Supplemental Online Content

NET EFFECTS OF SODIUM-GLUCOSE CO-TRANSPORTER-2 INHIBITION IN DIFFERENT PATIENT GROUPS: A META-ANALYSIS OF LARGE PLACEBO-CONTROLLED RANDOMIZED TRIALS

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SUPPLEMENTAL METHODS

Literature search methods

This systematic review and meta-analysis is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidance (1), and was registered on PROSPERO before the final database search (PROSPERO ID: CRD42021240468). The systematic database search of MEDLINE and EMBASE databases was undertaken via OVID using a pre-specified search strategy. The search was piloted on 16th February 2021, and the final database search was undertaken on 28th August 2021. The search terms used for interrogating the MEDLINE and EMBASE databases are summarised below. Validated filters for randomised controlled trials in MEDLINE and EMBASE were identified from the Cochrane Handbook for Systematic Reviews of Interventions were used (2).

Identified records were downloaded into a dedicated database and screened for duplicates. An initial screen of titles and abstracts was undertaken by a single reviewer (AJR), with subsequent full text screening undertaken by two reviewers independently and in duplicate (two of AJR, AR, AK, AW, SB), using a piloted spreadsheet. All screening was undertaken against predetermined inclusion criteria. Discrepancies between reviewers were resolved by a third reviewer (WGH). The database included main publications and all identified subsidiary peer-reviewed publications.

The inclusion criteria were as follows:

- Parallel-group randomized controlled trial in adults
- Randomization of at least 1000 participants to an SGLT-2 inhibitor (including SGLT-1/SGLT-2 inhibitors) versus placebo (including at least 500 participants in each group)
- Reporting any of the pre-specified main efficacy outcomes and any of the pre-specified safety outcomes

Where multiple reports from the same study were identified, these were collated by reference to the study acronym, or the National Clinical Trials (NCT) reference number. Reference lists of included studies and contemporary meta-analyses were screened for additional relevant studies.

Outcomes

Pre-specified outcomes comprised the following efficacy and safety outcomes.

Efficacy outcomes:

- Hospitalization for heart failure (HF) or cardiovascular death, overall and by components

- Major adverse cardiovascular events (MACE, defined as cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke), overall and by components
- Kidney disease progression (based on published definitions of categorical outcomes)
- Death from cardiovascular and non-cardiovascular causes considered separately (with effects on non-cardiovascular causes estimated from cardiovascular and all-cause mortality results when non-cardiovascular death results were not reported)

Safety outcomes:

- Acute kidney injury
- Ketoacidosis
- Severe hypoglycaemia (based on individual trial definitions)
- Lower limb amputation
- Bone fracture
- Mycotic genital infections and Fournier's gangrene
- Urinary tract infection

Data extraction

For each trial, relevant results were identified from the main (3-13) and/or subsidiary peer-reviewed publications (14-23) and extracted into spreadsheets for checking. Data extraction included each trial's main eligibility criteria; follow-up duration; selected participant characteristics (proportion with diabetes mellitus (DM), HF and the presented "average" kidney function); number of events and participants included in reported comparisons; event rate per 1000 patient years in each arm; and any reported hazard ratio for the effect of SGLT-2 inhibition versus placebo (and its 95% confidence interval [CI]). Intention-to-treat population data and analyses were used, wherever possible.

Risk of bias assessment

Risk of bias was assessed independently and in duplicate (AJR, AR, AK, AW) using the Cochrane Risk of Bias 2 (ROB2) tool, which assesses risk of bias in studies according to five domains: randomization process, deviations from the intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result.

Search terms and 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

	(random$ adj sampl$ adj7 ("cross section$" or questionnaire$1 or survey$ or database$1)).ti,ab.
21	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

Data from eligible trials not included in meta-analyses

InTandem3* (24) was identified by the systematic review but not included in meta-analyses as it was in a population with type 1 DM 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 summarized in the table below:

	Sotagliflozin (n=699) **Participants with events**	**Placebo (n=703)** **Participants with events**
Major cardiovascular event	2	0
Myocardial infarction	1	0
Coronary revascularization	1	0
Stroke	0	0
Hospitalization for heart failure or cardiovascular death	0	0
"Renal event"	5	3
Ketoacidosis	21	4
Severe hypoglycaemia	21	17
Amputation	0	0
Bone fracture	4	5
Urinary tract infection	25	27
Any death	1	0

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

The Dapagliflozin in Respiratory Failure in Patients With COVID-19 (DARE-19) trial (25) was identified by the systematic review but not included in meta-analysis given the study population (hospitalized 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 summarized below:

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

Additional statistical methods

Meta-analysis method for rare outcomes

Inverse-variance-weighted averages of log hazard ratios/relative risks (RRs) were used to estimate the treatment effects in each patient group and overall. For the very rare outcome of Fournier's gangrene, the observed minus expected number of events (O-E) and its variance, V (calculated from the 2x2 contingency table) were used to calculate the one-step estimate of the odds ratio for individual trials. The sum of the O-E and V in the relevant trials were used to estimate the treatment effects in each patient group and overall for this rare outcome. For ketoacidosis, trials with zero events in one arm had a zero cell count correction applied (by adding 0.5 to arms with no events).

Adjustment factor for different definitions of % decline in estimated glomerular filtration rate (eGFR)

A sensitivity analysis was performed to assess how different definitions of kidney disease progression might have affected results. These analyses used data from CANVAS from which effect sizes for different definitions of the composite kidney disease progression outcome using a range of eGFR decline thresholds (≥57% [equivalent to a doubling of creatinine], ≥50%, and ≥40%) have been reported (26). Adjustment factors from CANVAS were estimated from the relative differences in the log RR and the associated standard errors for each % decline compared to a ≥40% eGFR decline. For trials that have only reported kidney disease progression using either of a ≥50% decline in eGFR or a doubling of creatinine, our sensitivity analysis then used these CANVAS adjustment factors to re-estimate RRs and 95%CIs for the hypothetical scenario that their kidney disease progression outcomes had used a ≥40% decline in eGFR.

References for Supplemental Methods

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Supplemental table 1: Quality assessments

Unique ID	Study ID	Experimental	Comparator	D1	D2	D3	D4	D5	Overall
1	CREDENCE	Canagliflozin	Placebo	+	+	+	+	+	+
2	CANVAS	Canagliflozin	Placebo	+	+	+	+	+	+
3	DAPA-CKD	Dapagliflozin	Placebo	+	+	+	+	+	+
4	DAPA-HF	Dapagliflozin	Placebo	+	+	+	+	+	+
5	DECLARE-TIMI 58	Dapagliflozin	Placebo	+	+	+	+	+	+
6	EMPA-REG OUTCOME	Empagliflozin	Placebo	+	+	+	+	+	+
7	EMPEROR-PRESERVED	Empagliflozin	Placebo	+	+	+	+	+	+
8	EMPEROR-REDUCED	Empagliflozin	Placebo	+	+	+	+	+	+
9	InTANDEM3	Sotagliflozin	Placebo	+	+	+	+	+	+
10	SCORED	Sotagliflozin	Placebo	+	+	+	+	+	+
11	SOLOIST-WHF	Sotagliflozin	Placebo	+	+	+	+	+	+
12	VERTIS CV	Ertugliflozin	Placebo	+	+	+	+	+	+

Supplemental Table 2: Predicted absolute benefits and harms of SGLT-2 inhibitors per 1000 patient years of treatment, by patient group (sensitivity analysis using patient group-specific relative risks)

	Absolute rates and effects per 1000 patient years									
	STABLE HEART FAILURE				RECENTLY HOSPITALIZED FOR WORSENING HEART FAILURE		TYPE 2 DIABETES MELLITUS AT HIGH ATHEROSCLEROTIC CARDIOVASCULAR RISK		ALBUMINURIC CHRONIC KIDNEY DISEASE	
	REDUCED EJECTION FRACTION		PRESERVED EJECTION FRACTION							
	Event rate	Events avoided/ caused (SE) in SGLT-2i arms	Event rate	Events avoided/ caused (SE) in SGLT-2i arms	Event rate	Events avoided/ caused (SE) in SGLT-2i arms	Event rate	Events avoided/ caused (SE) in SGLT-2i arms	Event rate	Events avoided/ caused (SE) in SGLT-2i arms
Efficacy outcomes										
Hospitalization for heart failure	123	-38 (4)	60	-18 (2)	639	-196 (20)	10	-3 (0.4)	20	-7 (0.9)
Myocardial infarction	-	-	-	-	-	-	15	-1 (0.6)	9	-2 (0.7)
Cardiovascular death	80	-10 (4)	38	-5 (2)	125	-16 (6)	13	-2 (0.5)	21	-3 (1)
Kidney disease progression	20	-4 (2)	22	-5 (2)	-	-	9	-4 (0.4)	49	-19 (2)
Acute kidney injury	19	-6 (2)	-	-	59	-20 (5)	4	-1 (0.2)	15	-3 (1)
Safety outcomes										
Ketoacidosis	-	-	-	-	-	-	0.2	0.3 (0.2)	0.3	0.4 (0.2)
Amputation	4	-0.1 (0.8)	4	-0.1 (0.7)	2	-0.0 (0.5)	4	1 (0.4)	9	0.1 (1.2)

Patient group specific absolute effects estimated by applying the observed patient group-specific relative risk to the average event rate in the placebo arms (first event only). For the heart failure patient groups the placebo event rates were estimated separately for trials of stable heart failure with reduced ejection fraction (i.e. EMPEROR-REDUCED & DAPA-HF) versus stable heart failure with preserved ejection fraction (i.e. EMPEROR-PRESERVED) versus recent hospitalization for heart failure (i.e. SOLOIST-WHF). Standard errors (SE) in the numbers of events avoided or caused estimated from uncertainty in the relative risks. Kidney disease progression definitions were as reported by trials (i.e. not uniformly adjusted to a ≥40% eGFR decline). There were too few ketoacidosis events to estimate absolute effects in heart failure patient groups.

Supplemental Table 3: Predicted absolute benefits and harms of SGLT-2 inhibitors per 1000 patient years of treatment in A) STABLE HEART FAILURE and B) ALBUMINURIC CHRONIC KIDNEY DISEASE, by diabetes status

A) STABLE HEART FAILURE

	Absolute rates and effects per 1000 patient years							
	REDUCED EJECTION FRACTION				PRESERVED EJECTION FRACTION			
	Type 2 diabetes mellitus		No diabetes		Type 2 diabetes mellitus		No diabetes	
	Event rate	Events avoided/ caused (SE) in SGLT-2i arms	Event rate	Events avoided/ caused (SE) in SGLT-2i arms	Event rate	Events avoided/ caused (SE) in SGLT-2i arms	Event rate	Events avoided/ caused (SE) in SGLT-2i arms
Efficacy outcomes								
Hospitalization for heart failure or cardiovascular death	204	-48 (4)	141	-33 (3)	91	-21 (2)	66	-15 (1)
Kidney disease progression	42	-15 (1)	20	-7 (0.5)	23	-8 (0.6)	12	-4 (0.3)
Safety outcomes								
Ketoacidosis	-	-	-	-	2	2 (0.6)	-	-
Amputation	8	1 (0.6)	-	-	2	0.3 (0.1)	-	-

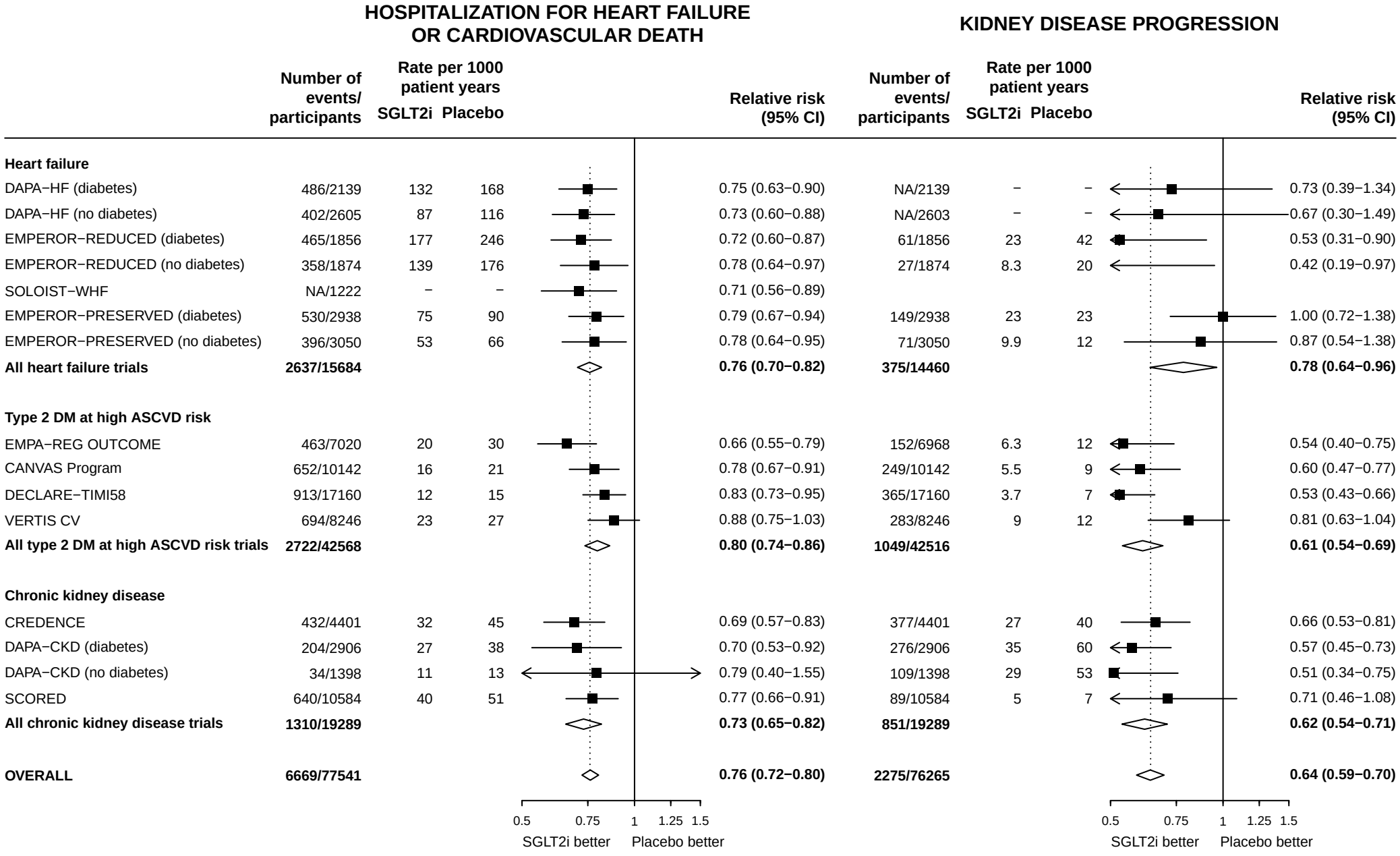
Patient group specific absolute effects estimated by applying the overall relative risk to the average event rate in the placebo arms (first event only). Standard errors (SE) in the numbers of events avoided or caused estimated from uncertainty in the relative risks. Kidney disease progression definitions were as reported by trials (i.e. not uniformly adjusted to a ≥40% eGFR decline). There were too few ketoacidosis events to estimate absolute effects in the heart failure patient group. There were too few ketoacidosis and amputation events to estimate absolute effects amongst patients without type 2 diabetes mellitus. Rates of amputation events among patients with type 2 diabetes mellitus not available in stable heart failure with preserved ejection fraction.

B) ALBUMINURIC CHRONIC KIDNEY DISEASE

	Absolute rates and effects per 1000 patient years			
	Type 2 diabetes mellitus		No diabetes	
	Event rate	Events avoided/ caused (SE) in SGLT-2i arms	Event rate	Events avoided/ caused (SE) in SGLT-2i arms
Efficacy outcomes				
Hospitalization for heart failure or cardiovascular death	42	-10 (0.8)	13	-3 (0.2)
Kidney disease progression	48	-17 (1)	53	-19 (1)
Safety outcomes				
Ketoacidosis	0.4	0.4 (0.1)	-	-
Amputation	11	2 (0.8)	-	-

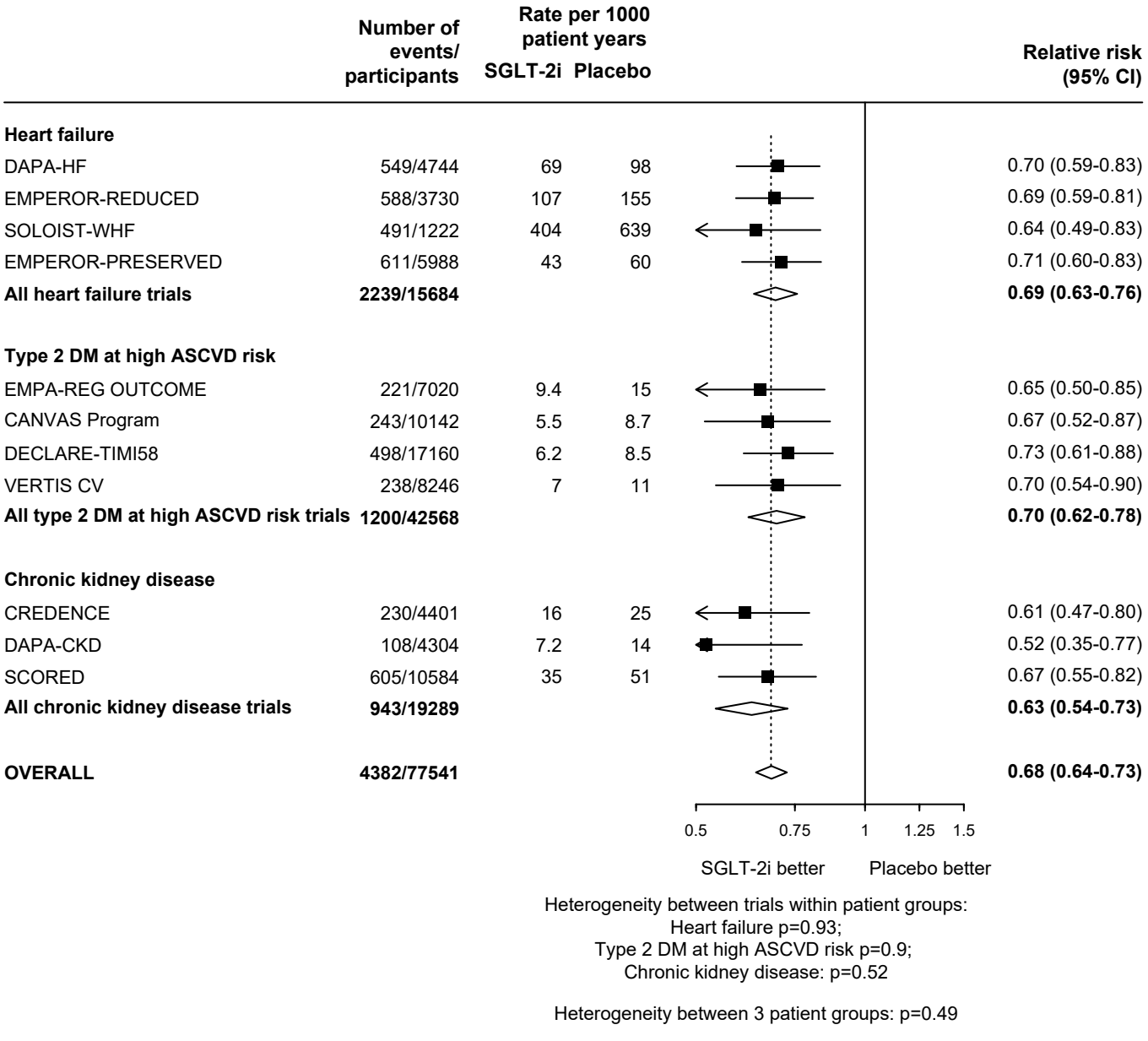
Patient group specific absolute effects estimated by applying the overall relative risk to the average event rate in the placebo arms (first event only). Standard errors (SE) in the numbers of events avoided or caused estimated from uncertainty in the relative risks. Kidney disease progression definitions were as reported by trials (i.e. not uniformly adjusted to a ≥40% eGFR decline). There were too few ketoacidosis and amputation events to estimate absolute effects amongst patients without type 2 diabetes mellitus.

Supplemental figure 1: Effect of SGLT2 inhibitors on (a) HOSPITALIZATION FOR HEART FAILURE OR CARDIOVASCULAR DEATH and (b) KIDNEY DISEASE PROGRESSION, by diabetes status and by trial



DM = diabetes mellitus. ASCVD = atherosclerotic cardiovascular disease. For hospitalization for heart failure or cardiovascular death, results for DAPA−HF include urgent visits for heart failure. Number of kidney disease progression events by diabetes subgroup not available (NA) for DAPA−HF. Kidney disease progression outcomes are not adjusted for different definitions: see footnote to Figure 3 for more details

Supplemental figure 2: Effect of SGLT2 inhibitors on HOSPITALIZATION FOR HEART FAILURE, by patient group and by trial

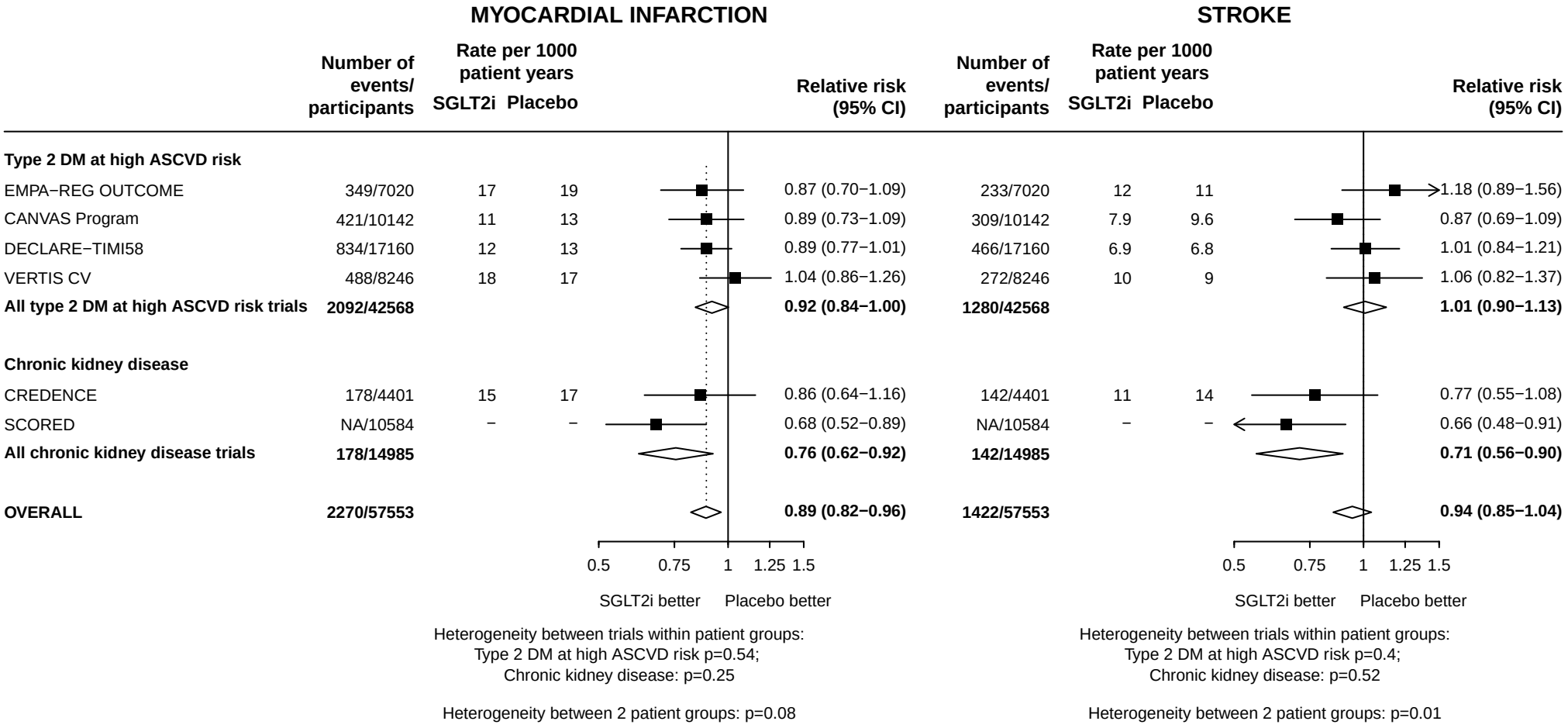


Heterogeneity between trials within patient groups:
Heart failure p=0.93;
Type 2 DM at high ASCVD risk p=0.9;
Chronic kidney disease: p=0.52

Heterogeneity between 3 patient groups: p=0.49

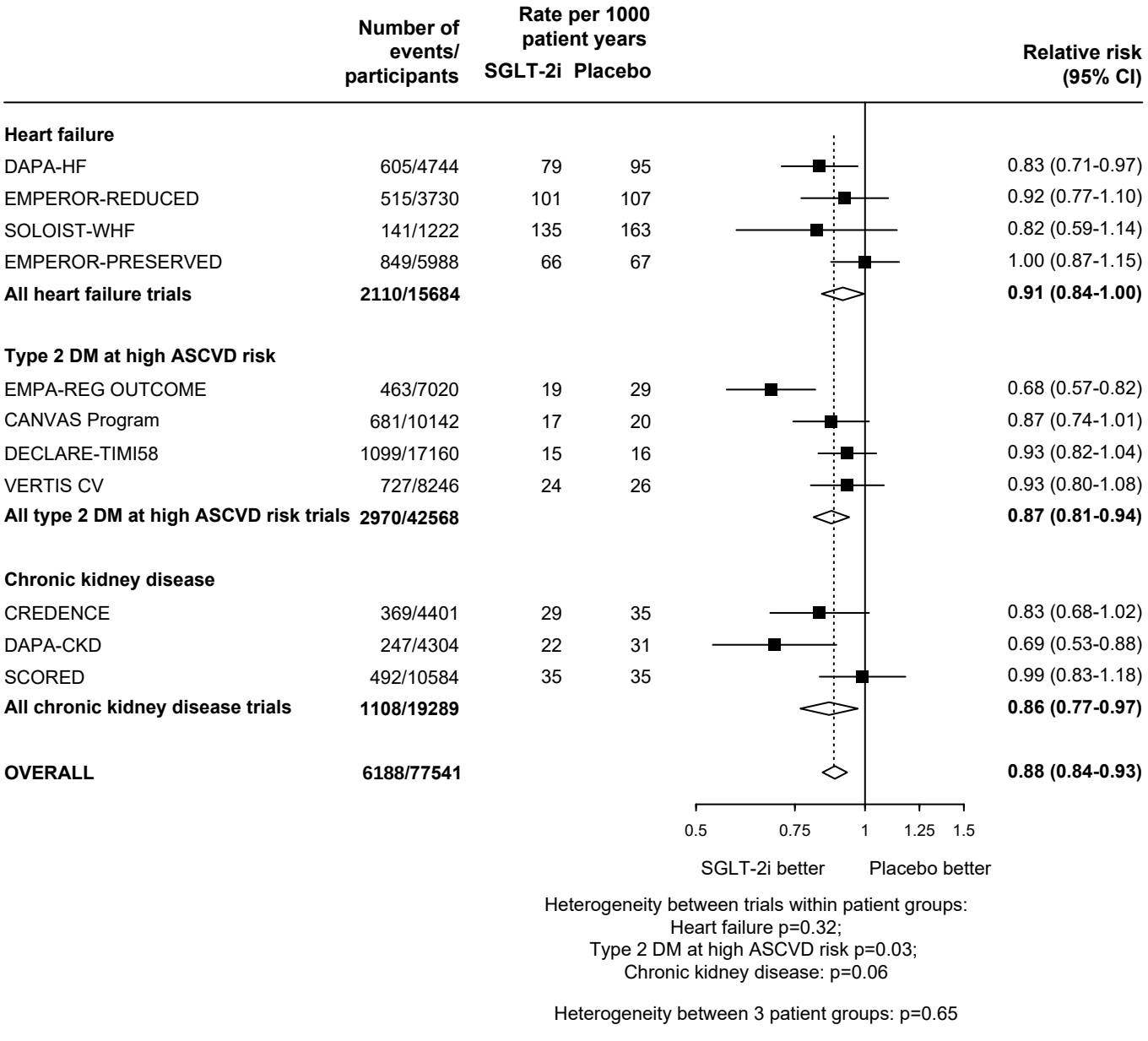
DM = diabetes mellitus. ASCVD = atherosclerotic cardiovascular disease. Results are based on time to first event analyses and exclude urgent visits for heart failure, wherever possible. Event rates estimated from number of events and follow-up duration for SCORED.

Supplemental figure 3: Effect of SGLT2 inhibition on (a) MYOCARDIAL INFARCTION and (b) STROKE, by patient group



DM = diabetes mellitus. ASCVD = atherosclerotic cardiovascular disease. Results unavailable for the heart failure patient group trials. Numbers of events unavailable for SCORED. EMPA−REG OUTCOME excluded silent myocardial infarction from its myocardial infarction outcome. DECLARE−TIMI58 included only ischaemic stroke in the presented stroke outcome.

Supplemental figure 4: Effect of SGLT2 inhibitors on DEATH from ANY CAUSE, by patient group

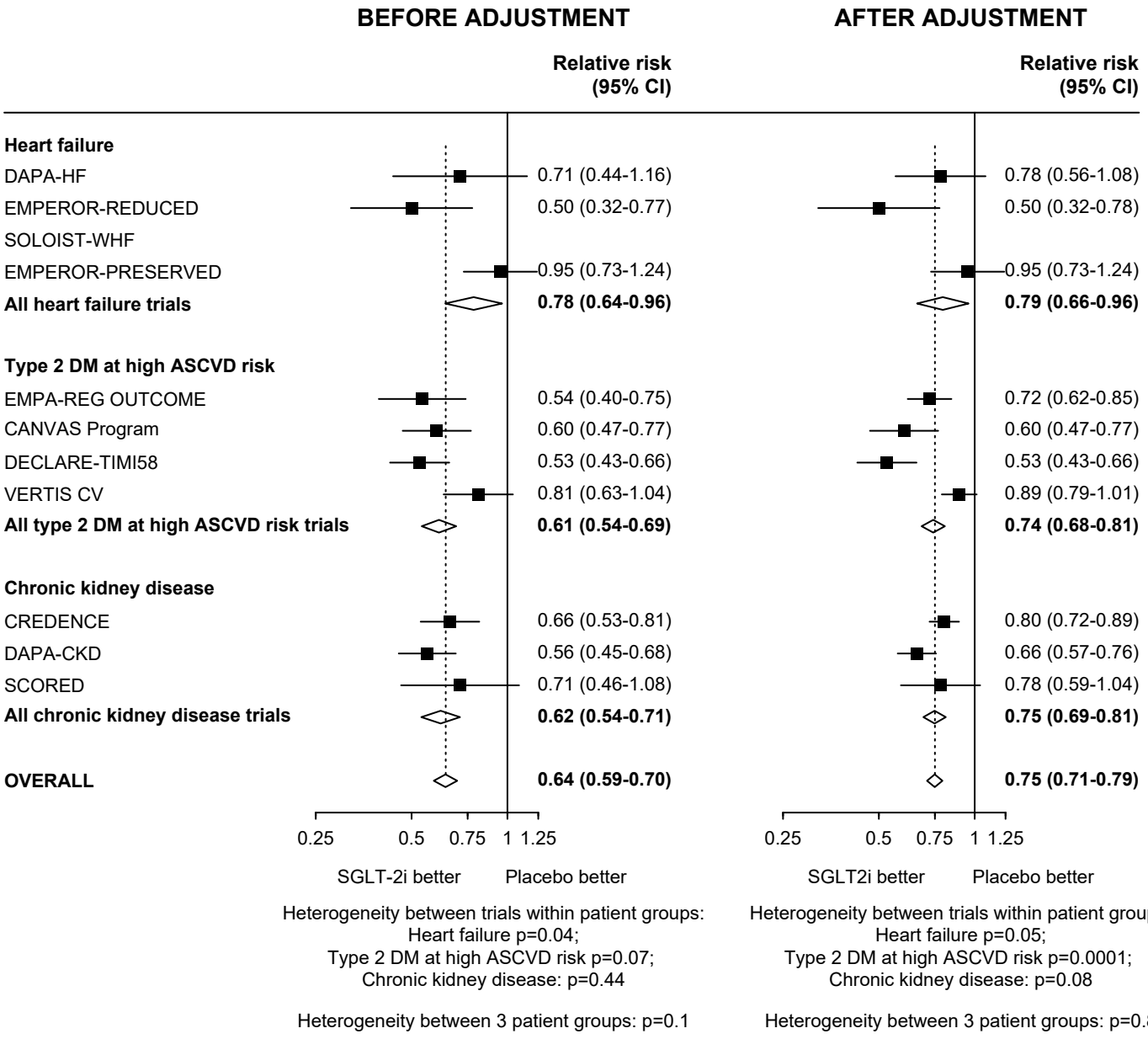


Heterogeneity between trials within patient groups:
Heart failure p=0.32;
Type 2 DM at high ASCVD risk p=0.03;
Chronic kidney disease: p=0.06

Heterogeneity between 3 patient groups: p=0.65

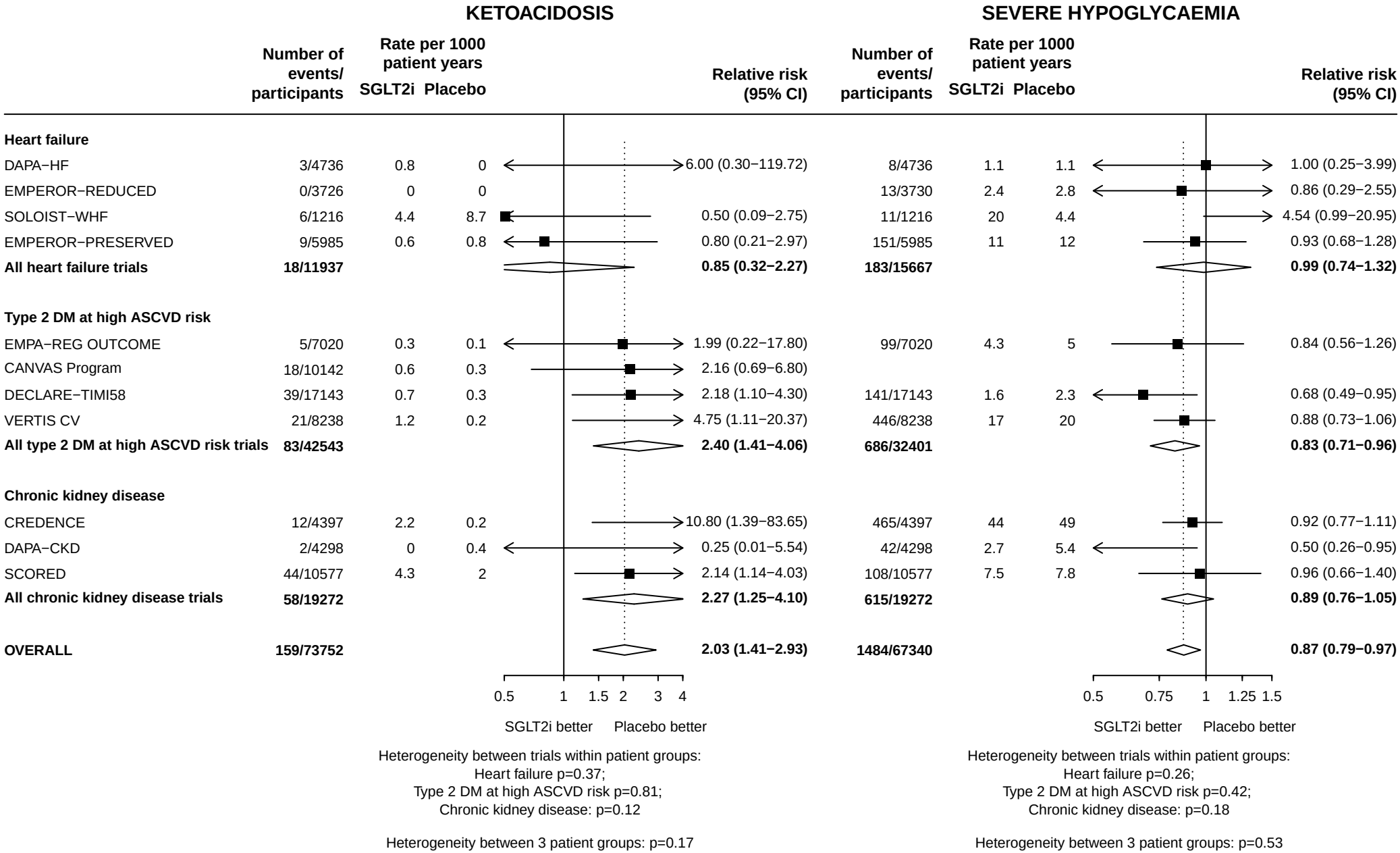
DM = diabetes mellitus. ASCVD = atherosclerotic cardiovascular disease.

Supplemental figure 5: Effect of SGLT-2 inhibitors on KIDNEY DISEASE PROGRESSION, by patient group and by trial, before and after applying adjustment factor for the different definitions of percent decline in eGFR



DM = diabetes mellitus. ASCVD = atherosclerotic cardiovascular disease. Kidney Disease Progression was generally defined as death from renal causes, commencement of renal replacement therapy, or a % decline in eGFR from baseline. The following trials used a ≥40% decline in eGFR: EMPEROR-REDUCED, EMPEROR-PRESERVED, CANVAS Program, DECLARE-TIMI58. The following trials used a ≥50% decline in eGFR: DAPA-HF, DAPA-CKD, SCORED. The following trials used a ≥57% decline in eGFR: EMPA-REG OUTCOME, VERTIS CV, CREDENCE. Results for kidney disease progression unavailable for SOLOIST-WHF. EMPA-REG OUTCOME population restricted to those that received at least one dose of study treatment. Effect sizes for different eGFR decline thresholds reported by CANVAS were used to calculate adjustment factors to allow relative risks and 95% confidence intervals to be re-estimated for the hypothetical scenario all trials had used a ≥40% decline in eGFR in the definition of their kidney disease progression composite outcome (see supplemental methods for full details).

Supplemental figure 6: Effect of SGLT2 inhibitors on (a) KETOACIDOSIS and (b) SEVERE HYPOGLYCAEMIA, by patient group and by trial



Heterogeneity between trials within patient groups:
Heart failure p=0.37;
Type 2 DM at high ASCVD risk p=0.81;
Chronic kidney disease: p=0.12

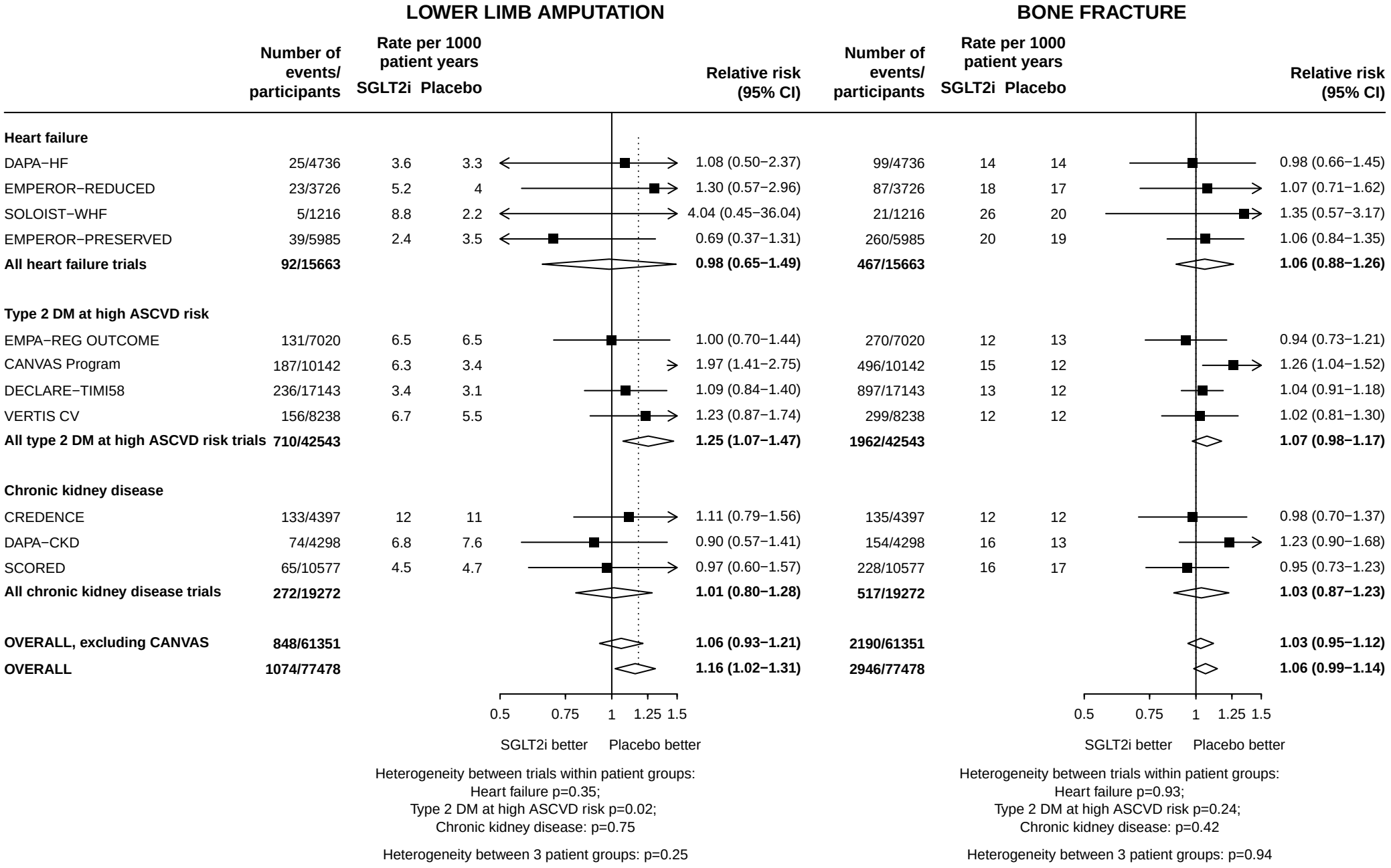
Heterogeneity between 3 patient groups: p=0.17

Heterogeneity between trials within patient groups:
Heart failure p=0.26;
Type 2 DM at high ASCVD risk p=0.42;
Chronic kidney disease: p=0.18

Heterogeneity between 3 patient groups: p=0.53

DM = diabetes mellitus. ASCVD = atherosclerotic cardiovascular disease. Some studies limited analyses to a safety population. Treatment effects for ketoacidosis estimated from numbers of events for several trials (DAPA−HF, EMPEROR−REDUCED, SOLOIST−WHF, EMPEROR−PRESERVED, EMPA−REG OUTCOME, VERTIS CV, DAPA−CKD and SCORED). Where unreported, event rates for ketoacidosis are estimated from median follow−up and other reported information (DAPA−HF, SOLOIST−WHF, EMPEROR−PRESERVED, EMPA−REG OUTCOME, DECLARE−TIMI58, VERTIS CV, DAPA−CKD and SCORED). Treatment effects for severe hypoglycaemia estimated from numbers of events for several trials (DAPA−HF, EMPEROR−REDUCED, SOLOIST−WHF, EMPEROR−PRESERVED, CANVAS Program, VERTIS CV, DAPA−CKD and SCORED). Where unreported, event rates for severe hypoglycaemia are estimated from median follow−up and other reported information (DAPA−HF, EMPEROR−REDUCED, SOLOIST−WHF, EMPEROR−PRESERVED, EMPA−REG OUTCOME, DECLARE−TIMI58, VERTIS CV, DAPA−CKD and SCORED). EMPEROR−PRESERVED data on severe hypoglycaemia unavailable, so data on all hypoglycaemia events are shown.

Supplemental figure 7: Effect of SGLT2 inhibitors on (a) LOWER LIMB AMPUTATION and (b) BONE FRACTURE, by patient group and by trial



Heterogeneity between trials within patient groups:
Heart failure p=0.35;
Type 2 DM at high ASCVD risk p=0.02;
Chronic kidney disease: p=0.75

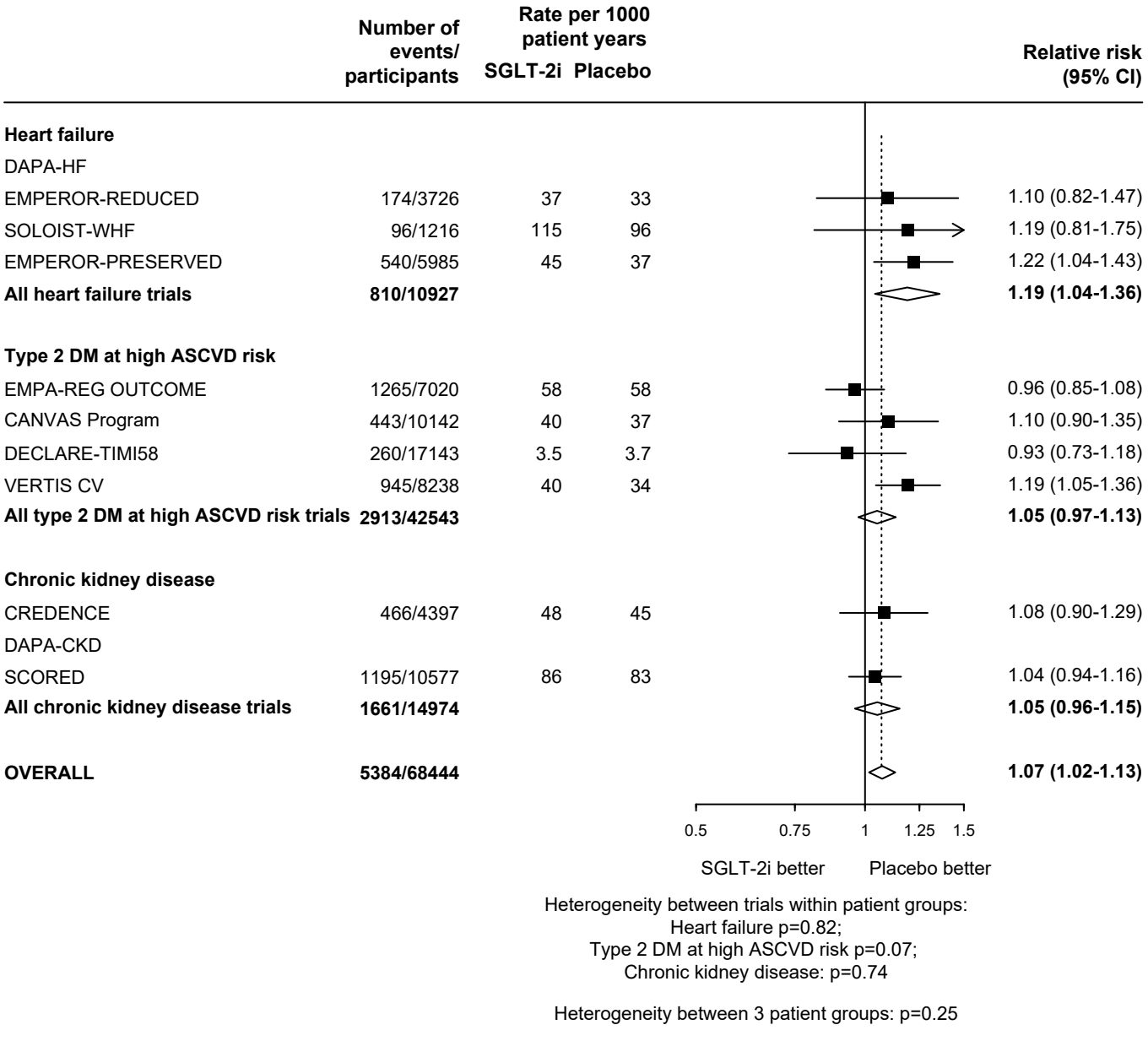
Heterogeneity between 3 patient groups: p=0.25

Heterogeneity between trials within patient groups:
Heart failure p=0.93;
Type 2 DM at high ASCVD risk p=0.24;
Chronic kidney disease: p=0.42

Heterogeneity between 3 patient groups: p=0.94

DM = diabetes mellitus. ASCVD = atherosclerotic cardiovascular disease. Some studies limited analyses to a safety population. Treatment effects for lower limb amputation estimated from numbers of events for several trials (DAPA−HF, EMPEROR−REDUCED, SOLOIST−WHF, EMPEROR−PRESERVED, VERTIS CV, DAPA−CKD and SCORED). Where unreported, event rates for lower limb amputation are estimated from median follow−up and other reported information (DAPA−HF, EMPEROR−REDUCED, SOLOIST−WHF, EMPEROR−PRESERVED, DECLARE−TIMI58, VERTIS CV, CREDENCE, DAPA−CKD and SCORED). Treatment effects for bone fracture estimated from numbers of events for several trials (DAPA−HF, EMPEROR−REDUCED, SOLOIST−WHF, EMPEROR−PRESERVED, VERTIS CV, DAPA−CKD and SCORED). Where unreported, event rates for bone fracture are estimated from median follow−up and other reported information (DAPA−HF, EMPA−REDUCED, SOLOIST−WHF, EMPEROR−PRESERVED, EMPA−REG OUTCOME, DECLARE−TIMI58, VERTIS CV, DAPA−CKD and SCORED)

Supplemental figure 8: Effect of SGLT2 inhibitors on URINARY TRACT INFECTION, by patient group and by trial

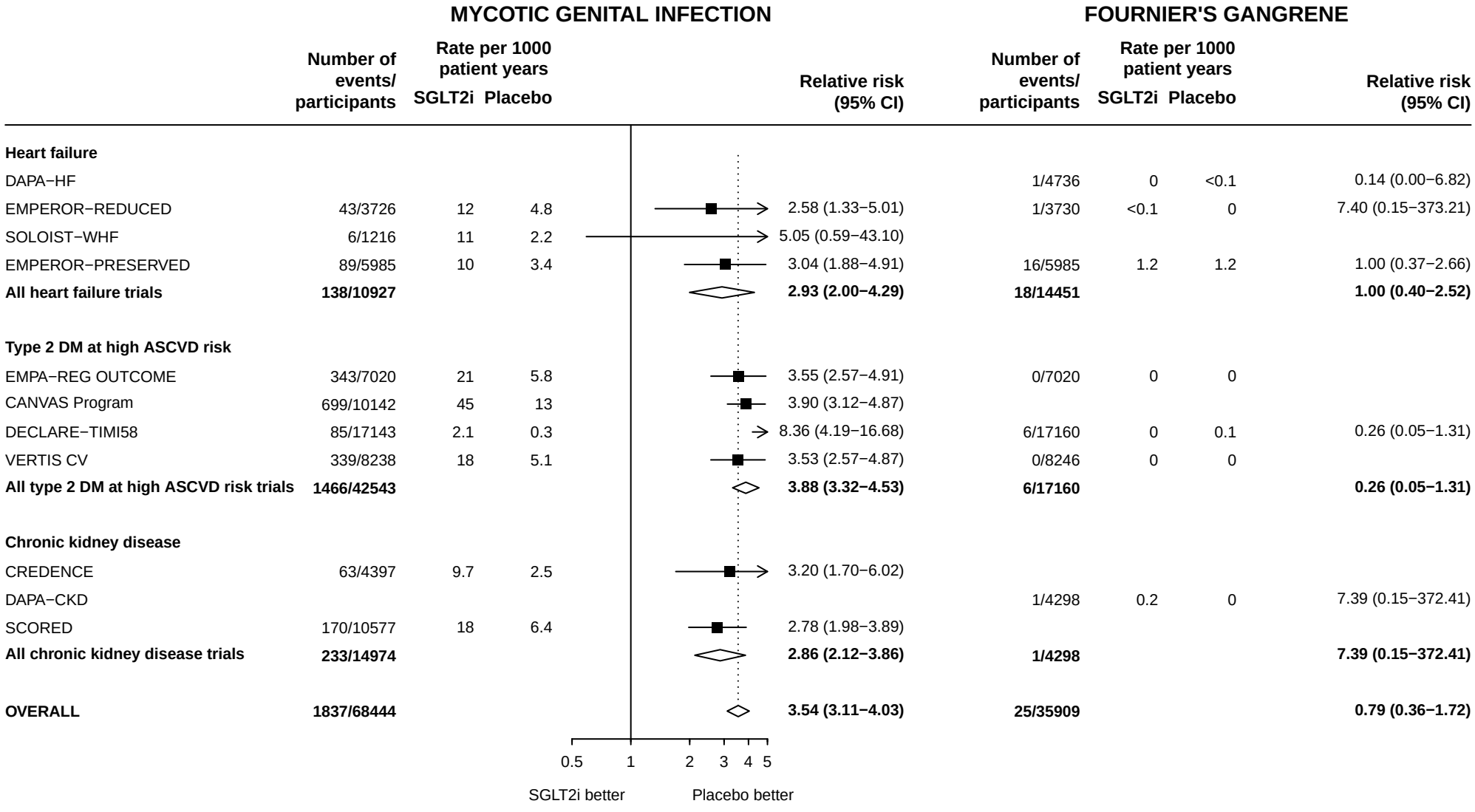


Heterogeneity between trials within patient groups:
Heart failure p=0.82;
Type 2 DM at high ASCVD risk p=0.07;
Chronic kidney disease: p=0.74

Heterogeneity between 3 patient groups: p=0.25

DM = diabetes mellitus. ASCVD = atherosclerotic cardiovascular disease. Some studies limited analyses to a safety population. DAPA-HF and DAPA -CKD not included as numbers of events (or aggregated numbers across multiple Preferred Terms) unavailable. Urinary tract infection outcomes generally included serious and non-serious advsere events. Treatment effects estimated from numbers of events for several trials (EMPEROR-REDUCED, SOLOIST-WHF, EMPEROR-PRESERVED, DECLARE-TIMI58, VERTIS CV and SCORED). Where unreported, event rates are estimated from median follow-up and other reported information (EMPEROR-REDUCED, SOLOIST-WHF, EMPEROR-PRESERVED, EMPA-REG-OUTCOME, DECLARE-TIMI58, VERTIS CV and SCORED).

Supplemental figure 9: Effect of SGLT2 inhibitors on (a) MYCOTIC GENITAL INFECTION and (b) FOURNIER'S GANGRENE, by patient group and by trial

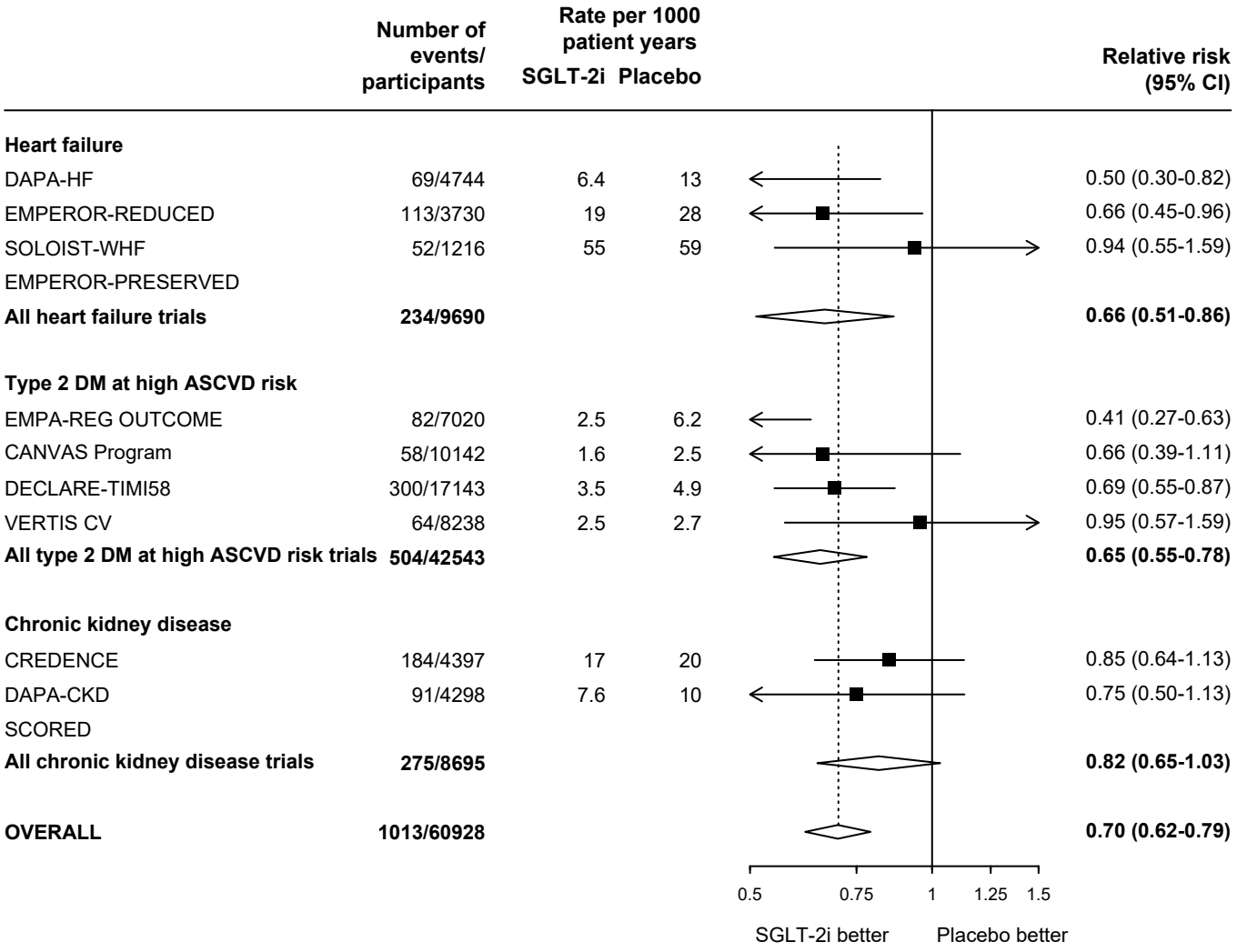


Heterogeneity between trials within patient groups:
Heart failure p=0.82;
Type 2 DM at high ASCVD risk p=0.15;
Chronic kidney disease: p=0.7

Heterogeneity between 3 patient groups: p=0.12

DM = diabetes mellitus. ASCVD = atherosclerotic cardiovascular disease. Some studies limited analyses to a safety population. Where sex−specific treatment effects and event rates were reported for mycotic genital infection, an inverse−variance weighted average was calculated (CANVAS Program and CREDENCE). Treatment effects for mycotic genital infection estimated from numbers of events for several trials (EMPEROR−REDUCED, SOLOIST−WHF, EMPEROR−PRESERVED, VERTIS CV and SCORED). Where unreported, event rates for mycotic genital infection are estimated from median follow−up and other reported information (EMPEROR−REDUCED, SOLOIST−WHF, EMPEROR−PRESERVED, EMPA−REG OUTCOME, DECLARE−TIMI58, VERTIS CV and SCORED). Formal peer−reviewed published results for Fournier's gangrene unavailable for SOLOIST−WHF, CANVAS Program, CREDENCE and SCORED. EMPEROR−PRESERVED data for Fournier's gangrene uses reports of 'complicated genital infections'. Due to rarity of Fournier's gangrene, Peto's method was used to combine results from trials. Trials with no events in either arm were not included in the meta−analysis.

Supplemental figure 10: Effect of SGLT2 inhibitors on ACUTE KIDNEY INJURY, by patient group and by trial



Heterogeneity between trials within patient groups:
Heart failure p=0.24;
Type 2 DM at high ASCVD risk p=0.08;
Chronic kidney disease: p=0.62

Heterogeneity between 3 patient groups: p=0.3

DM = diabetes mellitus. ASCVD = atherosclerotic cardiovascular disease. Treatment effects for acute kidney injury estimated from numbers of events for DAPA-HF, SOLOIST-WHF, EMPA-REG OUTCOME, VERTIS CV and DAPA-CKD. Where unreported, event rates for acute kidney injury are estimated from follow-up duration and other reported information for DAPA-HF, SOLOIST-WHF, EMPA-REG OUTCOME, DECLARE-TIMI58, VERTIS CV and DAPA-CKD. Some studies limited analyses for acute kidney injury to a safety population. Results for acute kidney injury from SCORED and EMPEROR-PRESERVED unavailable. EMPA-REG OUTCOME also reported effects on a standard MedDRA query of Acute Renal Failure: 246/4687 (rate 17) vs 155/2333 (rate 21), RR=0.79 (0.65-0.96). EMPEROR-PRESERVED also reported effects on Acute Renal Failure: 363/2996 (rate 56) vs 384/2989 (rate 59), RR=0.94 (0.82-1.08).