SUPPLEMENTARY APPENDIX

Table S1. Search strategy

EMBASE via Ovid

1. exp Sodium-Glucose Transporter 2/
2. Sodium-Glucose Transporter$.tw.
3. Sodium-Glucose Co-Transporter$.tw.
4. SGLT2.tw.
5. SGLT-2.tw.
6. Sodium-dependent glucose cotransporter$.tw.
7. (dapagliflozin$ or canagliflozin$ or ipragliflozin$ or tofogliflozin$ or empagliflozin$ or sergliflozin$ or remogliflozin$ or ertugliflozin$ or luseogliflozin$ or sotagliflozin).tw.
8. or/1-7
9. Exp Type 2 diabetes mellitus/
10. 8 and 9
11. exp Clinical Trial/
12. exp Random Allocation/
13. exp Single Blind Method/
14. exp Double Blind Method/
15. (random$ adj5 trial$).tw.
16. (random$ adj5 allocation$).tw.
17. (blind$ adj5 method$).tw.
18. or/11-17
19. 10 and 18
20. Limit 19 to (English language and humans)

MEDLINE via Ovid

1. exp Sodium-Glucose Transporter 2/
2. Sodium-Glucose Transporter$.tw.
3. Sodium-Glucose Co-Transporter$.tw.
4. SGLT2.tw.
5. SGLT-2.tw.
6. Sodium-dependent glucose cotransporter$.tw.
7. (dapagliflozin$ or canagliflozin$ or ipragliflozin$ or tofogliflozin$ or empagliflozin$ or sergliflozin$ or remogliflozin$ or ertugliflozin$ or luseogliflozin$ or sotagliflozin$).tw.
8. or/1-7
9. Exp Type 2 diabetes mellitus/
10. 8 and 9
11. exp Clinical Trial/
12. exp Random Allocation/
13. exp Single Blind Method/
14. exp Double Blind Method/
15. (random$ adj5 trial$).tw.
16. (random$ adj5 allocation$).tw.
17. (blind$ adj5 method$).tw.
18. or/11-17
19. 10 and 18
20. Limit 19 to (English language and humans)

Figure S1. Identification of eligible studies: flow diagram

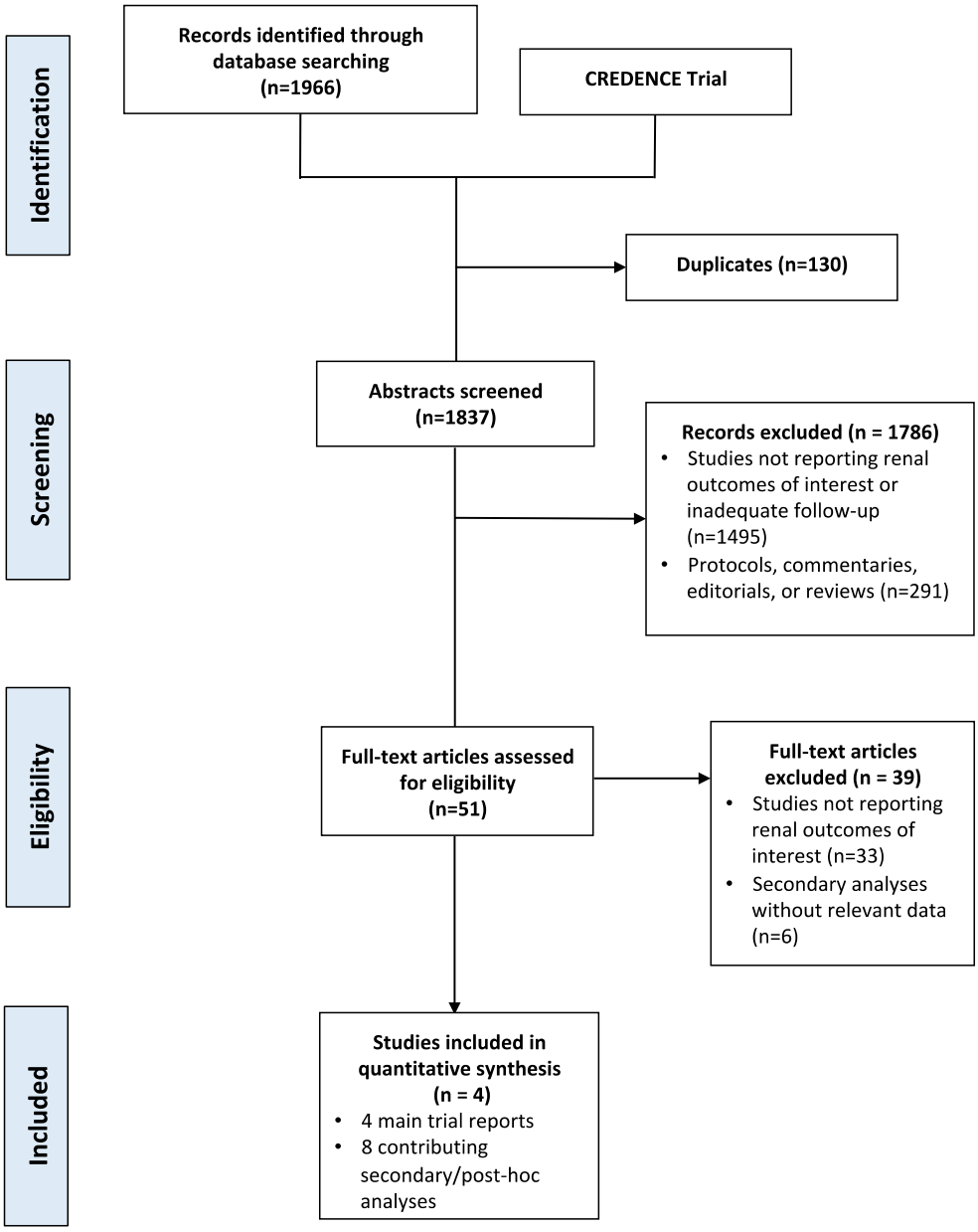


Table S2. Risk of bias assessment

	Sequence generation	Allocation sequence concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting
CREDENCE	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
DECLARE-TIMI 58	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
CANVAS Program	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
EMPA-REG OUTCOME	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

Table S3. Kidney outcome ascertainment and adjudication across included studies
ESKD: end-stage kidney disease; eGFR: estimated glomerular filtration rate; RRT: renal replacement therapy

Study	Pre-specified kidney outcomes[1]	Post-hoc kidney outcomes[1]	Repeat assessment and confirmation of changes in kidney function and initiation of dialysis	Independent adjudication of kidney outcomes
CREDENCE	• ESKD • Doubling of serum creatinine, ESKD or death due to kidney disease • Doubling of serum creatinine, ESKD, cardiovascular or death due to kidney disease • Doubling of serum creatinine • eGFR slope	• Dialysis, transplantation or death due to kidney disease	Yes	Yes
CANVAS Program	• ESKD • Doubling of serum creatinine, ESKD or death due to kidney disease • Doubling of serum creatinine, ESKD, death due to cardiovascular or kidney disease • Doubling of serum creatinine • eGFR slope	• Dialysis, transplantation or death due to kidney disease	Yes	Yes
DECLARE-TIMI 58	• 40% decline in eGFR to <60mL/min/1·73m^2, ESKD or death due to kidney disease • 40% decline in eGFR to <60mL/min/1·73m^2, ESKD, death due to cardiovascular or kidney disease	• None currently reported	Yes	Yes
EMPA-REG	• eGFR slope	• Doubling of serum creatinine to	No[2]	No

OUTCOME	eGFR <45 mL/min/1·73m^2, initiation of RRT or death due to kidney disease • Sustained initiation of RRT[2] • Sustained initiation of RRT or death due to kidney disease[2]

[1]Refers only to kidney outcomes included in this meta-analysis. Other pre-specified and post-hoc kidney outcomes have been reported by individual studies

[2]Main data on kidney outcomes from the EMPA-REG OUTCOME trial were not required to be sustained on repeated measurement. Sustained kidney outcome data were subsequently reported by Wanner et al.[36] These data were preferentially used whenever available. RRT was defined in the EMPA-REG OUTCOME as dialysis or transplantation.

Table S4. Definitions for ESKD-based kidney outcomes
ESKD: end-stage kidney disease; eGFR: estimated glomerular filtration rate; HR: hazard ratio; CI: confidence interval.

Study		Dialysis, transplantation or death due to kidney disease	ESKD	Substantial loss of kidney function, ESKD or death due to kidney disease/substantial loss of kidney function, ESKD, or death due to cardiovascular[1] or kidney disease
CREDENCE	Details	• Chronic dialysis for ≥30 days, transplantation, or death due to kidney disease • Death due to kidney disease refers to deaths in patients who reached ESKD who died prior to receiving dialysis or transplantation and no other cause of death was adjudicated	• Chronic dialysis for ≥30 days, transplantation, or eGFR <15 mL/min/1·73 m^2 sustained for ≥30 days	• Sustained and independently adjudicated doubling of serum creatinine, ESKD or death due to kidney disease • Doubling of serum creatinine defined as ≥2-fold from the baseline assessment that persisted for ≥30 days and was not thought to be due to reversible cause • Baseline serum creatinine was determined by averaging the 2 values closest to randomization
	Measure of effect used	• HR with 95% CI	• HR with 95% CI	• HR with 95% CI
CANVAS Program	Details	• Maintenance dialysis sustained for ≥30 days, transplantation, or death due to kidney disease	• Maintenance dialysis sustained for ≥30 days, transplantation, or sustained eGFR <15 mL/min/1·73^2 for ≥30 days	• Sustained and independently adjudicated doubling of serum creatinine, ESKD or death due to kidney disease • Doubling of serum creatinine sent for adjudication if sustained for two consecutive measures ≥30 days apart or if occurring on the last available measurement

	Measure of effect used	• HR and 95% CI	• HR and 95% CI	• HR and 95% CI
DECLARE-TIMI 58	Details	• Outcome not currently reported	• Outcome not currently reported	• Sustained ≥40% decrease in eGFR to <60 mL/min/1·73m2 and/or ESKD (defined as dialysis ≥90 days or kidney transplantation or confirmed sustained eGFR <15 mL/min/1·73 m^2)
	Measure of effect used	• N/A	• N/A	• HR with 95% CI
EMPA-REG OUTCOME	Details	• Initiation of RRT (dialysis or transplantation) when investigators reported "long term treatment" or the intervention had no stopping date	• Initiation of RRT (dialysis or transplant) when investigators reported "long term treatment" or the intervention had no stopping date	• Any (i.e. not required to be sustained) doubling of serum creatinine accompanied by eGFR <45 mL/min/1·73m^2, any initiation of RRT (dialysis or transplantation) or death due to kidney disease
	Measure of effect used	• Risk ratio based on number of events/participants for initiation of long-term RRT or death due to kidney disease	• HR and 95% CI	• HR and 95% CI

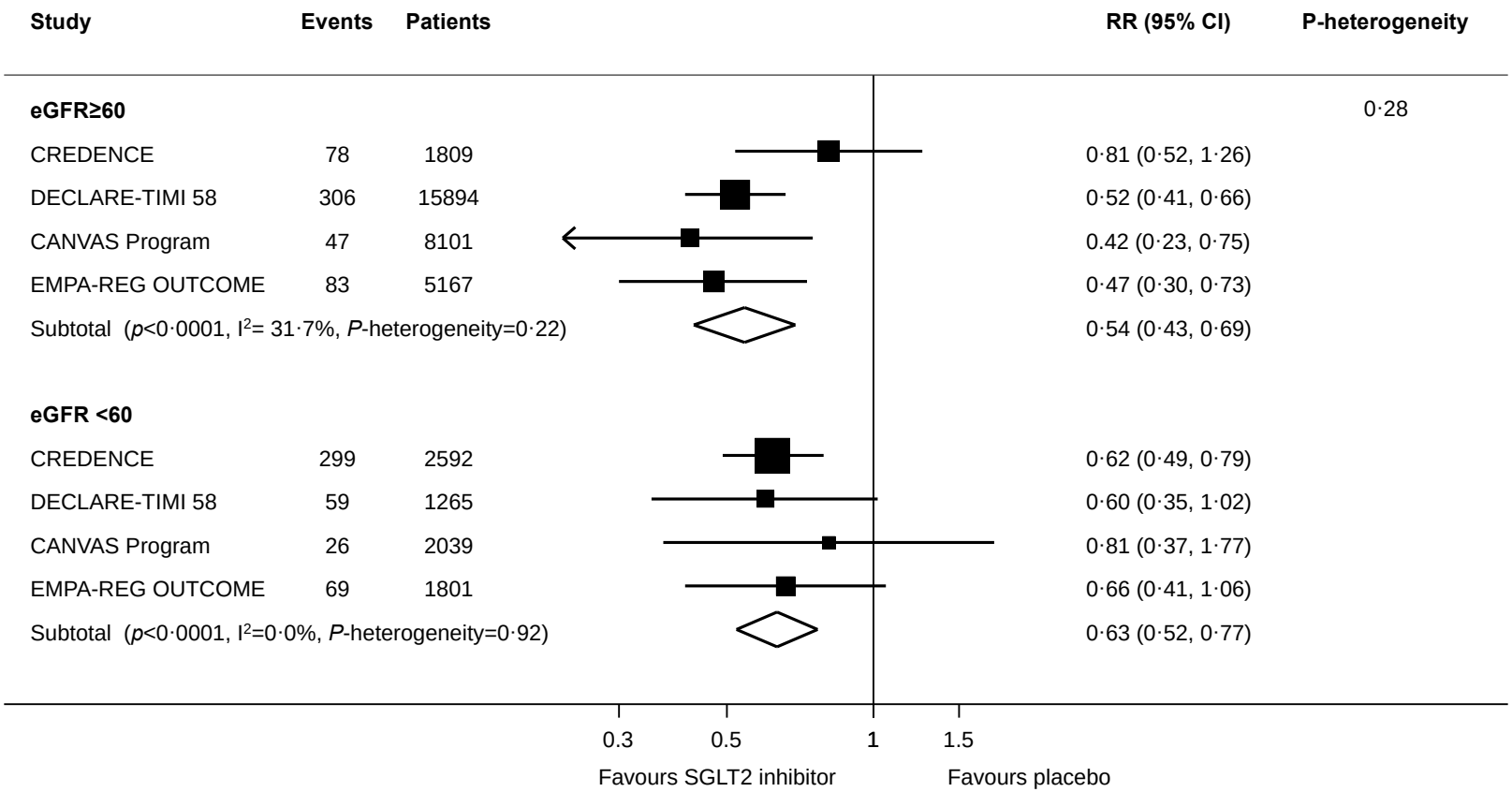
[1]Detailed definitions for cardiovascular death in each study have been previously published.[10-12]

Table S5. Definitions for non-ESKD based kidney outcomes
eGFR: estimated glomerular filtration rate; AKI: acute kidney injury; HR: hazard ratio; CI: confidence interval; N/A: Not applicable.

Study		eGFR slope	AKI
CREDENCE	Details	• Chronic slope from week 3 until end of treatment	• Serious and non-serious events reported spontaneously by investigators • Based on incidence of the single MedDRA preferred term acute kidney injury
	Measure of effect used	• Annual placebo-subtracted difference, mL/min/1·73m^2/year	• HR and 95% CI
CANVAS Program	Details	• Chronic slope from week 6 (CANVAS) or week 13 (CANVAS-R) until last eGFR value on treatment	• Only serious AKI reported across the CANVAS Program (i.e. CANVAS and CANVAS-R) • Serious and non-serious events collected for the duration of the CANVAS trial • Based on incidence of the single MedDRA preferred term acute kidney injury
	Measure of effect used	• Annual placebo-subtracted difference, mL/min/1·73m^2/year	• HR and 95% CI
DECLARE-TIMI 58	Details	• Outcome not currently reported	• Based on the MedDRA preferred term acute kidney injury • Only serious events reported
	Measure of effect used	• N/A	• HR and 95% CI
EMPA-REG OUTCOME	Details	• Post-hoc outcome • Chronic slope from week 4 until last eGFR value on treatment	• All events (investigator reported and serious adverse events) collected • Based on the narrow standardized MedDRA query “acute renal

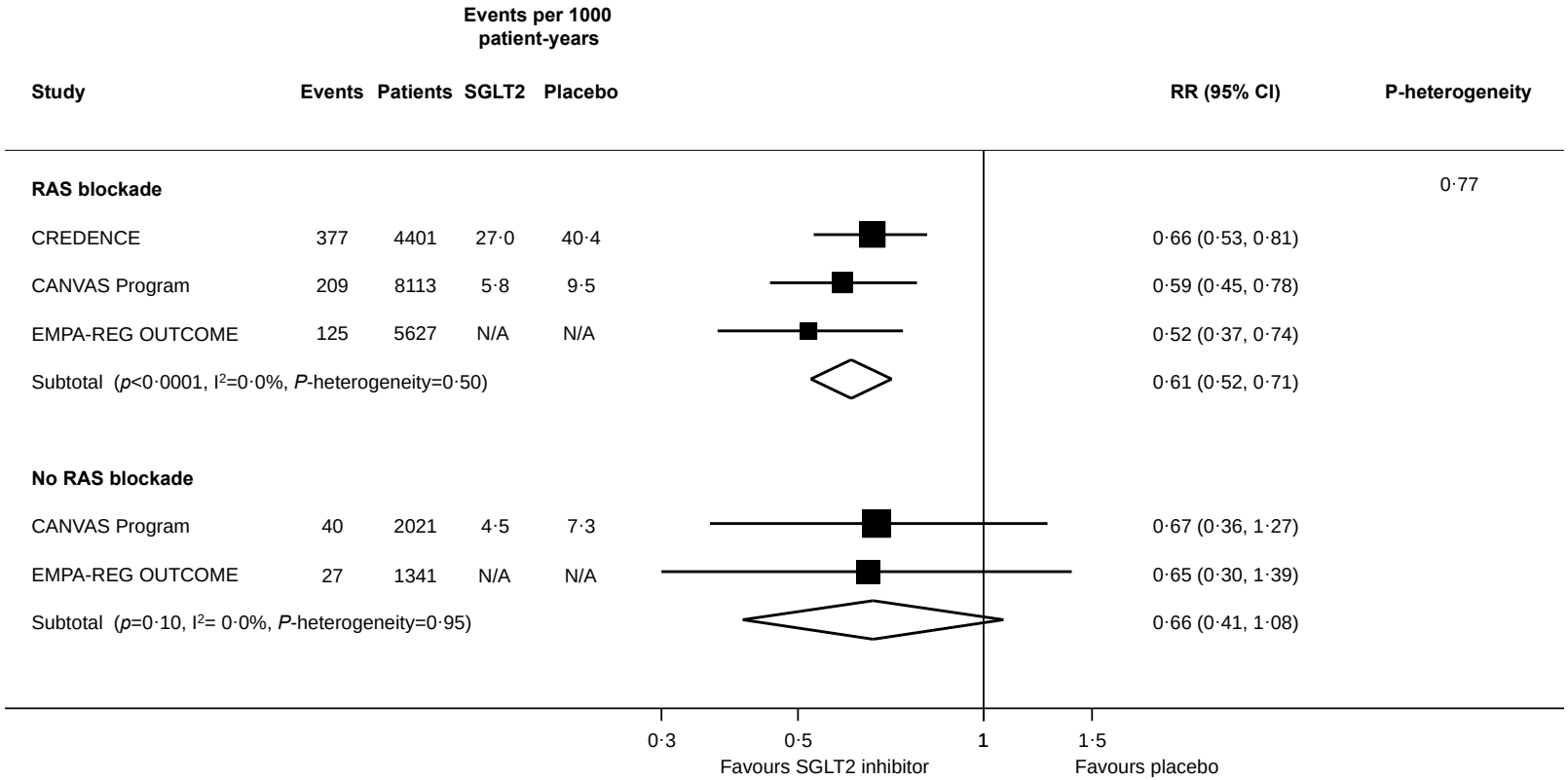
			failure", which included the preferred term acute kidney injury
	Measure of effect used	• Annual placebo-subtracted difference, mL/min/1·73m^2/year	• Incident rate ratio and 95% CI

Figure S2. Effects of SGLT2 inhibitors on substantial loss of kidney function, end-stage kidney disese, or death due to kidney disease in participants with eGFR <60 and ≥60 mL/min/1·73m^2.
SGLT2: sodium glucose cotransporter 2; eGFR: estimated glomerular filtration rate; RR: relative risk; CI: confidence interval.



P-heterogeneity was obtained from random effects meta-regression with restricted maximum likelihood and Hartung Knapp adjustment

Figure S3. Effects of SGLT2 inhibitors on substantial loss of kidney function, end-stage kidney disease, or death due to kidney disease by baseline use of renin-angiotensin system blockade.
RAS: renin-angiotensin system; SGLT2: sodium glucose cotransporter 2; RR: relative risk; CI: confidence interval.



P-heterogeneity was obtained from random effects meta-regression with restricted maximum likelihood and Hartung Knapp adjustment

Table S6. Sensitivity analyses for the outcome substantial loss of kidney function, ESKD or death due to kidney disease based on different endpoint definitions
eGFR: estimated glomerular filtration rate; RR: relative risk; CI: confidence interval. I^2 and *P*-heterogeneity values were obtained from random effects meta-analysis.

	Overall RR (95% CI)	I^2	*P*-heterogeneity
Main analysis[1]	0·58 (0·51-0·66)	0%	0·49
Excluding sustained 40% decline in eGFR[2]	0·61(0·52-0·72)	0%	0·48
Excluding non-sustained outcomes[3]	0·59 (0·59-0·68)	10·3%	0·33

[1] Substantial loss of kidney function was defined as doubling of serum creatinine or sustained 40% decline in eGFR
[2]The DECLARE-TIMI 58 trial reported sustained 40% decline in eGFR
[3]The EMPA-REG OUTCOME trial reported non-sustained doubling of serum creatinine, non-sustained initiation of RRT (dialysis or transplant), or death due to kidney disease

Table S7. Sensitivity analyses for the outcome substantial loss of kidney function, ESKD or death due to kidney disease by eGFR subgroups based on different endpoint definitions and statistical approach

eGFR: estimated glomerular filtration rate; RR: relative risk; CI: confidence interval.

	eGFR (mL/min/1·73m^2)	Subgroup RR (95% CI)	*P*-trend	*P*-heterogeneity
Main analysis	≥90	0·37 (0·21-0·63)	0·07	0·20
	60-<90	0·60 (0·48-0·74)		
	45-<60	0·55 (0·39-0·76)		
	<45	0·70 (0·54-0·91)		
Including the eGFR <60 mL/min/1·73m^2 subgroup from DECLARE-TIMI 58 in the eGFR 45-60 mL/min/1·73m^2 category	≥90	0·37 (0·21-0·63)	0·07	0·19
	60-<90	0·60 (0·48-0·74)		
	45-<60	0·56 (0·42-0·74)		
	<45	0·70 (0·54-0·91)		
Excluding sustained 40% decline in eGFR[1]	≥90	0·25 (0·13-0·49)	0·14	0·11
	60-<90	0·67 (0·49-0·90)		
	45-<60	0·55 (0·39-0·76)		
	<45	0·70 (0·54-0·91)		
Excluding non-sustained outcomes[2]	≥90	0·47 (0·33-0·67)	0·17	0·44
	60-<90	0·60 (0·45-0·81)		
	45-<60	0·50 (0·34-0·74)		
	<45	0·71 (0·54-0·94)		

Substantial loss of kidney function was defined as doubling of serum creatinine or sustained 40% decline in eGFR. *P*-heterogeneity and *P*-trend values were obtained from random effects meta-regression with restricted maximum likelihood and Hartung Knapp adjustment with eGFR subgroups fitted as independent and ordered categories, respectively.

[1]The DECLARE-TIMI 58 trial reported sustained 40% decline in eGFR

[2]The EMPA-REG OUTCOME trial reported non-sustained doubling of serum creatinine, non-sustained initiation of RRT (dialysis or transplantation), or death due to kidney disease

Table S8. Effect of SGLT2 inhibitors on eGFR slope by study and eGFR and UACR subgroups

eGFR: estimated glomerular filtration rate; UACR: urinary albumin:creatinine ratio; CI: confidence interval; N/A: not available.

Study/Subgroup	Annual change in eGFR with placebo, mL/min/1·73m2/year (95% CI)	Annual change in eGFR with SGLT2 inhibitor, mL/min/1·73m2/year (95% CI)	Annual placebo-subtracted difference, mL/min/1·73m2/year (95% CI)
CREDENCE	-4·59 (-4·86 to -4·32)	-1·85 (-2·10 to -1·60)	2·74 (2·37-3·11)
DECLARE-TIMI 58	N/A	N/A	N/A
CANVAS Program	-0·85 (-0·99 to -0·71)	0·33 (0·23-0·43)	1·18 (1·02-1·35)
EMPA-REG OUTCOME	-1·46 (-1·74 to -1·17)	0·23 (0·05-0·40)	1·68 (1·35-2·02)
eGFR ≥60			
CANVAS Program	–0·85 (-1·01 to -0·69)	0·35 (0·23-0·47)	1·20 (1·01-1·38)
EMPA-REG OUTCOME*	-1·60 (-1·93 to -1·27)*	0·08 (-0·12 to 0·28)*	1·68 (1·30-2·06)*
eGFR <60			
CANVAS Program	–0·89 (-1·18 to -0·60)	0·22 (-0·02 to 0·46)	1·11 (0·74-1·48)
EMPA-REG OUTCOME*	-1·11 (-1·65 to -0·57)*	0·60 (0·27-0·93)*	1·71 (1·08-2·34)*
UACR <30			
CANVAS Program	–0·47 (-0·63 to -0·31)	0·59 (0·49-0·69)	1·06 (0·88-1·25)
EMPA-REG OUTCOME*	-0·80 (-1·18 to -0·45)*	0·43 (0·20-0·64)*	1·23 (0·80-1·66)
UACR 30-300			
CANVAS Program	–1·14 (-1·43 to -0·85)	–0·15 (-0·37 to 0·07)	0·99 (0·61-1·36)
EMPA-REG OUTCOME	-1·88 (-2·43 to –1·33)*	0·42 (-0·09 to 0·74)*	2·31 (1·66-2·95)
UACR >300			
CANVAS Program	–4·77 (-5·51 to -4·03)	–1·76 (-2·39 to -1·13)	3·01 (2·03-3·99)
EMPA-REG OUTCOME*	-5·91 (-6·97 to -4·83)*	-1·14 (-1·74 to -0·54)*	4·78 (3·54-6·00)

Data expressed as mean ± SE or mean (95% CI) as reported in included studies.
*95% CI derived using image extraction