (or eGFR <10 mL/min/1.73m² in EMPA-KIDNEY), chronic dialysis, or kidney transplantation. Data for kidney failure not available for SCORED. CI = confidence interval. eGFR = estimated glomerular filtration rate. SGLT2i = sodium-glucose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

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



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.

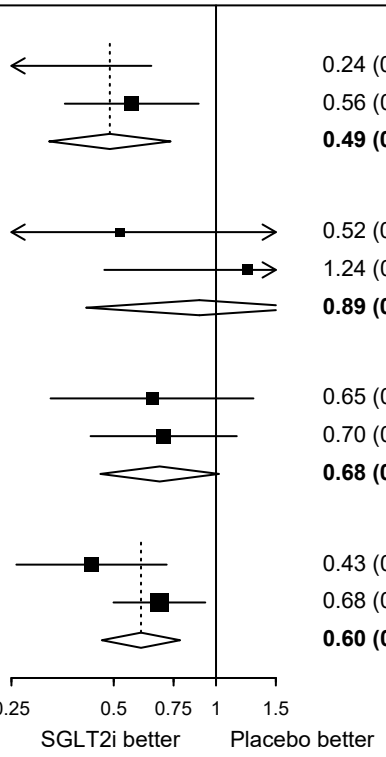
Webfigure 4: Effect of SGLT2 inhibitors on KIDNEY DISEASE outcomes, by diabetes status



Kidney disease progression: 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 (mL/min/1.73m²)	Events/participants		Rate per 1000 patient years		Relative risk (95% CI)
		SGLT2i	Placebo	SGLT2i	Placebo	
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 glomerulosclerosis						
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 glomeronephritis						
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)**

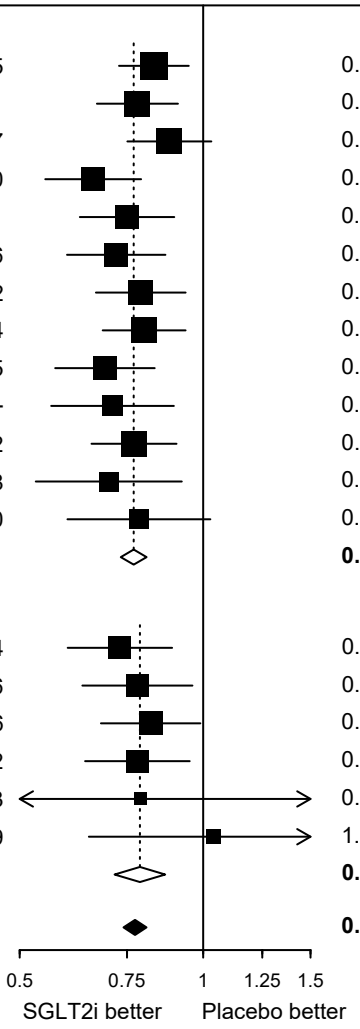


Heterogeneity across three subtypes of glomerular disease: p=0.30

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

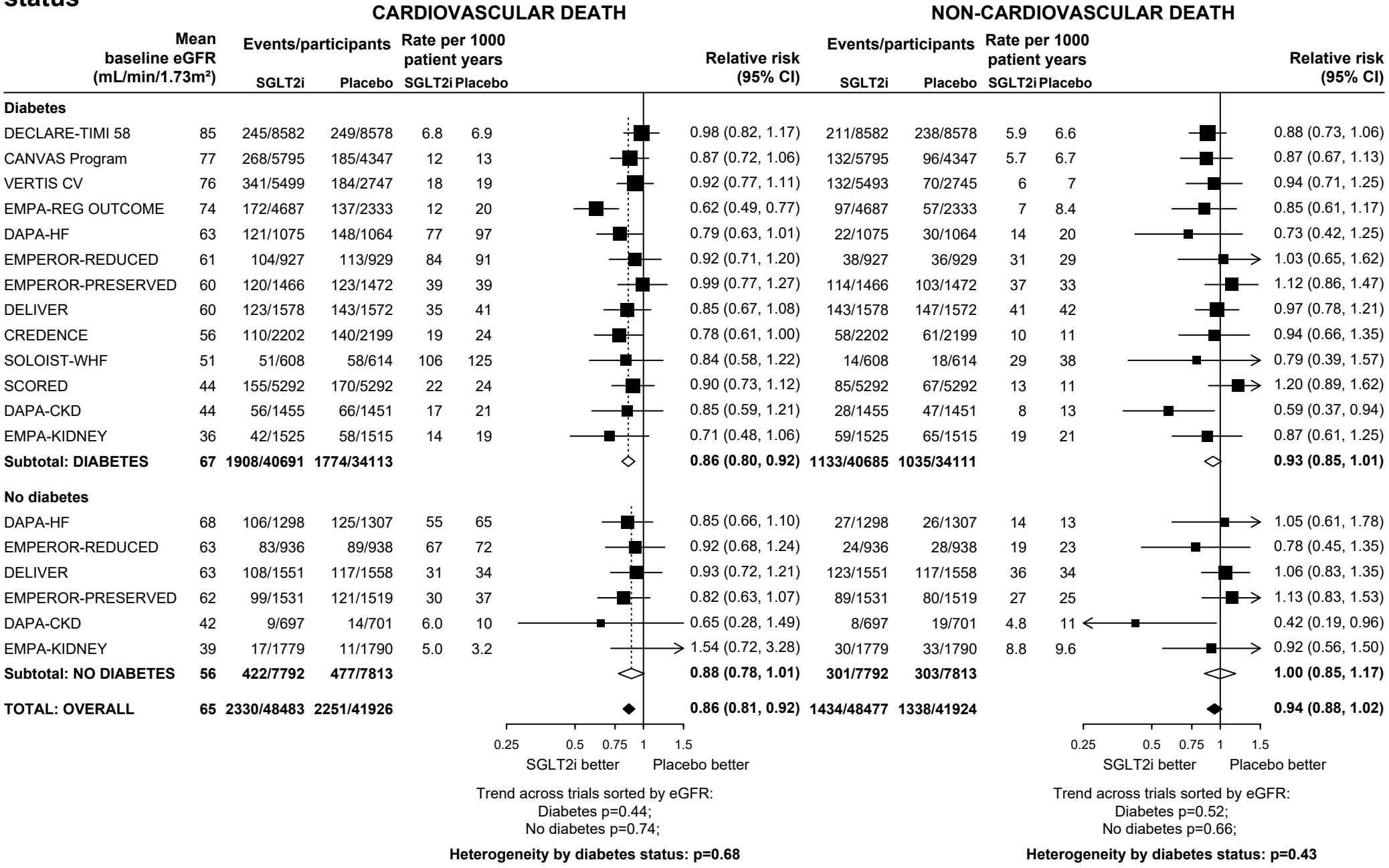
	Average baseline eGFR (mL/min/1.73m²)	Events/participants		Rate per 1000 patient years		Relative risk (95% CI)	Trend across trials sorted by eGFR
		SGLT2i	Placebo	SGLT2i	Placebo		
Diabetes							
DECLARE-TIMI 58	85	417/8582	496/8578	12	15	0.83 (0.73, 0.95)	
CANVAS Program	77	364/5795	288/4347	16	21	0.78 (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	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)	
DAPA-CKD	42	15/697	19/701	11	13	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**			**0.79 (0.72, 0.87)**	
TOTAL: OVERALL	**65**	**3816/48483**	**4176/41926**			**0.77 (0.74, 0.81)**	



Heterogeneity by diabetes status: p=0.67

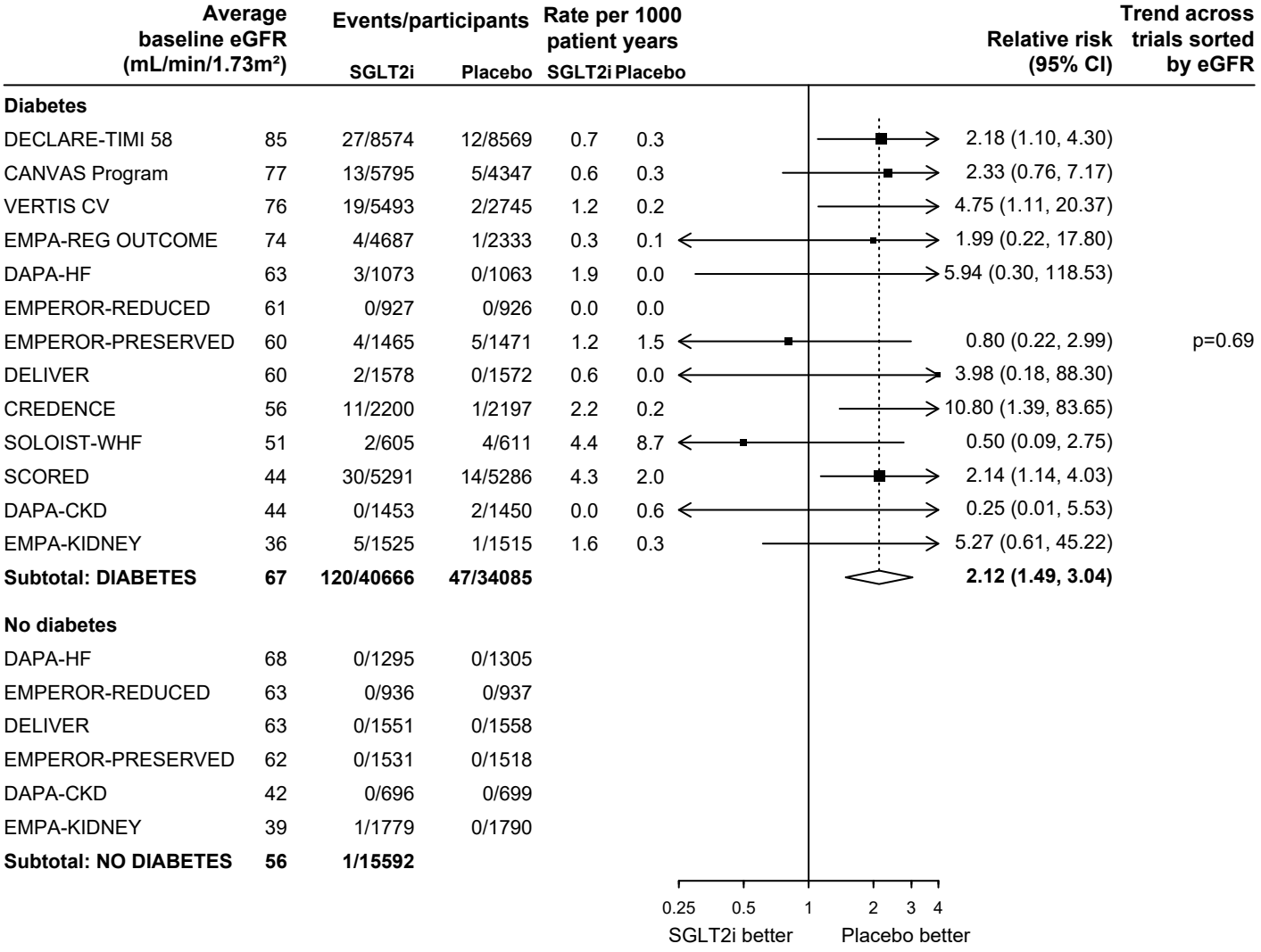
Excludes urgent heart failure visits. EMPA-REG OUTCOME cardiovascular death definition excluded stroke. CI = confidence interval. eGFR = estimated glomerular filtration rate. SGLT2i = sodium-glucose co-transporter-2 inhibitor.

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



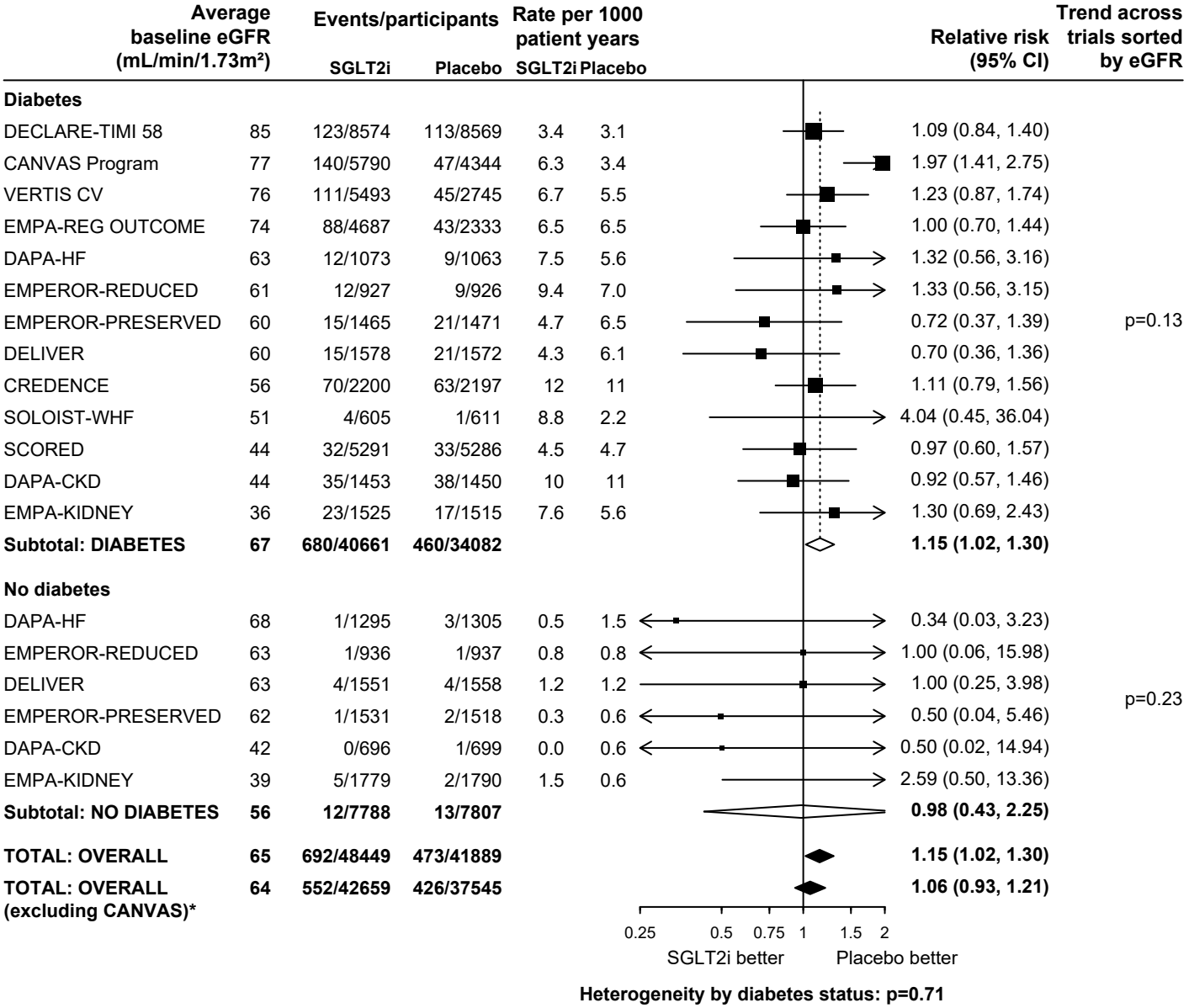
Webtable 2 provides details of when relative risks were estimated from numbers of events. CI = confidence interval. eGFR = estimated glomerular filtration rate. SGLT2i = sodium-glucose co-transporter-2 inhibitor.

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



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.

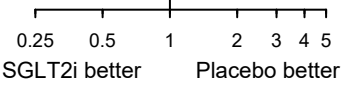
Webfigure 9: Effect of SGLT2 inhibitors on LOWER LIMB AMPUTATION, by diabetes status



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. SGLT2i = sodium-glucose co-transporter-2 inhibitor.

Webfigure 10: Effect of SGLT2 inhibitors on ADDITIONAL SAFETY outcomes

	Mean baseline eGFR (mL/min/1.73m²)	Events/participants SGLT2i	Events/participants Placebo	Relative risk (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	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**	**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**	**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)**



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.