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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This supplemental material has been provided by the authors to give readers additional information about their work.

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

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.
 - (canagliflozin\$ or dapagliflozin\$ or empagliflozin\$ or ertugliflozin\$ or ipragliflozin\$ or
- 18 Iuseogliflozin\$ 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

- Randomized controlled trial/
 Controlled clinical study/
 random\$.ti,ab.
 randomization/
 intermethod comparison/
 placebo.ti,ab.
 (compare or compared or comparison).ti. ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or
 comparing or comparison)).ab.
 (open adj label).ti,ab.
 ((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

- 14 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. not (comparative study/ or controlled study/ or randomi?ed controlled.ti,ab. or randomly

21 assigned.ti,ab.)

Cross-sectional study/ not (randomized controlled trial/ or controlled clinical study/ or controlled

- 22 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.

(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

- 32 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.

(canagliflozin\$ or dapagliflozin\$ or empagliflozin\$ or ertugliflozin\$ or ipragliflozin\$ or

- 43 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. Followup 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)	Placebo (n=703)
	Participants with events	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)	Placebo (n=625)
	Participants with events	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 (\geq 57% [equivalent to a doubling of creatinine], \geq 50%, and \geq 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 \geq 40% eGFR decline. For trials that have only reported kidney disease progression using either of a \geq 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 \geq 40% decline in eGFR.

References for Supplemental Methods

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Supplemental table 1: Quality assessments

Unique ID	Study ID	Experimental	Comparator	<u>D1</u>
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)

				Absolut	te rates and ef	fects per 1000 patie	ent years			
	REDUCI FR	STABLE HEART FAILURE EDUCED EJECTION PRESERVED EJECTION FRACTION FRACTION			RECENTLY FOR WOR F/	' HOSPITALIZED SENING HEART AILURE	TYPE MELLI ATHER CARDIOV	2 DIABETES IUS AT HIGH OSCLEROTIC ASCULAR RISK	ALBUMINURIC CHRONIC KIDNEY DISEASE	
	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-REDUCED & DAPA-HF) versus stable heart failure with preserved ejection fraction (i.e. EMPEROR-REDUCED & DAPA-HF) versus stable heart failure with preserved ejection fraction (i.e. EMPEROR-RESERVED) 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

			Abso	ute rates and effect	s per 1000 pa	tient years		
		REDUCED EJECT	TION FRACTI	ON		ΓΙΟΝ		
	Type 2 dia	betes mellitus	No	diabetes	Type 2 dia	betes 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

	Abs	olute rates and effec	ts per 1000 pat	ient years
	Type 2 di	abetes mellitus	No	diabetes
	Event rete	Events avoided/ caused (SE) in	Event rete	Events avoided/ caused (SE) in
	Event rate	SGLI-ZI anns	Event rate	SGLT-ZI anns
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

HOSPITALIZATION FOR HEART FAILURE OR CARDIOVASCULAR DEATH

KIDNEY DISEASE PROGRESSION

	Number of events/	Rate p patier	ber 1000 ht years		Relative risk	Number of events/	Rate patie	per 1000 ent years		Relative risk
	participants	SGL12i	Placebo		(95% CI)	participants	SGL12i	Placebo		(95% CI)
Heart failure				:					:	
DAPA-HF (diabetes)	486/2139	132	168	_	0.75 (0.63–0.90)	NA/2139	-	-	← -	0.73 (0.39–1.34)
DAPA-HF (no diabetes)	402/2605	87	116		0.73 (0.60–0.88)	NA/2603	-	-	← ■	0.67 (0.30–1.49)
EMPEROR-REDUCED (diabetes)	465/1856	177	246	_	0.72 (0.60–0.87)	61/1856	23	42	4	
EMPEROR-REDUCED (no diabetes)	358/1874	139	176		0.78 (0.64–0.97)	27/1874	8.3	20	<	0.42 (0.19–0.97)
SOLOIST-WHF	NA/1222	_	_	_	0.71 (0.56–0.89)					
EMPEROR-PRESERVED (diabetes)	530/2938	75	90		0.79 (0.67–0.94)	149/2938	23	23	— —	1.00 (0.72–1.38)
EMPEROR-PRESERVED (no diabetes)	396/3050	53	66		0.78 (0.64–0.95)	71/3050	9.9	12		0.87 (0.54–1.38)
All heart failure trials	2637/15684			\diamond	0.76 (0.70–0.82)	375/14460			\langle	0.78 (0.64–0.96)
Type 2 DM at high ASCVD risk										
EMPA-REG OUTCOME	463/7020	20	30	_	0.66 (0.55–0.79)	152/6968	6.3	12		0.54 (0.40–0.75)
CANVAS Program	652/10142	16	21		0.78 (0.67–0.91)	249/10142	5.5	9	←■	0.60 (0.47–0.77)
DECLARE-TIMI58	913/17160	12	15	÷.	0.83 (0.73–0.95)	365/17160	3.7	7	4	0.53 (0.43–0.66)
VERTIS CV	694/8246	23	27		0.88 (0.75–1.03)	283/8246	9	12		0.81 (0.63–1.04)
All type 2 DM at high ASCVD risk trials	2722/42568			\diamond	0.80 (0.74–0.86)	1049/42516			\diamond	0.61 (0.54–0.69)
Chronic kidney disease										
CREDENCE	432/4401	32	45	_	0.69 (0.57–0.83)	377/4401	27	40		- 0.66 (0.53–0.81)
DAPA-CKD (diabetes)	204/2906	27	38	_	0.70 (0.53–0.92)	276/2906	35	60	<-	0.57 (0.45–0.73)
DAPA-CKD (no diabetes)	34/1398	11	13	← ■	→ 0.79 (0.40–1.55)	109/1398	29	53		0.51 (0.34–0.75)
SCORED	640/10584	40	51		0.77 (0.66–0.91)	89/10584	5	7	← ■	0.71 (0.46–1.08)
All chronic kidney disease trials	1310/19289			\diamond	0.73 (0.65–0.82)	851/19289			$\langle \rangle$	0.62 (0.54–0.71)
OVERALL	6669/77541			\$	0.76 (0.72–0.80)	2275/76265			\diamond	0.64 (0.59–0.70)
				0.5 0.75 1	1.25 1.5				0.5 0.75	5 1 1.25 1.5
				SGLT2i better P	lacebo better				SGLT2i bett	er Placebo better

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

	Number of	Rate patie	per 1000 ent years					Rolativo risk
	participants	SGLT-2i	Placebo					(95% CI)
Heart failure					:			
DAPA-HF	549/4744	69	98					0.70 (0.59-0.83)
EMPEROR-REDUCED	588/3730	107	155		i=			0.69 (0.59-0.81)
SOLOIST-WHF	491/1222	404	639	\leftarrow				0.64 (0.49-0.83)
EMPEROR-PRESERVED	611/5988	43	60					0.71 (0.60-0.83)
All heart failure trials	2239/15684				\diamond			0.69 (0.63-0.76)
Type 2 DM at high ASCVD risk								
EMPA-REG OUTCOME	221/7020	9.4	15	\leftarrow				0.65 (0.50-0.85)
CANVAS Program	243/10142	5.5	8.7					0.67 (0.52-0.87)
DECLARE-TIMI58	498/17160	6.2	8.5		— —			0.73 (0.61-0.88)
VERTIS CV	238/8246	7	11		_			0.70 (0.54-0.90)
All type 2 DM at high ASCVD risk to	rials 1200/42568				\Leftrightarrow			0.70 (0.62-0.78)
Chronic kidney disease								
CREDENCE	230/4401	16	25	←	-			0.61 (0.47-0.80)
DAPA-CKD	108/4304	7.2	14	-				0.52 (0.35-0.77)
SCORED	605/10584	35	51	_				0.67 (0.55-0.82)
All chronic kidney disease trials	943/19289			<	>			0.63 (0.54-0.73)
OVERALL	4382/77541				\diamond			0.68 (0.64-0.73)
				0.5	0.75		1.25 1.5	
				SGL	T-2i better	Pla	acebo better	

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

		M	OCARDIAI		N	STROKE					
	Number of events/ participants	Rate patie SGLT2i	per 1000 ent years Placebo		Relative risk (95% Cl)	Number of events/ participants	Rate po patien SGLT2i P	er 1000 t years lacebo			Relative risk (95% Cl)
Type 2 DM at high ASCVD risk											
EMPA-REG OUTCOME	349/7020	17	19	_	0.87 (0.70–1.09)	233/7020	12	11	-	┼╼	→1.18 (0.89–1.56)
CANVAS Program	421/10142	11	13	_	0.89 (0.73–1.09)	309/10142	7.9	9.6		+	0.87 (0.69–1.09)
DECLARE-TIMI58	834/17160	12	13	- 	0.89 (0.77–1.01)	466/17160	6.9	6.8		- #	1.01 (0.84–1.21)
VERTIS CV	488/8246	18	17		— 1.04 (0.86–1.26)	272/8246	10	9	_	╡╋──	— 1.06 (0.82–1.37)
All type 2 DM at high ASCVD risk trials	s 2092/42568			\Diamond	0.92 (0.84–1.00)	1280/42568			-	\Rightarrow	1.01 (0.90–1.13)
Chronic kidney disease											
CREDENCE	178/4401	15	17		— 0.86 (0.64–1.16)	142/4401	11	14		+	0.77 (0.55–1.08)
SCORED	NA/10584	-		—	0.68 (0.52–0.89)	NA/10584	-	- ←			0.66 (0.48–0.91)
All chronic kidney disease trials	178/14985				0.76 (0.62–0.92)	142/14985			<>		0.71 (0.56–0.90)
OVERALL	2270/57553			\diamond	0.89 (0.82–0.96)	1422/57553			<	>	0.94 (0.85–1.04)
				,	i1			-	—	 ,	
			0.5	0.75 1	1.25 1.5			0.5	0.75	1 1.2	25 1.5
			S	GLT2i better Pla	acebo better			SC	LT2i better	Placeb	o better
		Heteroge Typ	eneity between t e 2 DM at high / Chronic kidney	rials within patient ASCVD risk p=0.5 disease: p=0.25	groups: 4;		Heteroger Typ	neity between e 2 DM at high Chronic kidne	trials within p ۱ ASCVD risk y disease: p=	atient gr p=0.4; 0.52	oups:
		Heterog	eneity between	2 patient groups:	p=0.08		Heteroge	eneity betweer	1 2 patient gr	oups: p=	0.01

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

	Number of	Rate patie	per 1000 ent years				Polativo risk
	participants	SGLT-2i	Placebo				(95% CI)
Heart failure					;		
DAPA-HF	605/4744	79	95			-	0.83 (0.71-0.97)
EMPEROR-REDUCED	515/3730	101	107			∎┿	0.92 (0.77-1.10)
SOLOIST-WHF	141/1222	135	163	-			0.82 (0.59-1.14)
EMPEROR-PRESERVED	849/5988	66	67		÷	- #	1.00 (0.87-1.15)
All heart failure trials	2110/15684				V	>	0.91 (0.84-1.00)
Type 2 DM at high ASCVD risk							
EMPA-REG OUTCOME	463/7020	19	29	_			0.68 (0.57-0.82)
CANVAS Program	681/10142	17	20			_	0.87 (0.74-1.01)
DECLARE-TIMI58	1099/17160	15	16			∎┼╴	0.93 (0.82-1.04)
VERTIS CV	727/8246	24	26			∎┼─	0.93 (0.80-1.08)
All type 2 DM at high ASCVD risk to	rials 2970/42568				\$	>	0.87 (0.81-0.94)
Chronic kidney disease							
CREDENCE	369/4401	29	35		_	_	0.83 (0.68-1.02)
DAPA-CKD	247/4304	22	31				0.69 (0.53-0.88)
SCORED	492/10584	35	35			- #	0.99 (0.83-1.18)
All chronic kidney disease trials	1108/19289				\langle	>	0.86 (0.77-0.97)
OVERALL	6188/77541				\diamond		0.88 (0.84-0.93)
				0.5	0.75	1 1.25	ר 1.5
				SGL	T-2i better	Placebo b	etter

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 \geq 40% decline in eGFR: EMPEROR-REDUCED, EMPEROR-PRESERVED, CANVAS Program, DECLARE-TIMI58. The following trials used a \geq 50% decline in eGFR: DAPA-HF, DAPA-CKD, SCORED. The following trials used a \geq 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 \geq 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

SEVERE HYPOGI YCAEMIA

KETOACIDOSIS

	Number of events/ participants	Rate pe patient SGLT2i P	er 1000 t years lacebo			Relative risk (95% Cl)	Number of events/ participants	Rate pe patient SGLT2i P	er 1000 t years lacebo			Relative risk (95% Cl)
Heart failure					:					:		
DAPA-HF	3/4736	0.8	0	←	→6.	00 (0.30–119.72)	8/4736	1.1	1.1	<	\Rightarrow	1.00 (0.25–3.99)
EMPEROR-REDUCED	0/3726	0	0				13/3730	2.4	2.8	< ∎	\rightarrow	0.86 (0.29–2.55)
SOLOIST-WHF	6/1216	4.4	8.7	K		0.50 (0.09–2.75)	11/1216	20	4.4		\rightarrow	4.54 (0.99–20.95)
EMPEROR-PRESERVED	9/5985	0.6	0.8	< ∎		0.80 (0.21–2.97)	151/5985	11	12		∎┤───	0.93 (0.68–1.28)
All heart failure trials	18/11937					0.85 (0.32–2.27)	183/15667			\sim	\rightarrow	0.99 (0.74–1.32)
Type 2 DM at high ASCVD risk												
EMPA-REG OUTCOME	5/7020	0.3	0.1	←		1.99 (0.22–17.80)	99/7020	4.3	5	_	<u> </u>	0.84 (0.56–1.26)
CANVAS Program	18/10142	0.6	0.3		>	2.16 (0.69–6.80)						
DECLARE-TIMI58	39/17143	0.7	0.3		>	2.18 (1.10–4.30)	141/17143	1.6	2.3	← ■	-	0.68 (0.49–0.95)
VERTIS CV	21/8238	1.2	0.2		× 4	4.75 (1.11–20.37)	446/8238	17	20		+	0.88 (0.73–1.06)
All type 2 DM at high ASCVD risk tr	ials 83/42543					2.40 (1.41–4.06)	686/32401			\sim	~	0.83 (0.71–0.96)
Chronic kidney disease												
CREDENCE	12/4397	2.2	0.2		<u> </u>	0.80 (1.39–83.65)	465/4397	44	49		┢┼╴	0.92 (0.77–1.11)
DAPA-CKD	2/4298	0	0.4	←	\rightarrow	0.25 (0.01–5.54)	42/4298	2.7	5.4	<	-	0.50 (0.26–0.95)
SCORED	44/10577	4.3	2			2.14 (1.14–4.03)	108/10577	7.5	7.8			0.96 (0.66–1.40)
All chronic kidney disease trials	58/19272			-		2.27 (1.25–4.10)	615/19272			<	>	0.89 (0.76–1.05)
OVERALL	159/73752					2.03 (1.41–2.93)	1484/67340			\langle	>	0.87 (0.79–0.97)
				0.5 1 1	.5 2 3 4					0.5 0.75	1 1.25 1.5	5
				SGLT2i better	Placebo bette	er				SGLT2i better	Placebo bet	ter
		Heteroge Typ	eneity bet He be 2 DM a Chronic	ween trials withi art failure p=0.3 t high ASCVD ri kidney disease:	n patient groups 7; isk p=0.81; p=0.12	:		Heteroge Typ	eneity betv Hea be 2 DM a Chronic I	ween trials within art failure p=0.26 t high ASCVD ris kidney disease: p	patient group k p=0.42; =0.18	s:
		Heterog	geneity be	tween 3 patient	groups: p=0.17			Heteroç	geneity be	tween 3 patient g	roups: p=0.53	3

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-REDUCED, SOLOIST-WHF, EMPEROR-PRESERVED, 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-REDUCED, SOLOIST-WHF, EMPEROR-REDUCED, SOLOIST-WHF, 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-REDUCED, SOLOIST-WHF, 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

BONE FRACTURE

LOWER LIMB AMPUTATION

	Number of events/ participants	Rate pe patient SGLT2i P	er 1000 years lacebo			Relative risk (95% Cl)	Number of events/ participants	Rate pe patient SGLT2i PI	r 1000 years acebo			Relative risk (95% Cl)
Heart failure					:							
DAPA-HF	25/4736	3.6	3.3	←		1.08 (0.50–2.37)	99/4736	14	14	——I	4	0.98 (0.66–1.45)
EMPEROR-REDUCED	23/3726	5.2	4		╺───	• 1.30 (0.57–2.96)	87/3726	18	17		┼ब──>	▶ 1.07 (0.71–1.62)
SOLOIST-WHF	5/1216	8.8	2.2	←	\rightarrow	↓ 4.04 (0.45–36.04)	21/1216	26	20		╞──■>	1.35 (0.57–3.17)
EMPEROR-PRESERVED	39/5985	2.4	3.5	← ■		0.69 (0.37–1.31)	260/5985	20	19		┼┳───	1.06 (0.84–1.35)
All heart failure trials	92/15663					0.98 (0.65–1.49)	467/15663			<	\Rightarrow	1.06 (0.88–1.26)
Type 2 DM at high ASCVD risk												
EMPA-REG OUTCOME	131/7020	6.5	6.5		- #	1.00 (0.70–1.44)	270/7020	12	13		· 	0.94 (0.73–1.21)
CANVAS Program	187/10142	6.3	3.4		>	1.97 (1.41–2.75)	496/10142	15	12			▶ 1.26 (1.04–1.52)
DECLARE-TIMI58	236/17143	3.4	3.1	-		1.09 (0.84–1.40)	897/17143	13	12	_	╆═╾	1.04 (0.91–1.18)
VERTIS CV	156/8238	6.7	5.5	-		• 1.23 (0.87–1.74)	299/8238	12	12		┢━───	1.02 (0.81–1.30)
All type 2 DM at high ASCVD risk t	rials 710/42543					1.25 (1.07–1.47)	1962/42543				\diamond	1.07 (0.98–1.17)
Chronic kidney disease												
CREDENCE	133/4397	12	11			• 1.11 (0.79–1.56)	135/4397	12	12	— — •	.	0.98 (0.70–1.37)
DAPA-CKD	74/4298	6.8	7.6			0.90 (0.57–1.41)	154/4298	16	13	_	┼╼╾>	▶ 1.23 (0.90-1.68)
SCORED	65/10577	4.5	4.7			• 0.97 (0.60–1.57)	228/10577	16	17		⊬	0.95 (0.73–1.23)
All chronic kidney disease trials	272/19272			<		1.01 (0.80–1.28)	517/19272			<	\Rightarrow	1.03 (0.87–1.23)
OVERALL, excluding CANVAS	848/61351				\diamond	1.06 (0.93–1.21)	2190/61351				\diamond	1.03 (0.95–1.12)
OVERALL	1074/77478				\sim	1.16 (1.02–1.31)	2946/77478				\diamond	1.06 (0.99–1.14)
			(0.5 0.75	1 1.25 1	ı .5			0.5	0.75	1 1.25 1	י 5.
				SGLT2i better	Placebo be	etter			SC	GLT2i better	Placebo b	etter
		Heteroge Typ Heterog	neity betw Hea e 2 DM at Chronic F	veen trials withir art failure p=0.35 t high ASCVD ris kidney disease: p tween 3 patient	n patient grou 5; sk p=0.02; p=0.75 groups: p=0.2	ps:		Heteroge Type	neity betwee Heart fa e 2 DM at hig Chronic kidn eneity betwee	n trials within p ailure p=0.93; Jh ASCVD risk ley disease: p= en 3 patient gr	p=0.24; 0.42	ıps: 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, 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

	Number of events/ participants	Rate per 1000 patient years				Polativo risk	
		SGLT-2i	Placebo				(95% CI)
Heart failure							
DAPA-HF							
EMPEROR-REDUCED	174/3726	37	33				1.10 (0.82-1.47)
SOLOIST-WHF	96/1216	115	96			<u> </u>	1.19 (0.81-1.75)
EMPEROR-PRESERVED	540/5985	45	37				1.22 (1.04-1.43)
All heart failure trials	810/10927						1.19 (1.04-1.36)
Type 2 DM at high ASCVD risk							
EMPA-REG OUTCOME	1265/7020	58	58		_	╼┼┊	0.96 (0.85-1.08)
CANVAS Program	443/10142	40	37				1.10 (0.90-1.35)
DECLARE-TIMI58	260/17143	3.5	3.7			·	0.93 (0.73-1.18)
VERTIS CV	945/8238	40	34				1.19 (1.05-1.36)
All type 2 DM at high ASCVD risk tr	ials 2913/42543					\Rightarrow	1.05 (0.97-1.13)
Chronic kidney disease							
CREDENCE	466/4397	48	45				1.08 (0.90-1.29)
DAPA-CKD							
SCORED	1195/10577	86	83				1.04 (0.94-1.16)
All chronic kidney disease trials	1661/14974						1.05 (0.96-1.15)
OVERALL	5384/68444					\diamond	1.07 (1.02-1.13)
				0.5	0.75	1 1.25 1.5	
				SGL	T-2i better	Placebo better	

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

MYCOTIC GENITAL INFECTION

FOURNIER'S GANGRENE

	Number of events/Rate per 1000 patient yearsRelative riskparticipantsSGLT2i Placebo(95% Cl)		Number of events/ participants	Rate per 1000 patient years SGLT2i Placebo		Relative risk (95% Cl)				
Heart failure					:					
DAPA-HF							1/4736	0	<0.1	0.14 (0.00-6.82)
EMPEROR-REDUCED	43/3726	12	4.8		 →	2.58 (1.33–5.01)	1/3730	<0.1	0	7.40 (0.15–373.21)
SOLOIST-WHF	6/1216	11	2.2		>	5.05 (0.59–43.10)				
EMPEROR-PRESERVED	89/5985	10	3.4			3.04 (1.88–4.91)	16/5985	1.2	1.2	1.00 (0.37–2.66)
All heart failure trials	138/10927				>	2.93 (2.00–4.29)	18/14451			1.00 (0.40–2.52)
Type 2 DM at high ASCVD risk										
EMPA-REG OUTCOME	343/7020	21	5.8		i	3.55 (2.57–4.91)	0/7020	0	0	
CANVAS Program	699/10142	45	13		- 	3.90 (3.12–4.87)				
DECLARE-TIMI58	85/17143	2.1	0.3		\rightarrow	8.36 (4.19–16.68)	6/17160	0	0.1	0.26 (0.05–1.31)
VERTIS CV	339/8238	18	5.1			3.53 (2.57–4.87)	0/8246	0	0	
All type 2 DM at high ASCVD risk trials	1466/42543				\diamond	3.88 (3.32–4.53)	6/17160			0.26 (0.05–1.31)
Chronic kidney disease										
CREDENCE	63/4397	9.7	2.5		\longrightarrow	3.20 (1.70–6.02)				
DAPA-CKD							1/4298	0.2	0	7.39 (0.15–372.41)
SCORED	170/10577	18	6.4			2.78 (1.98–3.89)				
All chronic kidney disease trials	233/14974				$\langle \rangle$	2.86 (2.12–3.86)	1/4298			7.39 (0.15–372.41)
OVERALL	1837/68444				\$	3.54 (3.11–4.03)	25/35909			0.79 (0.36–1.72)
			г О.	5 1	2 3 4 5					
			SGLT2	i better	Placebo bet	ter				

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

	Number of	Rate patie	per 1000 nt years			Deletive riek	
	participants	SGLT-2i	Placebo				(95% CI)
Heart failure					:		
DAPA-HF	69/4744	6.4	13	←			0.50 (0.30-0.82)
EMPEROR-REDUCED	113/3730	19	28	←	-		0.66 (0.45-0.96)
SOLOIST-WHF	52/1216	55	59			∎┼──>	0.94 (0.55-1.59)
EMPEROR-PRESERVED							
All heart failure trials	234/9690			<	>		0.66 (0.51-0.86)
Type 2 DM at high ASCVD risk							
EMPA-REG OUTCOME	82/7020	2.5	6.2	←	-		0.41 (0.27-0.63)
CANVAS Program	58/10142	1.6	2.5	←	-	<u> </u>	0.66 (0.39-1.11)
DECLARE-TIMI58	300/17143	3.5	4.9				0.69 (0.55-0.87)
VERTIS CV	64/8238	2.5	2.7			∎ →	0.95 (0.57-1.59)
All type 2 DM at high ASCVD risk t	rials 504/42543			<	>		0.65 (0.55-0.78)
Chronic kidney disease							
CREDENCE	184/4397	17	20				0.85 (0.64-1.13)
DAPA-CKD	91/4298	7.6	10	←			0.75 (0.50-1.13)
SCORED							
All chronic kidney disease trials	275/8695				\leftarrow	>	0.82 (0.65-1.03)
OVERALL	1013/60928				\overleftrightarrow		0.70 (0.62-0.79)
				0.5	0.75	1 1.25 1.5	
				SGL	-2i better	Placebo better	

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).