SGLT2 Inhibitors and Kidney Outcomes by Glomerular Filtration Rate and Albuminuria: A Collaborative Meta-Analysis

Supplemental Appendix

Table S1. Summary of included trials

Patient group Trial acronym (drug & daily dose)	**Size**	**Median follow-up, years**	**Vital status known at end of follow-up (%)**	**Mean age (SD), years**	**Female n (%)**	**Proportion with diabetes n (%)**	**Proportion with heart failure n (%)**	**Mean (SD) eGFR, mL/min/1.73m^2**	**Median (IQR) urinary ACR, mg/g**	**Key eligibility criteria**
CANVAS Program (canagliflozin 100-300mg)	10142	2.4	10100 (99.6)	63.3 (8.3)	3633 (35.8)	10142 (100)	1461 (14)	77 (21)	12.3 (6.7-42.1)	• Type 2 diabetes • History of coronary, cerebral or peripheral vascular disease OR age >50y with at least 2 CV risk factors • eGFR ≥30
DECLARE-TIMI 58 (dapagliflozin 10mg)	17160	4.2	17130 (99.8)	63.9 (6.8)	6422 (37.4)	17160 (100)	1724 (10)	85 (16)	13.1 (6.0-43.6)	• Type 2 diabetes • Age 40y + history of coronary, cerebral or peripheral vascular disease OR age ≥55y in men/≥60y in women with at least 1 CV risk factor • Creatinine clearance ≥60 mL/min
EMPA-REG OUTCOME (empagliflozin 10mg or 25mg)	7020	3.1	6967 (99.2)	63.1 (8.7)	2004 (28.5)	7020 (100)	706 (10)	74 (21)	17.7 (7.1-72.5)	• Type 2 diabetes • History of coronary, cerebral or peripheral vascular disease • eGFR ≥30
Heart failure										
DAPA-HF (dapagliflozin 10mg)	4744	1.5	4742 (99.9)	66.3 (10.9)	1109 (23.4)	2139 (45)*	4744 (100)	66 (19)	NR	• Symptomatic chronic heart failure (NYHA class II–IV) with LVEF ≤40% (ie, reduced ejection fraction) • NT-proBNP ≥600 pg/mL • eGFR ≥30 • Appropriate doses of medical therapy and use of medical devices
DELIVER (dapagliflozin 10mg)	6263	2.3	6259 (99.9)	71.6 (9.6)	2747 (43.9)	3150 (50) †	6263 (100)	61 (19)	NR	• Symptomatic heart failure (NYHA class II–IV) with LVEF >40% (ambulatory or hospitalised) • Echocardiographic evidence of structural heart disease • NT-proBNP ≥300 pg/mL (or ≥600 pg/mL if in atrial fibrillation)
EMPEROR-REDUCED (empagliflozin 10mg)	3730	1.3	3709 (99.4)	66.8 (11.0)	893 (23.9)	1856 (50)	3730 (100)	62 (22)	22.1 (8.0-81.3)	• Class II-IV chronic HF with LVEF ≤40% (i.e. reduced ejection fraction) • NT-proBNP above a certain threshold (stratified by LVEF)

Patient group Trial acronym (drug & daily dose)	**Size**	**Median follow-up, years**	**Vital status known at end of follow-up (%)**	**Mean age (SD), years**	**Female n (%)**	**Proportion with diabetes n (%)**	**Proportion with heart failure n (%)**	**Mean (SD) eGFR, mL/min/1.73m^2**	**Median (IQR) urinary ACR, mg/g**	**Key eligibility criteria**
										• Appropriate doses of medical therapy and use of medical devices
EMPEROR-PRESERVED (empagliflozin 10mg)	5988	2.2	5952 (99.4)	71.8 (9.5)	2676 (44.7)	2938 (49)	5988 (100)	61 (20)	21.0 (8.0-71.6)	• Symptomatic chronic HF (class II-IV) with LVEF >40% • Echocardiographic evidence of structural heart disease or hospitalisation for heart failure in the last year • NT-proBNP >300 pg/mL (or >900 pg/mL if in AF) • eGFR ≥20 • No recent coronary event
Chronic kidney disease										
CREDENCE (canagliflozin 100mg)	4401	2.6	4395 (99.9)	63.0 (9.2)	1494 (33.9)	4401 (100)	652 (15)	56 (18)	927 (463-1833)	• Type 2 diabetes • eGFR 30-90 • uACR 300-5000 mg/g • Stable maximally tolerated RAS blockade • Excluded suspected non-diabetic kidney disease
DAPA-CKD (dapagliflozin 10mg)	4304	2.4	4299 (99.9)	61.9 (12.1)	1425 (33.1)	2906 (68)	468 (11)	43 (12)	949 (477-1885)	• eGFR 25-75 • uACR 200-5000 mg/g • Stable maximally tolerated RAS blockade, unless documented intolerance • Excluded polycystic kidney disease, lupus nephritis, or anti-neutrophil cytoplasmic antibody-associated vasculitis.
EMPA-KIDNEY (empagliflozin 10mg)	6609	2.0	6591 (99.8)	63.9 (13.9)	2192 (33.2)	3040 (46) †	658 (10)	37.3 (14)	412 (94–1190)	• eGFR 20-45 or eGFR 45-90 with uACR ≥200 mg/g at screening‡ • Clinically appropriate RAS blockade, unless not indicated or not tolerated • Excluded polycystic kidney disease

* Includes patients with HbA1c ≥6·5% at enrolment. †Includes patients with HbA1c ≥6.5% at baseline or history and/or prevalent use of a glucose-lowering agent. ‡ 254 participants with an eGFR<20mL/min/1·73m^2 at randomisation and 68 with type 1 diabetes. AF = atrial fibrillation; ASCVD = atherosclerotic cardiovascular disease; CV = cardiovascular; eGFR = estimated glomerular filtration rate (mL/min/1.73m^2); HF = heart failure; LVEF = left ventricular ejection fraction; NR = not reported; NT-proBNP = N-terminal prohormone brain natriuretic peptide; RAS = renin angiotensin system; uACR = urinary albumin:creatinine ratio.

Table S2. Risk of bias assessments

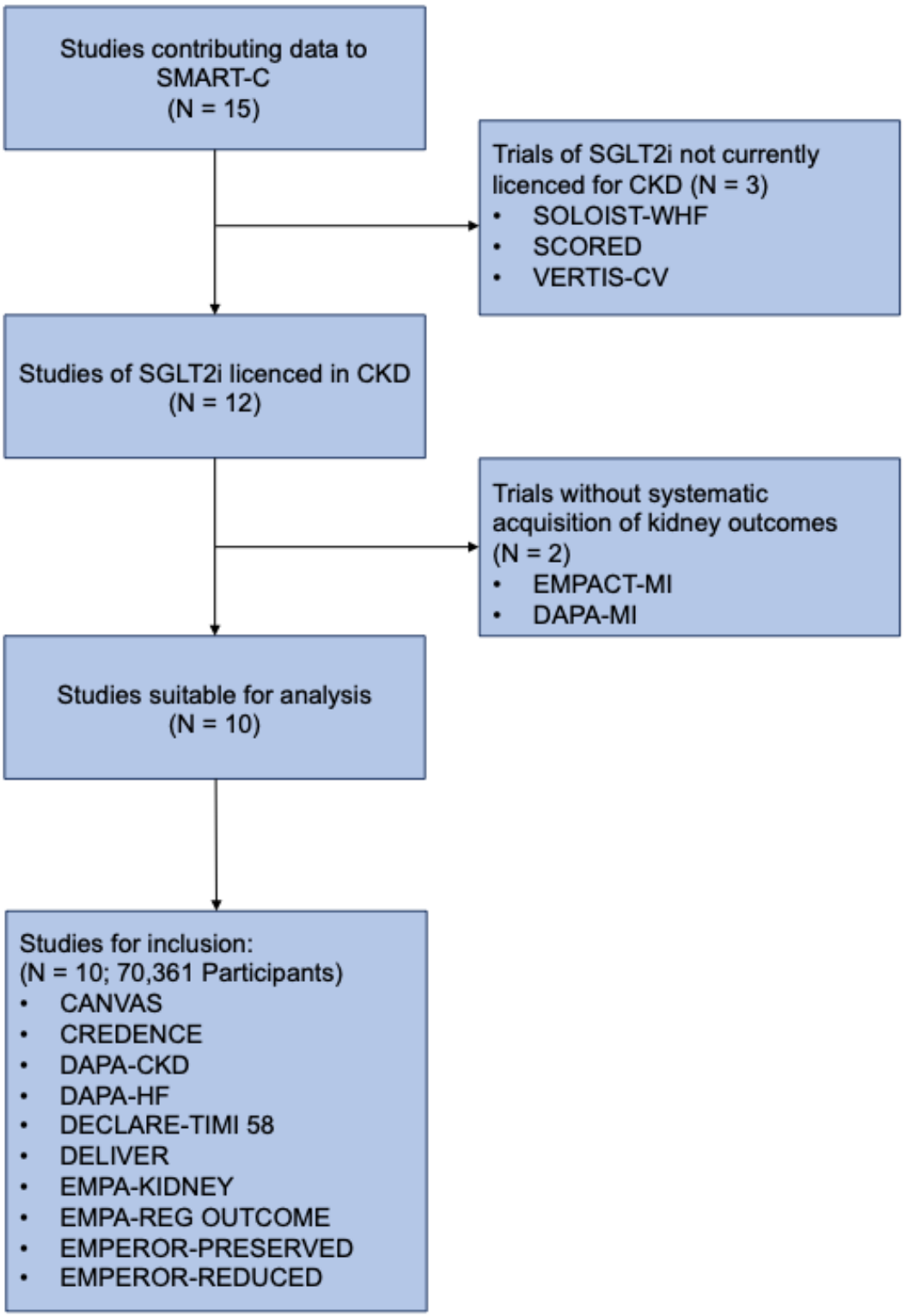
Study ID	Intervention	Comparator	Randomisation process	Deviations from the intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result
CANVAS Program	Canagliflozin	Placebo	+	+	+	+	+
DECLARE-TIMI 58	Dapagliflozin	Placebo	+	+	+	+	+
EMPA-REG OUTCOME	Empagliflozin	Placebo	+	+	+	+	+
DAPA-HF	Dapagliflozin	Placebo	+	+	+	+	+
DELIVER	Dapagliflozin	Placebo	+	+	+	+	+
EMPEROR-REDUCED	Empagliflozin	Placebo	+	+	+	+	+
EMPEROR-PRESERVED	Empagliflozin	Placebo	+	+	+	+	+
CREDENCE	Canagliflozin	Placebo	+	+	+	+	+
DAPA-CKD	Dapagliflozin	Placebo	+	+	+	+	+
EMPA-KIDNEY	Empagliflozin	Placebo	+	+	+	+	+

Risk of bias of included trials as assessed using the Cochrane Risk of Bias 2 (ROB2) tool applied to the primary outcome of included trial.

Key:

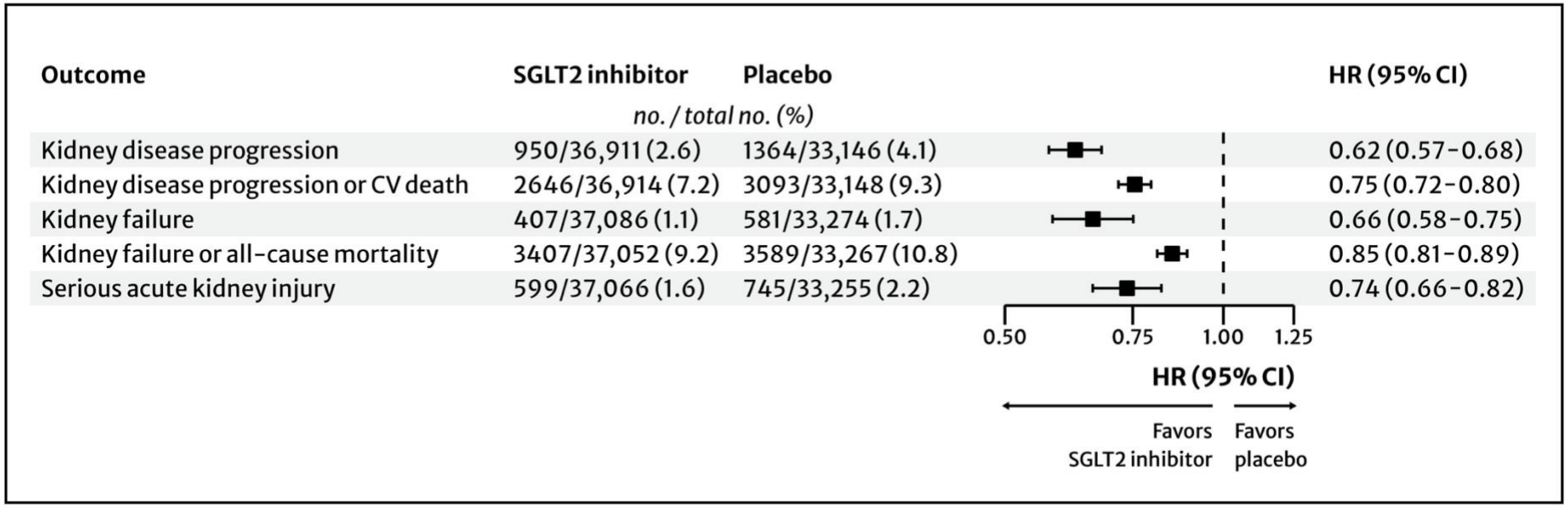
+	Low risk of bias
!	Some concerns
-	High risk of bias

Figure S1. PRISMA flow diagram



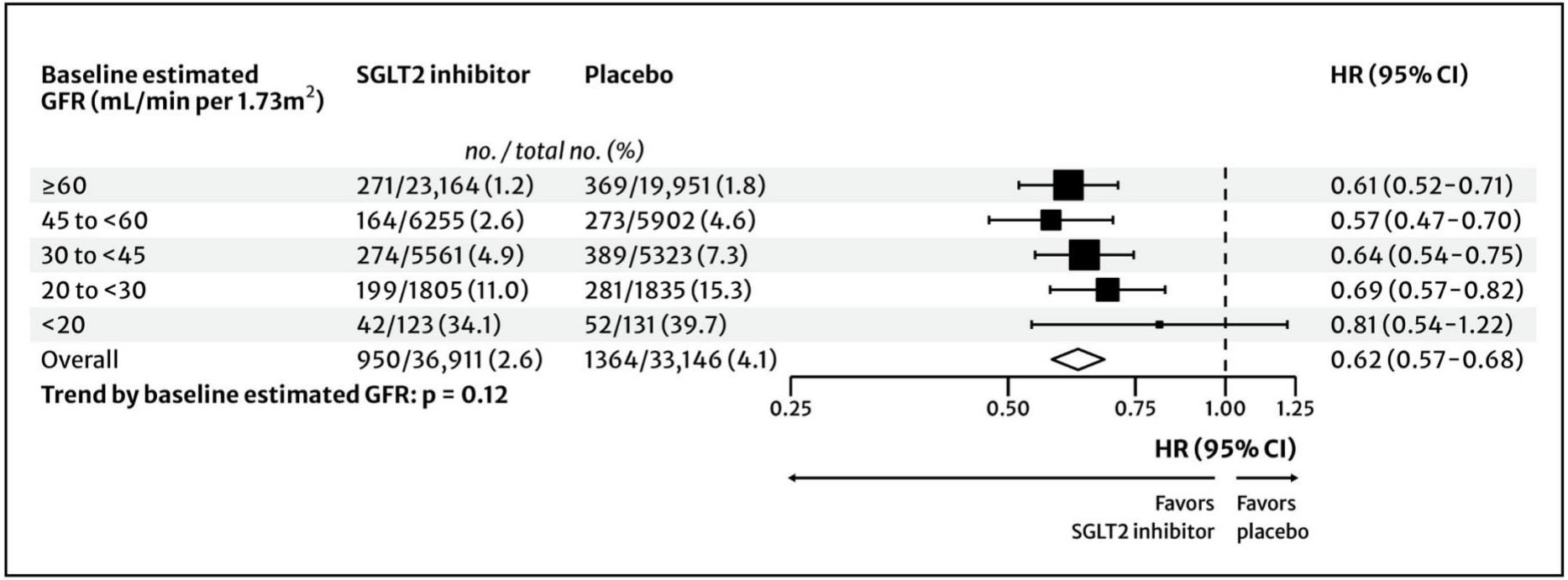
SMART-C: SGLT2 Inhibitor Meta-Analysis Cardio-Renal Trialists' Consortium; SGLT2i: sodium-glucose cotransporter 2 inhibitor

Figure S2. Summary of the effects of SGLT2i on clinical kidney outcomes.



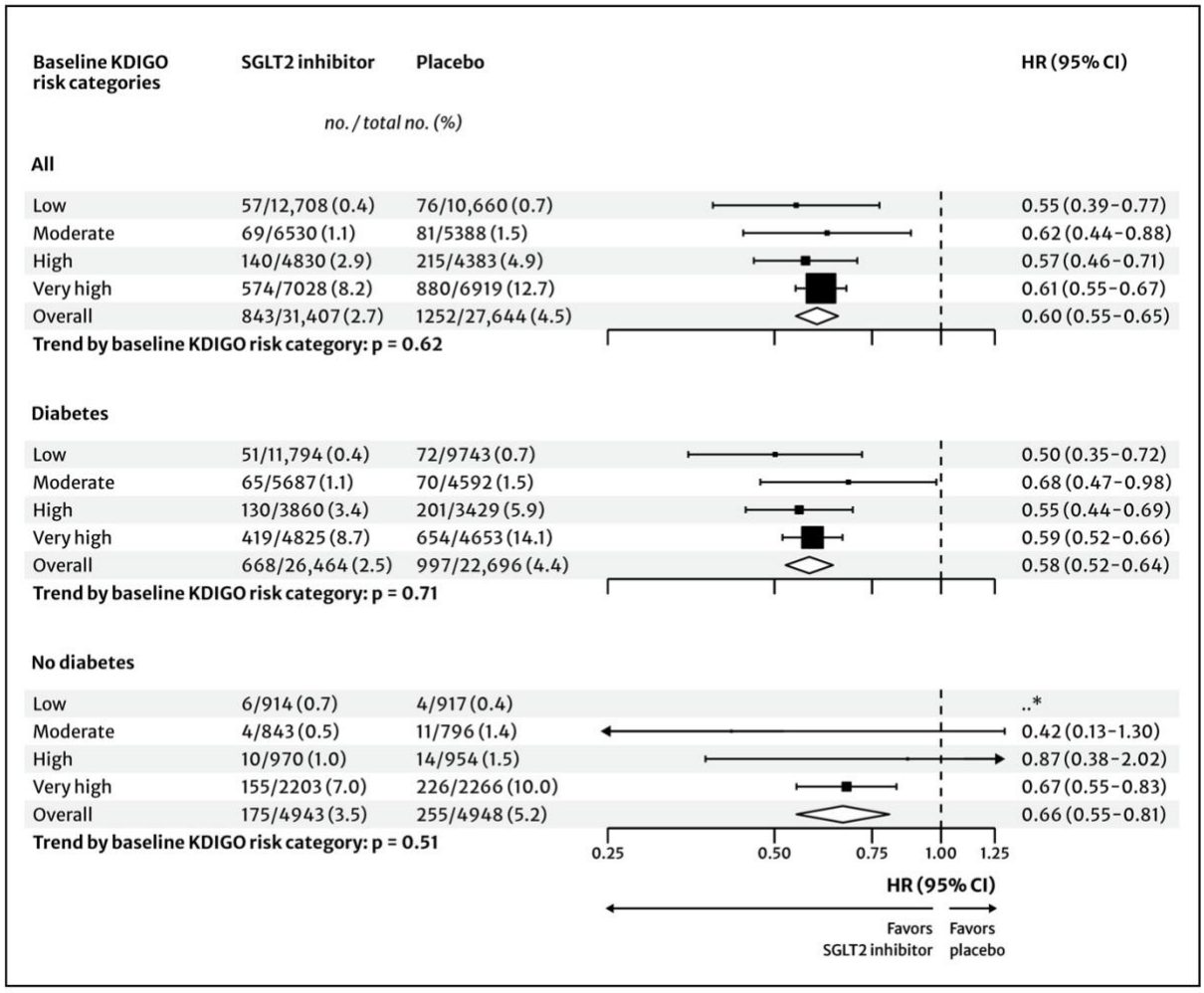
Kidney disease progression (primary outcome) defined as ≥50%reduction in estimated glomerular filtration rate, kidney failure or death due to kidney failure. Kidney failure was defined as chronic dialysis, transplantation or sustained low eGFR (<15 mL/min/1.73m^2).Cardiovascular death was adjudicated by blinded clinical events committees in each trial according to trial-specific definitions. Serious acute kidney injury based on investigator-reported adverse events (using the MedDRA term “acute kidney injury”) restricted to serious adverse events. CV: cardiovascular; SGLT2: sodium-glucose cotransporter 2; HR: hazard ratio; CI: confidence interval.

Figure S3. Effects of SGLT2i on CKD progression according to baseline eGFR, including in participants with eGFR <20 mL/min/1.73m^2.



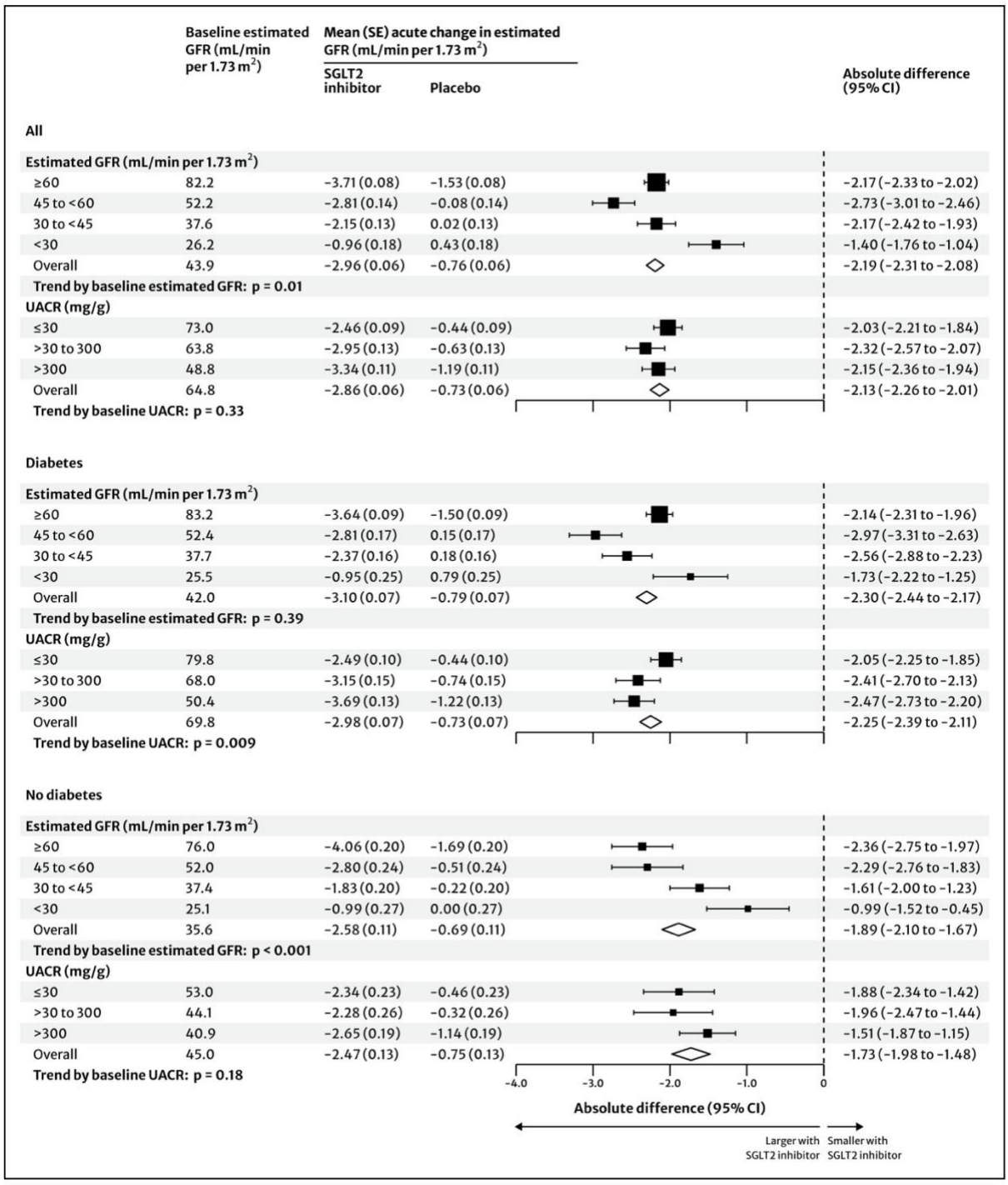
Box sizes are inversely proportional to the standard error of the treatment effect. Chronic kidney disease (CKD) progression defined as ≥50%reduction in estimated glomerular filtration rate, kidney failure or death due to kidney failure. eGFR: estimated glomerular filtration rate; SGLT2: sodium-glucose cotransporter 2; HR: hazard ratio; CI: confidence interval.

Figure S4. Effects of SGLT2i on CKD progression according to baseline KDIGO risk categories, overall and by diabetes status.



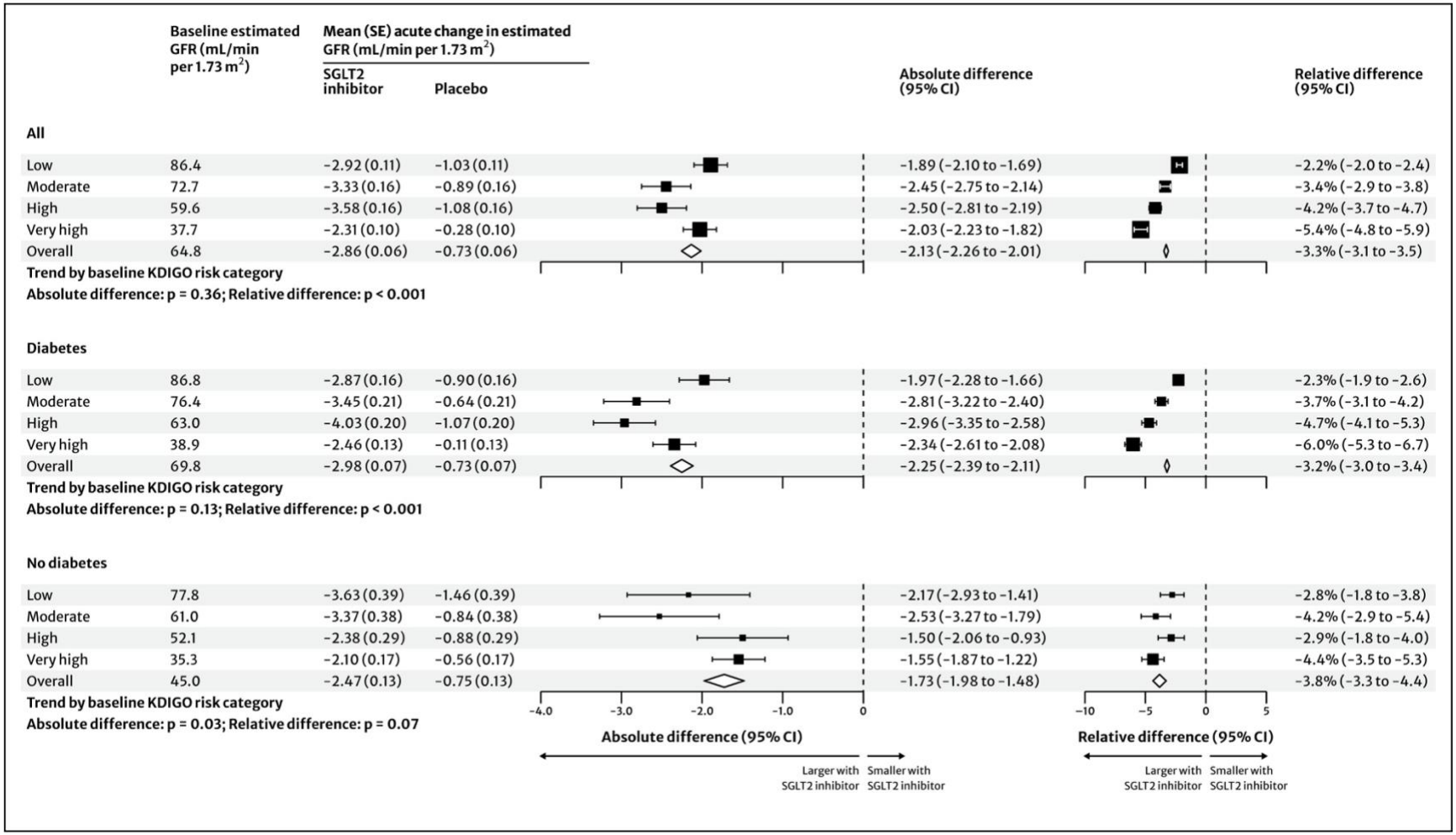
Box sizes are inversely proportional to the standard error of the treatment effect. Chronic kidney disease (CKD) progression defined as ≥50%reduction in estimated glomerular filtration rate, kidney failure or death due to kidney failure. KDIGO: Kidney Disease Improving Global Outcomes; SGLT2: sodium-glucose cotransporter 2; HR: hazard ratio; CI: confidence interval

Figure S5. Absolute effects of SGLT2i on acute changes in eGFR according to eGFR and UACR, overall, and by diabetes status.



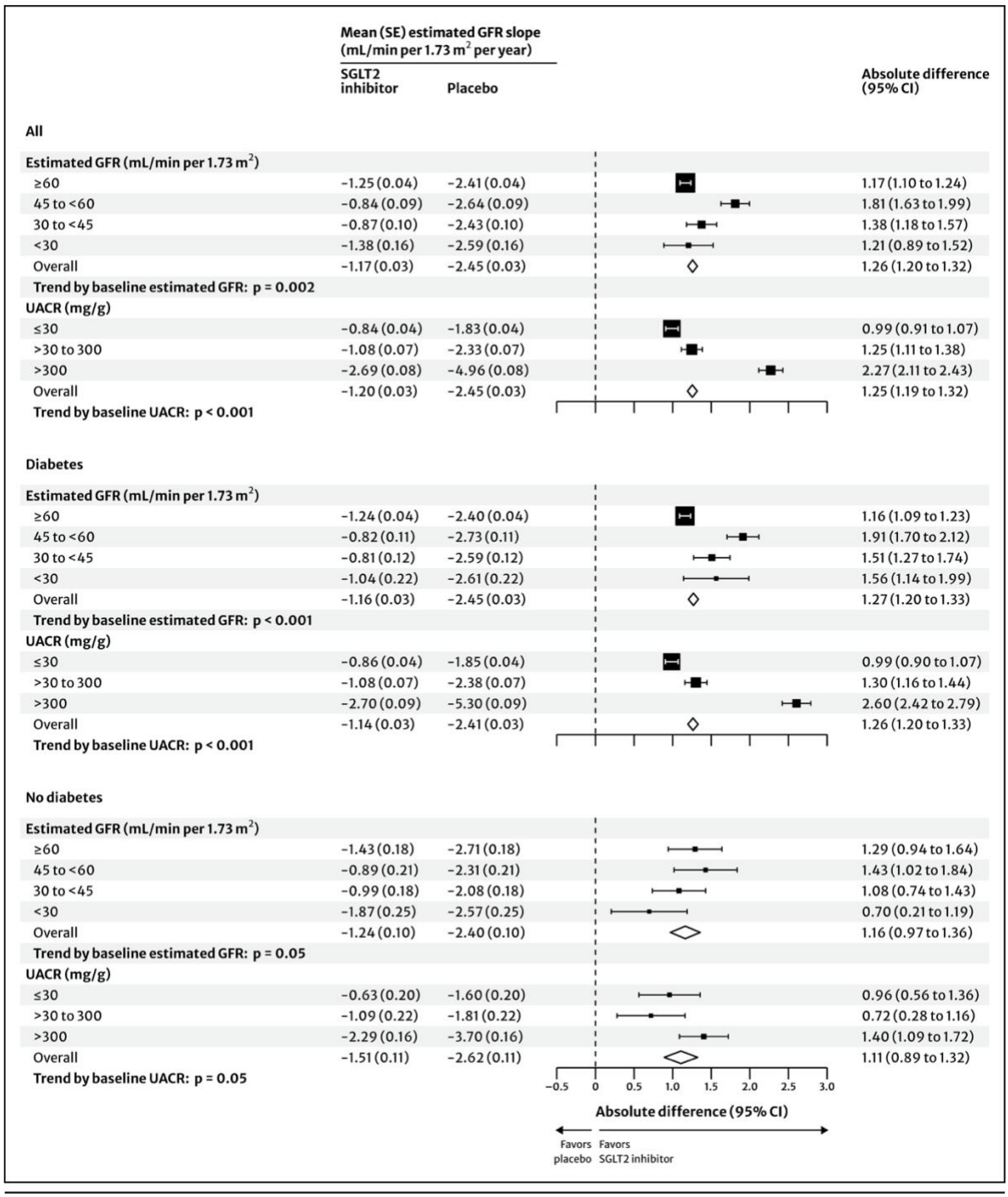
Box sizes are inversely proportional to the standard error of the treatment effect. eGFR: estimated glomerular filtration rate; UACR: urinary albumin:creatinine ratio; SE: standard error; SGLT2: sodium-glucose cotransporter 2; CI: confidence interval.

Figure S6. Relative and absolute effects of SGLT2i on acute changes in eGFR according to baseline KDIGO risk, overall and by diabetes status.



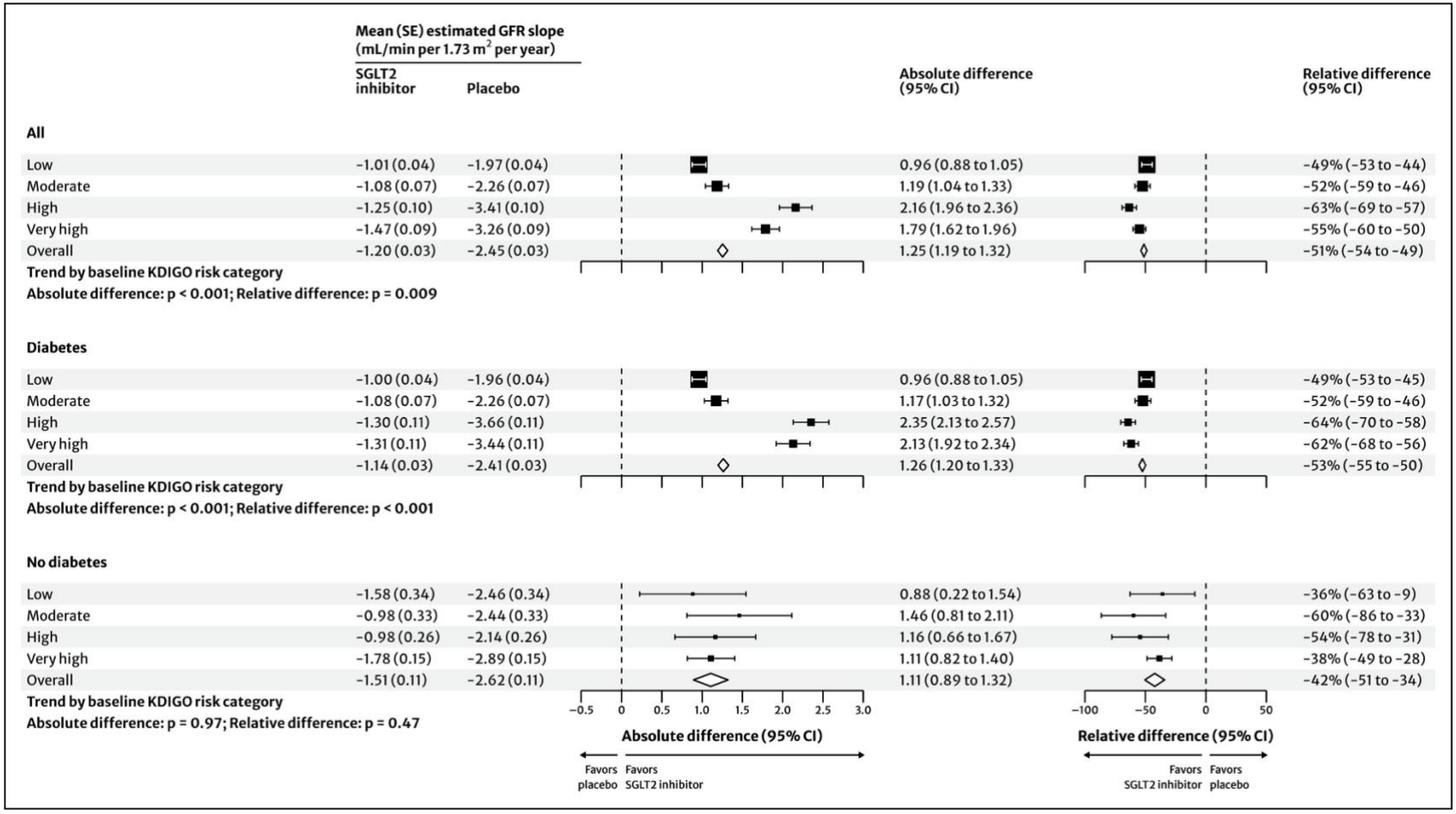
Box sizes are inversely proportional to the standard error of the treatment effect. KDIGO: Kidney Disease Improving Global Outcomes; SE: standard error; SGLT2: sodium-glucose cotransporter 2; CI: confidence interval.

Figure S7. Absolute effects of SGLT2i on chronic eGFR slope according to baseline eGFR and UACR, overall, and by diabetes status.



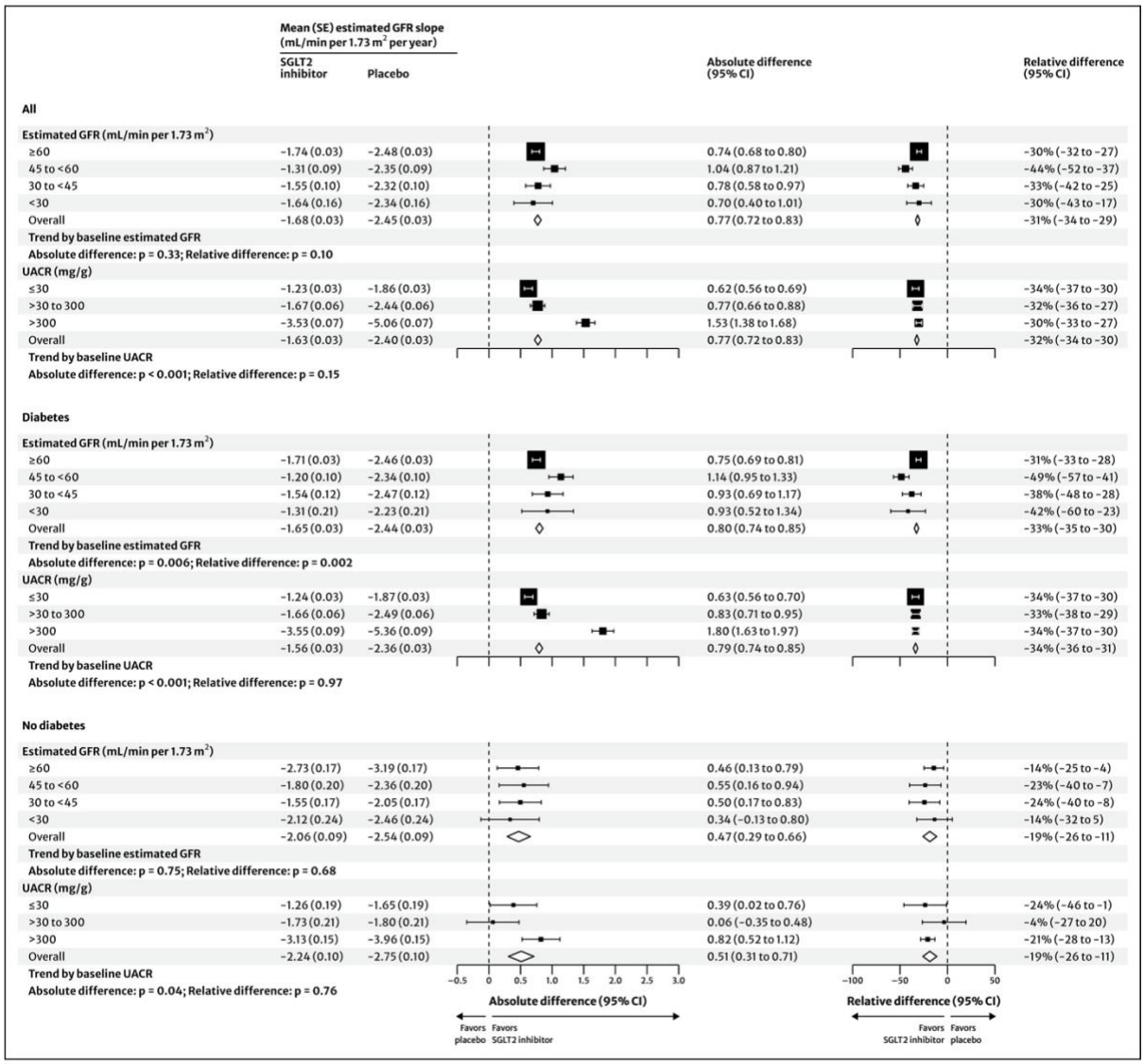
Box sizes are inversely proportional to the standard error of the treatment effect. eGFR: estimated glomerular filtration rate; UACR: urinary albumin:creatinine ratio; SE: standard error; SGLT2: sodium-glucose cotransporter 2; CI: confidence interval.

Figure S8. Relative and absolute effects of SGLT2i on chronic eGFR slope according to baseline KDIGO risk, overall, and by diabetes status



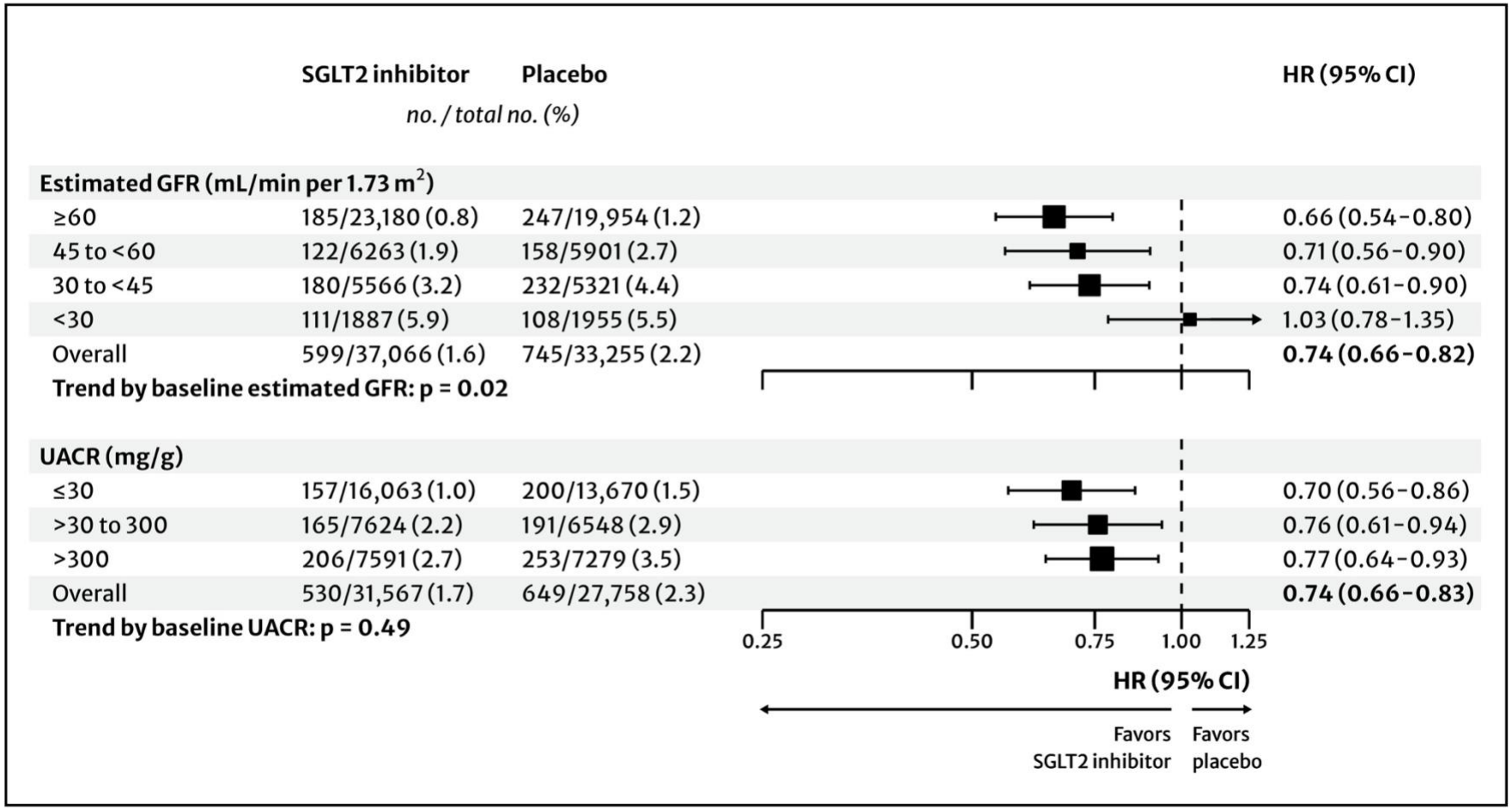
Box sizes are inversely proportional to the standard error of the treatment effect. KDIGO: Kidney Disease Improving Global Outcomes; SE: standard error; SGLT2: sodium-glucose cotransporter 2; CI: confidence interval.

Figure S9. Effects of SGLT2i on total eGFR slope according to baseline eGFR and UACR, overall, and by diabetes status.



Box sizes are inversely proportional to the standard error of the treatment effect. eGFR: estimated glomerular filtration rate; UACR: urinary albumin:creatinine ratio; SGLT2: sodium-glucose cotransporter 2; CI: confidence interval.

Figure S10. Effect of SGLT2i on serious AKI by baseline eGFR and UACR.



Box sizes are inversely proportional to the standard error of the treatment effect. Serious acute kidney injury based on investigator-reported adverse events (using the MedDRA term “acute kidney injury”) restricted to serious adverse events. eGFR: estimated glomerular filtration rate; UACR: urinary albumin:creatinine ratio; SGLT2: sodium-glucose cotransporter 2; HR: hazard ratio; CI: confidence interval.