SUPPLEMENTARY APPENDIX

Table S1. Characteristics of participants with UACR <30, 30-300, and >300 mg/g at baseline.

	Normal albuminuria (<30 mg/g) (N = 7007)	**Moderately increased albuminuria (30-300 mg/g)** (N = 2266)	**Severely increased albuminuria (>300 mg/g)** (N = 760)
Age, years, mean (SD)	63.0 (8.2)	63.9 (8.3)	63.6 (8.3)
Sex, No. (%)			
Male	4332 (61.8)	1574 (69.5)	532 (70.0)
Female	2675 (38.2)	692 (30.5)	228 (30.0)
Race, No. (%)			
White	5522 (78.8)	1752 (77.3)	573 (75.4)
Asian	850 (12.1)	324 (14.3)	109 (14.3)
Black or African American	231 (3.3)	70 (3.1)	29 (3.8)
Other[a]	404 (5.8)	120 (5.3)	49 (6.4)
Current smoker, No. (%)	1238 (17.7)	401 (17.7)	137 (18.0)
History of hypertension, No. (%)	6210 (88.6)	2097 (92.5)	714 (93.9)
History of heart failure, No. (%)	965 (13.8)	349 (15.4)	122 (16.1)
Duration of diabetes, years, mean (SD)	13.1 (7.7)	14.4 (7.8)	15.7 (7.8)
Drug therapy, No. (%)			
Insulin	3267 (46.6)	1264 (55.8)	514 (67.6)
Sulfonylurea	3089 (44.1)	974 (43.0)	263 (34.6)
Metformin	5503 (78.5)	1727 (76.2)	503 (66.2)
GLP-1 receptor agonist	274 (3.9)	95 (4.2)	33 (4.3)
DPP-4 inhibitor	860 (12.3)	278 (12.3)	110 (14.5)
Statin	5214 (74.4)	1734 (76.5)	577 (75.9)
Antithrombotic	5138 (73.3)	1682 (74.2)	580 (76.3)
RAAS inhibitor	5549 (79.2)	1846 (81.5)	628 (82.6)
Beta blocker	3729 (53.2)	1239 (54.7)	402 (52.9)
Diuretic	2938 (41.9)	1096 (48.4)	402 (52.9)
Microvascular disease history, No. (%)			
Retinopathy	1298 (18.5)	549 (24.2)	257 (33.8)
Nephropathy	793 (11.3)	614 (27.1)	347 (45.7)
Neuropathy	2028 (28.9)	759 (33.5)	281 (37.0)
Atherosclerotic vascular disease history, No. (%)[b]			
Coronary	3993 (57.0)	1268 (56.0)	404 (53.2)
Cerebrovascular	1319 (18.8)	448 (19.8)	172 (22.6)
Peripheral	1363 (19.5)	503 (22.2)	227 (29.9)
Any	5064 (72.3)	1628 (71.8)	558 (73.4)
CV disease history, No. (%)[c]	4600 (65.6)	1473 (65.0)	519 (68.3)

History of amputation, No. (%)	102 (1.5)	73 (3.2)	60 (7.9)
Body mass index, kg/m^2, mean (SD)	31.8 (5.9)	32.3 (6.0)	32.0 (6.1)
Systolic BP, mmHg, mean (SD)	134.9 (15.1)	139.3 (15.8)	144.9 (17.7)
Diastolic BP, mmHg, mean (SD)	77.4 (9.4)	78.0 (10.0)	79.6 (9.9)
Glycated haemoglobin, %, mean (SD)	8.2 (0.9)	8.4 (1.0)	8.5 (1.0)
Total cholesterol, mmol/L, mean (SD)	4.3 (1.1)	4.4 (1.1)	4.6 (1.3)
Triglycerides, mmol/L, mean (SD)	1.9 (1.3)	2.2 (1.6)	2.4 (1.8)
HDL-C, mmol/L, mean (SD)	1.2 (0.3)	1.1 (0.3)	1.2 (0.3)
LDL-C, mmol/L, mean (SD)	2.3 (0.9)	2.3 (0.9)	2.4 (1.1)
LDL-C:HDL-C ratio, mean (SD)	2.0 (0.9)	2.1 (0.9)	2.2 (1.1)
eGFR, mL/min/1.73 m², mean (SD)	78.3 (19.7)	74.4 (21.3)	66.4 (22.3)
UACR, mg/g, median (IQR)	8.3 (3.7-13.3)	68.7 (43.4-124.4)	722.1 (445.9-1328.5)

UACR, urinary albumin:creatinine ratio; SD, standard deviation; GLP-1, glucagon-like peptide 1; DPP-4, dipeptidyl peptidase-4; RAAS, renin-angiotensin-aldosterone system; CV, cardiovascular; BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; IQR, interquartile range

Table S2. Effect on total eGFR slope* for the overall trial population and in participants with UACR <30, 30-300, and >300 mg/g at baseline.
UACR: urinary albumin:creatinine ratio; eGFR: estimated glomerular filtration rate; CI: confidence intervals.

Total eGFR slope	Canagliflozin (95% CI)	Placebo (95% CI)	Difference (95% CI)	P value for difference	P-heterogeneity
All	-0.92 (-1.08 to -0.77)	-2.15 (-2.35 to -1.96)	1.23 (0.99 to 1.48)	<0.0001	<0.0001
<30	0.23 (0.13 to 0.34)	-0.52 (-0.66 to -0.37)	0.75 (0.57 to 0.93)	<0.0001	
30-300	-0.60 (-0.79 to -0.41)	-1.24 (-1.51 to -0.98)	0.64 (0.32 to 0.97)	<0.0001	
>300	-2.40 (-2.81 to -2.00)	-4.70 (-5.19 to -4.21)	2.30 (1.66 to 2.93)	<0.0001	

*Data reported as mL/min/1.73 m^2/year

Table S3. Effect of canagliflozin on cardiovascular and renal outcomes by baseline albuminuria adjusted for competing risk of death.

	N event	N censored	N competing event	HR (95% CI)	P-heterogeneity
MACE	1011	8927	204	**0.86 (0.75, 0.97)**	0.47
<30	596	6283	128	0.84 (0.71, 0.98)	
30-300	272	1939	55	0.98 (0.77, 1.25)	
>300	134	607	19	0.76 (0.54, 1.07)	
CV death	453	9461	228	**0.88 (0.73, 1.06)**	0.65
<30	233	6632	142	0.92 (0.70, 1.19)	
30-300	132	2073	61	0.99 (0.69, 1.42)	
>300	85	652	23	0.70 (0.46, 1.08)	
Fatal/non-fatal MI	421	9147	574	**0.90 (0.74, 1.10)**	0.38
<30	266	6423	318	0.89 (0.69, 1.14)	
30-300	112	1989	165	1.08 (0.73, 1.59)	
>300	40	634	86	0.64 (0.35, 1.18)	
Fatal/non-fatal stroke	309	9223	610	**0.88 (0.70, 1.10)**	0.47
<30	181	6482	344	0.76 (0.57, 1.02)	
30-300	79	2017	170	0.93 (0.59, 1.46)	
>300	44	624	92	1.28 (0.70, 2.35)	
Hospitalized or fatal heart failure	276	9276	590	**0.71 (0.56, 0.89)**	0.94
<30	133	6535	339	0.67 (0.48, 0.95)	
30-300	84	2019	163	0.75 (0.49, 1.15)	
>300	59	618	83	0.76 (0.46, 1.26)	
Renal composite*	249	9248	645	**0.61 (0.47, 0.79)**	0.02
<30	89	6551	367	0.51 (0.33, 0.78)	
30-300	70	2012	184	0.99 (0.60, 1.65)	
>300	88	582	90	0.52 (0.34, 0.79)	

HR, hazard ratio; CI, confidence interval; CV, cardiovascular; MI, myocardial infarction; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease.

*40% reduction in eGFR, ESKD, or renal death

Table S4. Trend tests across UACR subgroups (<30, 30-300, and >300 mg/g) and interaction tests using log transformed UACR fitted as a continuous variable for cardiovascular and renal outcomes.

Outcome	P-trend	P-heterogeneity, continuous log transformed UACR
MACE	0.97	0.91
CV death	0.42	0.75
Fatal/non-fatal MI	0.69	0.69
Fatal/non-fatal stroke	0.25	0.69
Hospitalized or fatal heart failure	0.85	0.33
Renal composite*	0.80	0.94

*40% reduction in eGFR, ESKD, or renal death

Figure S1. Change in intermediate outcomes for canagliflozin and placebo treated participants by UACR (<30, 30-300, and >300 mg/g).

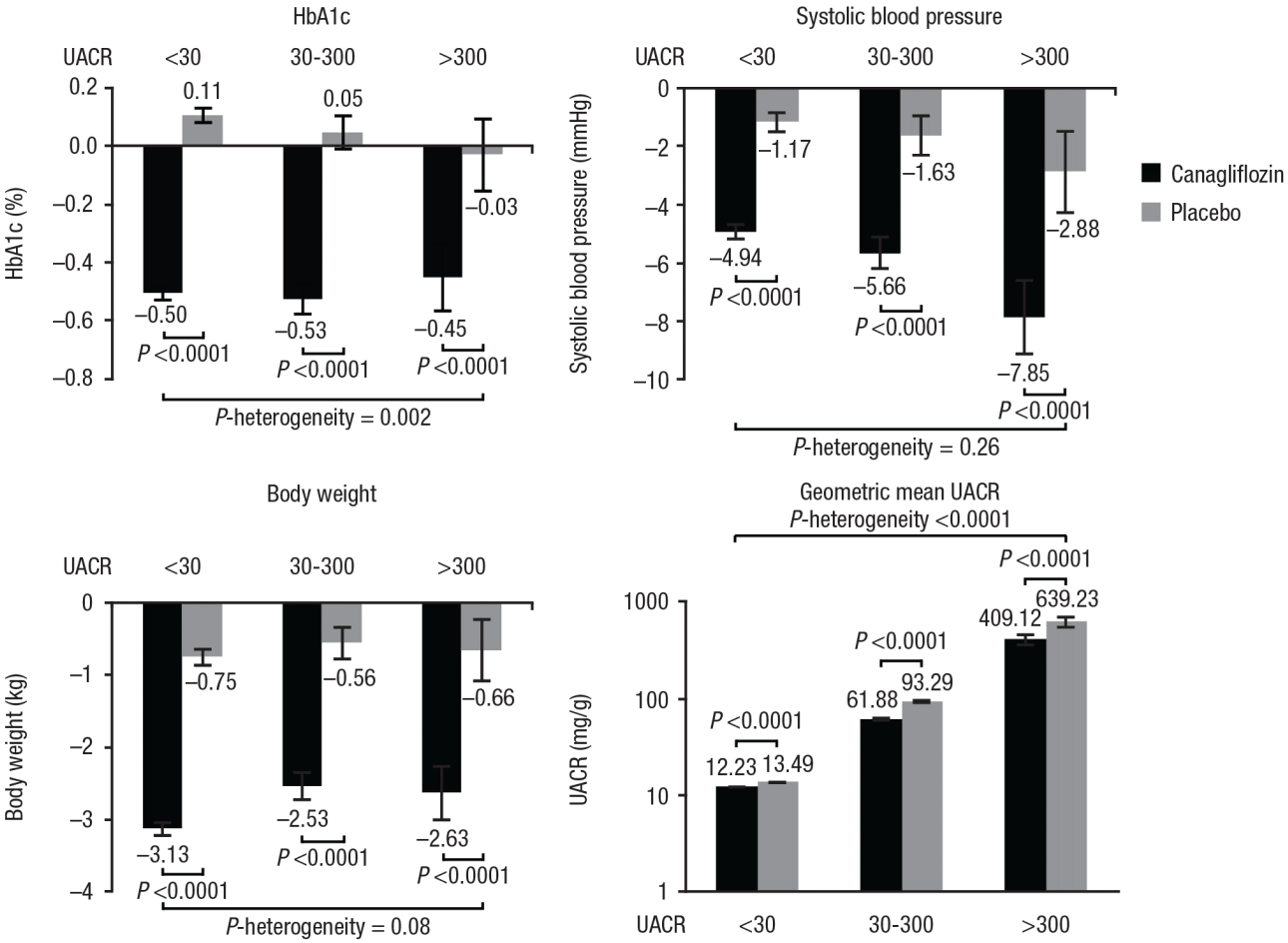
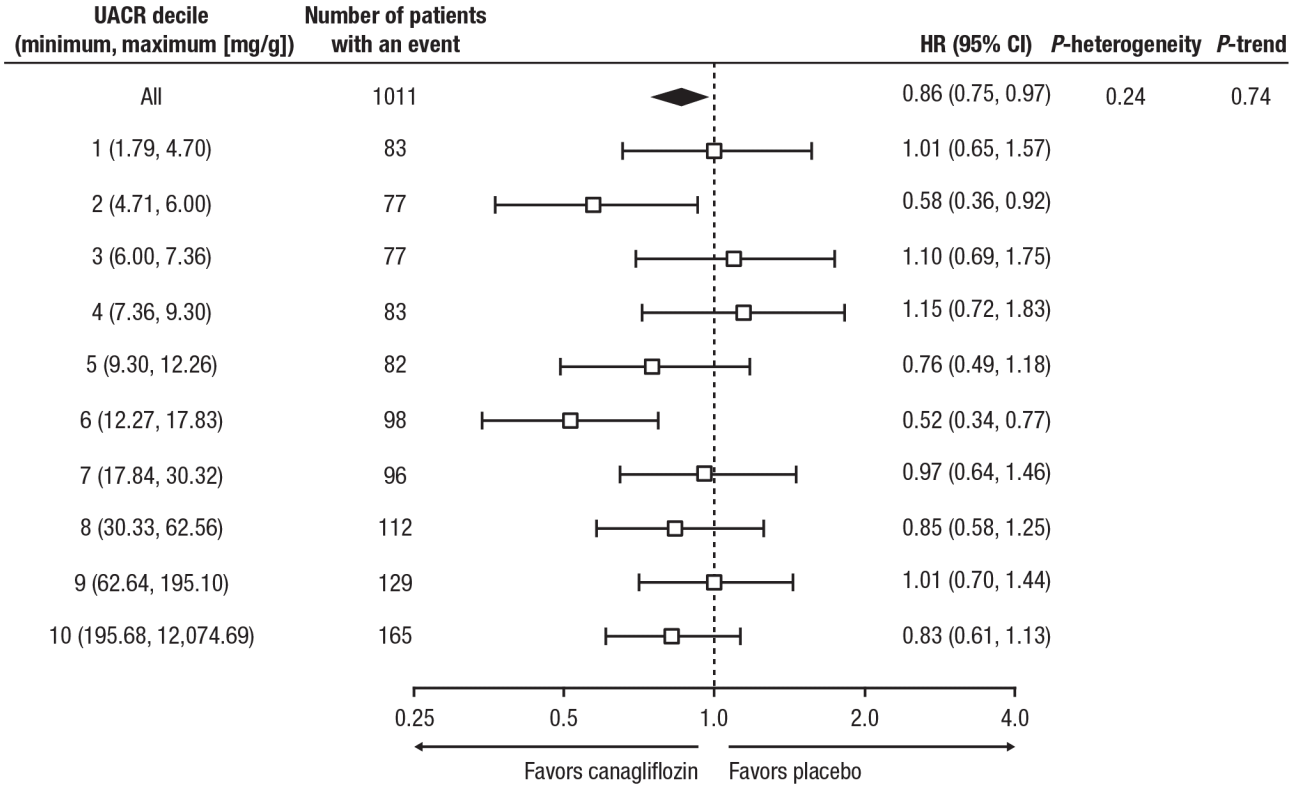


Figure S2. Effect of canagliflozin on the (A) primary cardiovascular outcome, (B) hospitalized or fatal heart failure, (C) renal composite outcome, and (D) all-cause mortality in participants stratified into deciles of baseline UACR.

A



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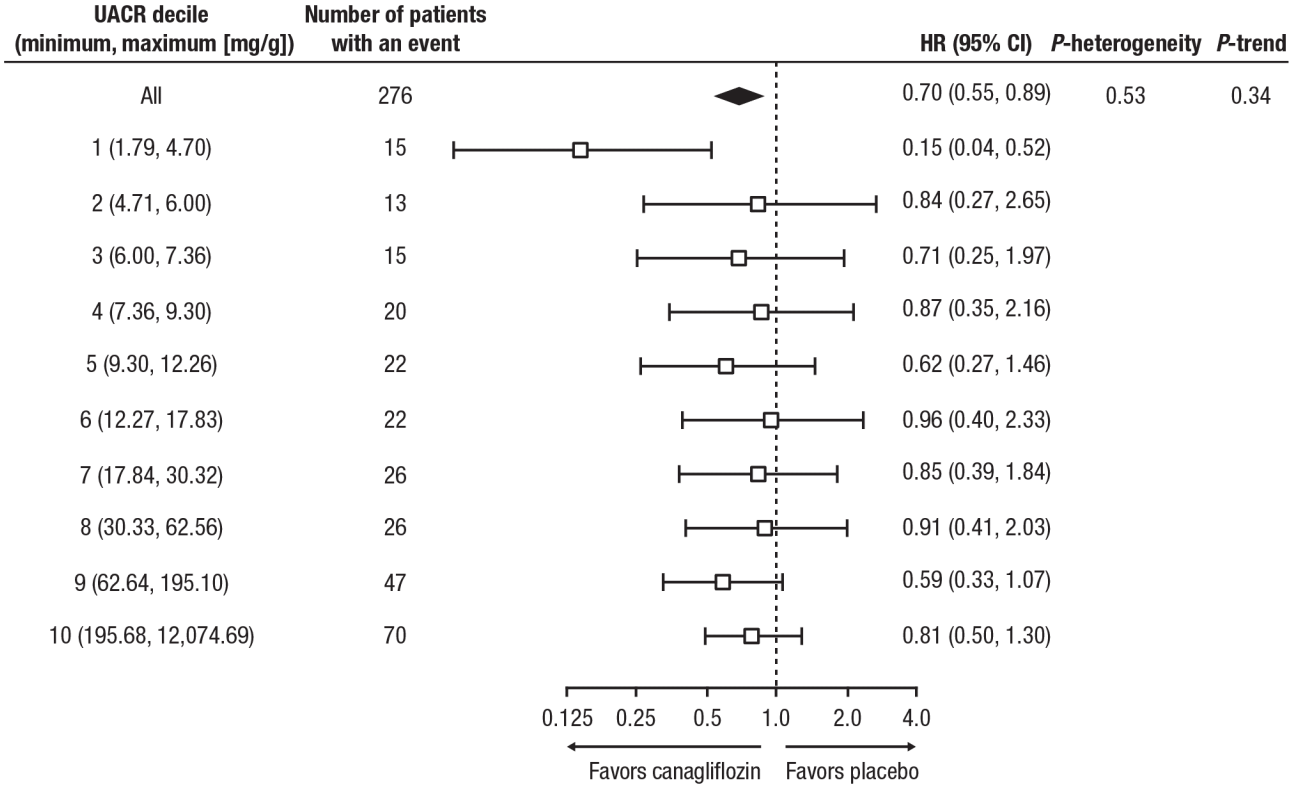
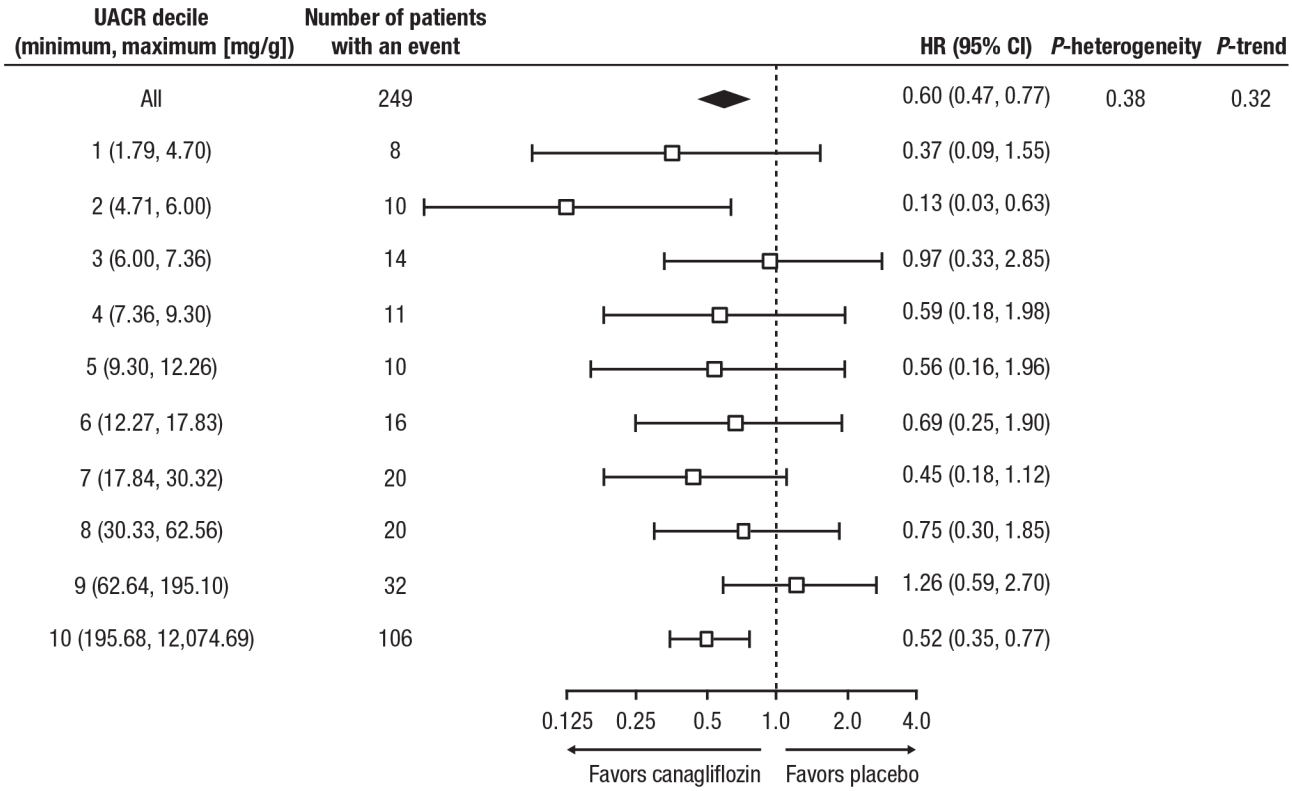
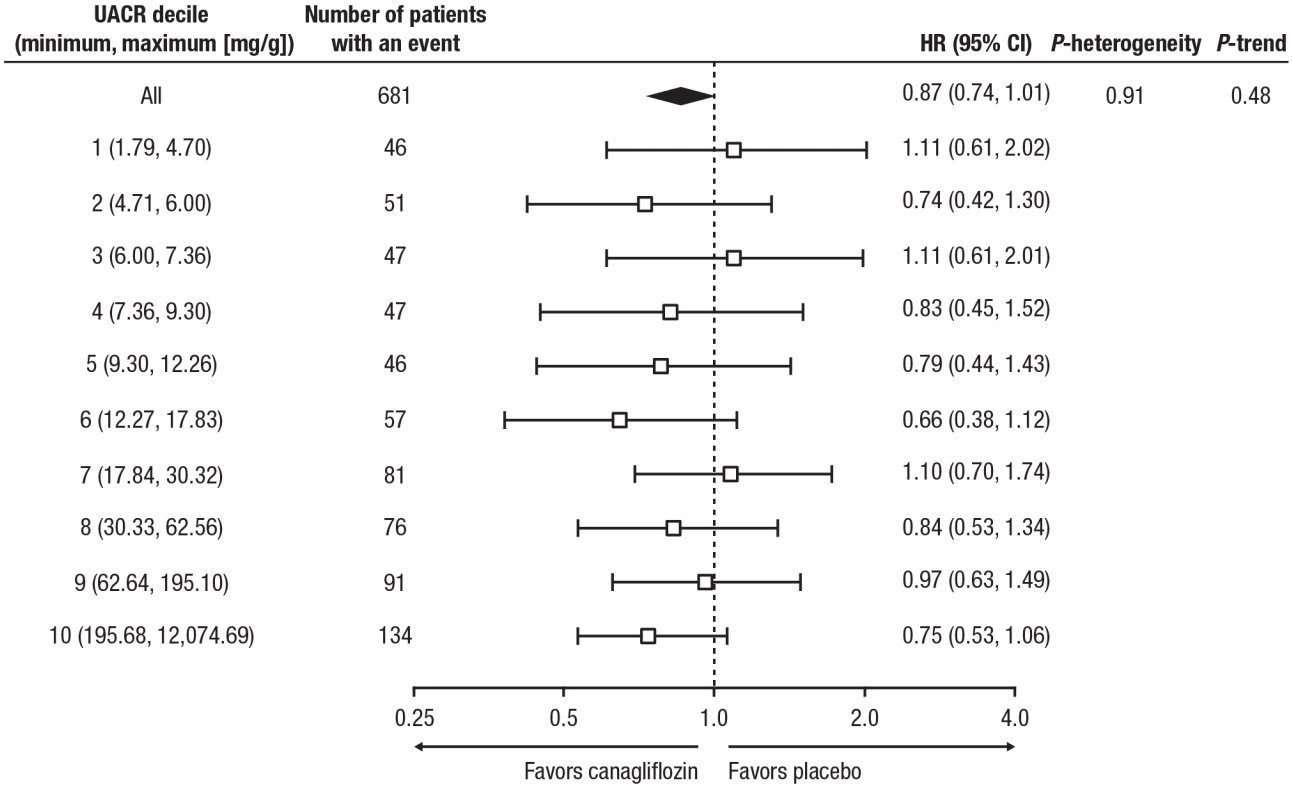

UACR decile (minimum, maximum [mg/g])
Number of patients with an event
HR (95% CI)
P-heterogeneity
P-trend
All 276 0.70 (0.55, 0.89) 0.53 0.34
1 (1.79, 4.70) 15 0.15 (0.04, 0.52)
2 (4.71, 6.00) 13 0.84 (0.27, 2.65)
3 (6.00, 7.36) 15 0.71 (0.25, 1.97)
4 (7.36, 9.30) 20 0.87 (0.35, 2.16)
5 (9.30, 12.26) 22 0.62 (0.27, 1.46)
6 (12.27, 17.83) 22 0.96 (0.40, 2.33)
7 (17.84, 30.32) 26 0.85 (0.39, 1.84)
8 (30.33, 62.56) 26 0.91 (0.41, 2.03)
9 (62.64, 195.10) 47 0.59 (0.33, 1.07)
10 (195.68, 12,074.69) 70 0.81 (0.50, 1.30)
0.125 0.25 0.5 1.0 2.0 4.0
Favors canagliflozin
Favors placebo

C

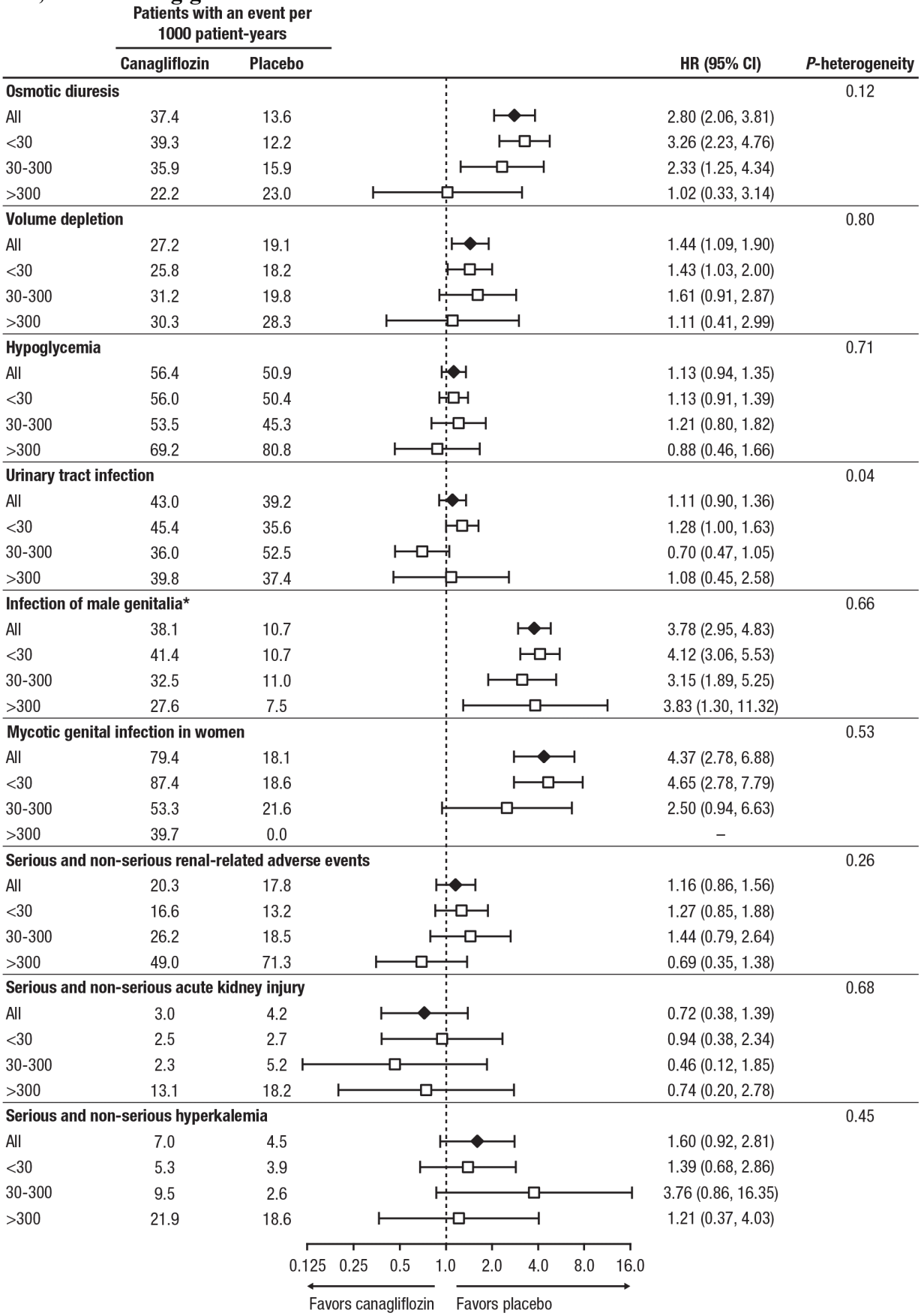

UACR decile (minimum, maximum [mg/g])
Number of patients with an event
HR (95% CI)
P-heterogeneity
P-trend
All 249 0.60 (0.47, 0.77) 0.38 0.32
1 (1.79, 4.70) 8 0.37 (0.09, 1.55)
2 (4.71, 6.00) 10 0.13 (0.03, 0.63)
3 (6.00, 7.36) 14 0.97 (0.33, 2.85)
4 (7.36, 9.30) 11 0.59 (0.18, 1.98)
5 (9.30, 12.26) 10 0.56 (0.16, 1.96)
6 (12.27, 17.83) 16 0.69 (0.25, 1.90)
7 (17.84, 30.32) 20 0.45 (0.18, 1.12)
8 (30.33, 62.56) 20 0.75 (0.30, 1.85)
9 (62.64, 195.10) 32 1.26 (0.59, 2.70)
10 (195.68, 12,074.69) 106 0.52 (0.35, 0.77)
0.125 0.25 0.5 1.0 2.0 4.0
Favors canagliflozin
Favors placebo

D



UACR, urinary albumin:creatinine ratio; HR, hazard ratio; CI, confidence interval.

Figure S3. Safety outcomes collected in CANVAS alone in participants with UACR <30, 30-300, and >300 mg/g at baseline.



UACR, urinary albumin:creatinine ratio; HR, hazard ratio; CI, confidence interval.