

**Electronic Supplementary Material (ESM) to: Effects of the SGLT2 Inhibitor
Canagliflozin on Plasma Biomarkers TNFR-1, TNFR-2, and KIM-1 in the CANVAS Trial**

Sen T. et. al

ESM Table 1. Associations of the quartiles and the doubling of TNFR-1, TNFR-2, and KIM-1 with the composite cardiovascular outcome

Biomarker		Model 1		Model 2		Model 3		Model 4	
		HR (95% CI)	<i>p</i> value	HR (95% CI)	<i>p</i> value	HR (95% CI)	<i>p</i> value	HR (95% CI)	<i>p</i> value
TNFR-1									
	Per doubling	1.7 (1.4, 2.1)	<0.01	1.6 (1.3, 1.9)	<0.01	1.5 (1.2, 1.9)	<0.01	1.3 (1.0, 1.6)	0.05
	Quartile 1	(reference)		(reference)		(reference)		(reference)	
	Quartile 2	1.1 (0.9, 1.4)	0.42	1.0 (0.8, 1.3)	0.78	1.0 (0.8, 1.3)	0.96	1.0 (0.8, 1.3)	0.95
	Quartile 3	1.2 (0.9, 1.5)	0.20	1.1 (0.9, 1.4)	0.43	1.0 (0.8, 1.4)	0.74	1.0 (0.8, 1.3)	0.98
	Quartile 4	1.6 (1.3, 2.1)	<0.01	1.4 (1.1, 1.9)	0.01	1.3 (1.0, 1.7)	0.09	1.1 (0.8, 1.5)	0.42
TNFR-2									
	Per doubling	1.5 (1.3, 1.8)	<0.01	1.4 (1.2, 1.7)	<0.01	1.4 (1.1, 1.6)	<0.01	1.2 (1.0, 1.5)	0.07
	Quartile 1	(reference)		(reference)		(reference)		(reference)	
	Quartile 2	1.0 (0.8, 1.3)	0.98	1.0 (0.7, 1.3)	0.79	0.9 (0.7, 1.2)	0.70	0.9 (0.7, 1.2)	0.67
	Quartile 3	1.1 (0.8, 1.4)	0.55	1.0 (0.8, 1.3)	0.91	1.0 (0.8, 1.3)	0.93	1.0 (0.7, 1.3)	0.77
	Quartile 4	1.8 (1.4, 2.3)	<0.01	1.6 (1.3, 2.1)	<0.01	1.5 (1.2, 2.0)	<0.01	1.4 (1.0, 1.8)	0.03

KIM-1

Per doubling	1.3 (1.2, 1.4)	<0.01	1.2 (1.1, 1.3)	<0.01	1.1 (1.0, 1.2)	0.01	1.0 (0.9, 1.1)	0.56
Quartile 1	(reference)		(reference)		(reference)		(reference)	
Quartile 2	1.0 (0.8, 1.3)	0.75	1.0 (0.7, 1.2)	0.70	0.9 (0.7, 1.2)	0.58	0.9 (0.7, 1.1)	0.35
Quartile 3	1.1 (0.9, 1.4)	0.38	1.0 (0.8, 1.3)	0.98	1.0 (0.8, 1.3)	0.85	0.9 (0.7, 1.2)	0.38
Quartile 4	1.5 (1.2, 1.9)	<0.01	1.2 (0.9, 1.5)	0.17	1.1 (0.9, 1.4)	0.41	0.9 (0.7, 1.1)	0.31

NOTE: Models are adjusted for the following covariates. Model 1: baseline biomarker (TNFR-1, TNFR-2, or KIM-1 in quartiles or continuous), age, sex, race, and randomised treatment. Model 2: covariates of model 1 + history of CVD, HbA_{1c}, current smoking, systolic and diastolic BP, BMI, and LDL cholesterol. Model 3: covariates of model 2 + baseline eGFR. Model 4: covariates of model 3 + log transformed baseline UACR. KIM-1, kidney injury molecule-1; TNFR-1, tumour necrosis factor receptor-1; TNFR-2, tumour necrosis factor receptor-2; UACR, urine albumin/creatinine ratio.

ESM Table 2. Associations of the quartiles of TNFR-1, TNFR-2, and KIM-1 with the heart failure outcome

Biomarker		Model 1		Model 2		Model 3		Model 4	
		HR (95% CI)	<i>p</i> value	HR (95% CI)	<i>p</i> value	HR (95% CI)	<i>p</i> value	HR (95% CI)	<i>p</i> value
TNFR-1									
	Per doubling	3.2 (2.2, 4.6)	<0.01	2.0 (1.4, 2.9)	<0.01	1.7 (1.0, 2.7)	0.03	1.1 (0.7, 1.8)	0.60
	Quartile 1	(reference)		(reference)		(reference)		(reference)	
	Quartile 2	1.3 (0.7, 2.6)	0.41	1.1 (0.5, 2.1)	0.87	1.0 (0.5, 2.0)	0.97	1.0 (0.5, 2.0)	0.95
	Quartile 3	2.3 (1.2, 4.3)	0.01	1.6 (0.9, 3.1)	0.13	1.5 (0.8, 2.8)	0.24	1.3 (0.7, 2.5)	0.39
	Quartile 4	3.9 (2.2, 7.1)	<0.01	2.3 (1.3, 4.3)	0.01	1.9 (1.0, 3.7)	0.06	1.5 (0.7, 2.9)	0.26
TNFR-2									
	Per doubling	2.2 (1.7, 2.9)	<0.01	1.7 (1.2, 2.4)	<0.01	1.4 (0.9, 2.1)	0.12	1.0 (0.7, 1.6)	0.89
	Quartile 1	(reference)		(reference)		(reference)		(reference)	
	Quartile 2	1.6 (0.9, 2.8)	0.14	1.2 (0.7, 2.2)	0.48	1.2 (0.6, 2.2)	0.61	1.2 (0.6, 2.1)	0.64
	Quartile 3	1.3 (0.7, 2.4)	0.41	0.9 (0.5, 1.8)	0.87	0.9 (0.5, 1.6)	0.64	0.8 (0.4, 1.5)	0.52
	Quartile 4	3.1 (1.8, 5.3)	<0.01	1.9 (1.1, 3.3)	0.03	1.5 (0.8, 2.7)	0.21	1.1 (0.6, 2.1)	0.70

KIM-1

Per doubling	1.6 (1.3, 1.9)	<0.01	1.4 (1.2, 1.7)	<0.01	1.4 (1.1, 1.6)	<0.01	1.1 (0.9, 1.3)	0.40
Quartile 1	(reference)		(reference)		(reference)		(reference)	
Quartile 2	0.9 (0.5, 1.8)	0.85	0.8 (0.4, 1.5)	0.43	0.7 (0.4, 1.4)	0.35	0.7 (0.3, 1.3)	0.21
Quartile 3	1.8 (1.0, 3.2)	0.03	1.5 (0.9, 2.6)	0.16	1.4 (0.8, 2.5)	0.22	1.2 (0.7, 2.1)	0.57
Quartile 4	2.7 (1.6, 4.5)	<0.01	1.8 (1.1, 3.2)	0.03	1.6 (0.9, 2.8)	0.10	1.0 (0.5, 1.8)	0.96

NOTE: Models are adjusted for the following covariates. Model 1: age, sex, race, and randomised treatment. Model 2: covariates of model 1 + history of CVD, HbA_{1c}, current smoking, systolic and diastolic BP, BMI, and LDL cholesterol. Model 3: covariates of model 2 + baseline eGFR. Model 4: covariates of model 3 + log transformed baseline UACR.

KIM-1, kidney injury molecule-1; TNFR-1, tumour necrosis factor receptor-1; TNFR-2, tumour necrosis factor receptor-2; UACR, urine albumin/creatinine ratio.

ESM Table 3. C-statistics of the Cox-proportional hazard regression models used to assess the association between doubling in biomarker with outcomes with and without biomarker

	Full model without biomarker	TNFR-1	TNFR-2	KIM-1
Kidney outcome				
C-statistic (95% CI)	0.789 (0.747, 0.830)	0.807 (0.769, 0.845)	0.813 (0.775, 0.850)	0.797 (0.757, 0.838)
IDI (SD); <i>p</i> value	-	0.011 (0.004); <i>p</i> <0.01	0.013 (0.004); <i>p</i> <0.01	0.012 (0.004); <i>p</i> <0.01
NRI (SD); <i>p</i> value	-	0.290 (0.087); <i>p</i> <0.01	0.411 (0.087); <i>p</i> <0.01	0.2544 (0.087); <i>p</i> <0.01
CV outcome				
C-statistic (95% CI)	0.680 (0.656, 0.704)	0.681 (0.657, 0.705)	0.682 (0.658, 0.706)	0.680 (0.657, 0.704)
IDI (SD); <i>p</i> value	-	0.001 (0.001); <i>p</i> =0.09	0.001 (0.001); <i>p</i> =0.10	0.000 (0.000); <i>p</i> =0.80
NRI (SD); <i>p</i> value	-	0.093 (0.047); <i>p</i> =0.04	0.059 (0.047); <i>p</i> =0.21	0.026 (0.047); <i>p</i> =0.57
HF outcome				
C-statistic (95% CI)	0.799 (0.765, 0.833)	0.798 (0.764, 0.833)	0.799 (0.765, 0.833)	0.800 (0.766, 0.834)
IDI (SD); <i>p</i> value	-	0.001 (0.000); <i>p</i> =0.10	0.000 (0.000); <i>p</i> =0.30	0.000 (0.001); <i>p</i> =0.99
NRI (SD); <i>p</i> value	-	-0.035 (0.090); <i>p</i> =0.99	-0.026 (0.090); <i>p</i> =0.99	0.057 (0.090); <i>p</i> =0.53

NOTE: The full model without biomarker was adjusted for the following covariates: age, sex, race, and randomised treatment, history of CVD, HbA_{1c}, current smoking, systolic and diastolic BP, BMI, and LDL cholesterol, baseline eGFR, log transformed baseline urine albumin/creatinine ratio.

ESM Table 4. Time dependent AUC values of baseline biomarkers during 6 years follow-up for the kidney, CV, and HF outcome

C-statistic	
Kidney outcome	
TNFR-1	0.710
TNFR-2	0.727
KIM-1	0.730
CV outcome	
TNFR-1	0.577
TNFR-2	0.574
KIM-1	0.574
HF outcome	
TNFR-1	0.662
TNFR-2	0.627
KIM-1	0.641

Note: Time dependent AUC values are obtained from unadjusted models

ESM Table 5. Associations of the quartiles of each change in TNFR-1, TNFR-2, and KIM-1 from baseline to year 1 with the composite cardiovascular outcome

Biomarker		Model 1		Model 2		Model 3		Model 4		Model 5	
	Median change	HR (95% CI)	<i>p</i> value	HR (95% CI)	<i>p</i> value	HR (95% CI)	<i>p</i> value	HR (95% CI)	<i>p</i> value	HR (95% CI)	<i>p</i> value
TNFR-1											
Per 10% reduction		1.0 (0.9, 1.1)	0.54	1.0 (0.9, 1.1)	0.83	1.0 (0.9, 1.1)	0.91	1.0 (0.9, 1.1)	0.74	1.0 (1.0, 1.1)	0.47
Quartile 1	-11.7	1.0 (0.7, 1.3)	0.99	1.0 (0.8, 1.4)	0.89	1.0 (0.7, 1.3)	1.00	1.0 (0.8, 1.4)	0.88	1.0 (0.8, 1.4)	0.91
Quartile 2	-0.6	(reference)		(reference)		(reference)		(reference)		(reference)	
Quartile 3	8.2	0.9 (0.7, 1.2)	0.46	0.9 (0.6, 1.2)	0.39	0.9 (0.7, 1.2)	0.42	0.9 (0.6, 1.2)	0.34	0.9 (0.6, 1.2)	0.31
Quartile 4	21.1	1.0 (0.7, 1.4)	0.99	1.0 (0.7, 1.3)	0.79	0.9 (0.7, 1.3)	0.62	0.9 (0.6, 1.2)	0.41	0.8 (0.6, 1.1)	0.21
TNFR-2											
Per 10% reduction		1.0 (0.9, 1.0)	0.63	1.0 (0.9, 1.1)	0.96	1.0 (0.9, 1.1)	0.83	1.0 (0.9, 1.1)	0.85	1.0 (0.9, 1.1)	0.77
Quartile 1	-12.8	1.0 (0.7, 1.3)	0.96	1.0 (0.7, 1.4)	0.97	1.0 (0.7, 1.3)	0.89	1.0 (0.7, 1.3)	0.95	1.0 (0.8, 1.4)	0.93
Quartile 2	-2.2	(reference)		(reference)		(reference)		(reference)		(reference)	
Quartile 3	6.2	0.9 (0.7, 1.2)	0.43	0.9 (0.6, 1.2)	0.34	0.9 (0.6, 1.2)	0.37	0.8 (0.6, 1.1)	0.28	0.9 (0.6, 1.2)	0.32
Quartile 4	20.0	1.1 (0.8, 1.5)	0.44	1.1 (0.8, 1.4)	0.70	1.1 (0.8, 1.4)	0.68	1.0 (0.7, 1.4)	0.97	1.0 (0.7, 1.4)	0.99

KIM-1

Per 10% reduction		1.0 (0.9, 1.0)	0.02	1.0 (0.9, 1.0)	0.02	1.0 (0.9, 1.0)	0.19	1.0 (0.9, 1.0)	0.22	1.0 (1.0, 1.0)	0.71
Quartile 1	-34.0	0.7 (0.5, 1.0)	0.03	0.7 (0.5, 1.0)	0.03	0.7 (0.5, 1.0)	0.06	0.7 (0.5, 1.0)	0.06	0.8 (0.6, 1.0)	0.10
Quartile 2	-13.3	(reference)		(reference)		(reference)		(reference)		(reference)	
Quartile 3	2.9	1.0 (0.7, 1.3)	0.83	1.0 (0.7, 1.3)	0.84	0.9 (0.7, 1.2)	0.60	0.9 (0.7, 1.2)	0.61	0.9 (0.7, 1.2)	0.57
Quartile 4	33.1	1.2 (0.9, 1.6)	0.29	1.2 (0.9, 1.6)	0.32	1.1 (0.8, 1.4)	0.64	1.1 (0.8, 1.4)	0.70	1.0 (0.7, 1.3)	0.77

NOTE: Models are adjusted for the following covariates. Model 1: baseline biomarker (TNFR-1, TNFR-2, or KIM-1), age, sex, race, and randomised treatment. Model 2: covariates of model 1 + change in eGFR from baseline to year 1 and baseline eGFR. Model 3: covariates of model 1 + change in UACR from baseline to year 1 and baseline UACR. Model 4: covariates of model 1 + change in eGFR and UACR from baseline to year 1 and baseline eGFR and UACR. Model 5: covariates of model 1 + history of CVD, current smoking, HbA_{1c}, systolic and diastolic BP, BMI, LDL cholesterol, eGFR, baseline UACR, and change in eGFR, UACR, systolic BP, BMI, and HbA_{1c} from baseline to year 1.

KIM-1, kidney injury molecule-1; TNFR-1, tumour necrosis factor receptor-1; TNFR-2, tumour necrosis factor receptor-2; UACR, urine albumin/creatinine ratio.

ESM Table 6. Associations of the quartiles of each change in TNFR-1, TNFR-2, and KIM-1 from baseline to year 1 with the composite heart failure outcome

Biomarker		Model 1		Model 2		Model 3		Model 4		Model 5	
	Median change	HR (95% CI)	<i>p</i> value	HR (95% CI)	<i>p</i> value	HR (95% CI)	<i>p</i> value	HR (95% CI)	<i>p</i> value	HR (95% CI)	<i>p</i> value
TNFR-1											
Per 10% reduction		0.9 (0.8, 1.0)	0.14	0.9 (0.8, 1.1)	0.26	0.9 (0.8, 1.1)	0.38	1.0 (0.8, 1.1)	0.60	1.0 (0.9, 1.2)	0.89
Quartile 1	-12.4	1.7 (0.9, 3.3)	0.10	1.8 (0.9, 3.4)	0.08	1.7 (0.9, 3.3)	0.09	1.8 (0.9, 3.4)	0.08	1.9 (1.0, 3.6)	0.06
Quartile 2	-0.4	(reference)		(reference)		(reference)		(reference)		(reference)	
Quartile 3	8.1	1.9 (1.0, 3.6)	0.06	1.8 (0.9, 3.6)	0.07	1.8 (1.0, 3.6)	0.07	1.8 (0.9, 3.5)	0.08	1.8 (0.9, 3.5)	0.09
Quartile 4	19.2	2.3 (1.2, 4.4)	0.01	2.2 (1.2, 4.3)	0.02	2.0 (1.1, 3.8)	0.03	1.9 (1.0, 3.7)	0.05	1.7 (0.9, 3.2)	0.12
TNFR-2											
Per 10% reduction		0.9 (0.9, 1.0)	0.07	0.9 (0.9, 1.0)	0.18	0.9 (0.9, 1.0)	0.08	0.9 (0.9, 1.0)	0.20	1.0 (0.8, 1.1)	0.39
Quartile 1	-13.7	2.1 (1.1, 4.0)	0.03	2.1 (1.1, 4.0)	0.03	2.0 (1.0, 3.9)	0.04	2.0 (1.1, 4.0)	0.03	2.2 (1.1, 4.4)	0.02
Quartile 2	-2.1	(reference)		(reference)		(reference)		(reference)		(reference)	
Quartile 3	6.0	1.8 (0.9, 3.5)	0.09	1.7 (0.9, 3.4)	0.12	1.8 (0.9, 3.6)	0.08	1.7 (0.9, 3.4)	0.11	1.8 (0.9, 3.5)	0.11
Quartile 4	18.2	2.4 (1.2, 4.6)	0.01	2.1 (1.1, 4.2)	0.03	2.2 (1.1, 4.2)	0.02	2.0 (1.0, 3.9)	0.05	1.9 (0.9, 3.7)	0.07

KIM-1

Per 10% reduction		0.9 (0.9, 1.0)	0.05	0.9 (0.9, 1.0)	0.06	1.0 (0.9, 1.0)	0.28	1.0 (0.9, 1.0)	0.38	1.0 (0.9, 1.0)	0.20
Quartile 1	-41.3	0.6 (0.3, 1.2)	0.14	0.6 (0.4, 1.2)	0.14	0.7 (0.4, 1.3)	0.23	0.7 (0.4, 1.3)	0.24	0.7 (0.4, 1.2)	0.18
Quartile 2	-14.3	(reference)		(reference)		(reference)		(reference)		(reference)	
Quartile 3	3.0	1.1 (0.6, 1.8)	0.81	1.1 (0.6, 1.8)	0.82	1.0 (0.6, 1.7)	1.00	1.0 (0.6, 1.7)	0.98	1.1 (0.6, 1.9)	0.80
Quartile 4	28.8	1.0 (0.6, 1.8)	0.89	1.0 (0.6, 1.8)	1.00	0.9 (0.5, 1.6)	0.70	0.8 (0.5, 1.5)	0.56	0.9 (0.5, 1.6)	0.74

NOTE: Models are adjusted for the following covariates. Model 1: baseline biomarker (TNFR-1, TNFR-2, or KIM-1), age, sex, race, and randomised treatment. Model 2: covariates of model 1 + change in eGFR from baseline to year 1 and baseline eGFR. Model 3: covariates of model 1 + change in UACR from baseline to year 1 and baseline UACR. Model 4: covariates of model 1 + change in eGFR and UACR from baseline to year 1 and baseline eGFR and UACR. Model 5: covariates of model 1 + history of CVD, current smoking, HbA_{1c}, systolic and diastolic BP, BMI, LDL cholesterol, eGFR, baseline UACR, and change in eGFR, UACR, systolic BP, BMI, and HbA_{1c} from baseline to year 1.

KIM-1, kidney injury molecule-1; TNFR-1, tumour necrosis factor receptor-1; TNFR-2, tumour necrosis factor receptor-2; UACR, urine albumin/creatinine ratio.

ESM Table 7. Associations within the canagliflozin group of quartiles of 1-year change from baseline in TNFR-1, TNFR-2, and KIM-1 with the composite kidney, cardiovascular, and heart failure outcome in the fully adjusted model

Biomarker	Kidney outcome		Cardiovascular outcome		Heart failure outcome	
	HR (95% CI)	<i>p</i> value	HR (95% CI)	<i>p</i> value	HR (95% CI)	<i>p</i> value
TNFR-1						
Per 10% reduction	0.90 (0.74, 1.11)	0.34	1.05 (0.97, 1.14)	0.24	1.04 (0.85, 1.26)	0.72
Quartile 1	0.70 (0.30, 1.63)	0.41	1.01 (0.70, 1.44)	0.98	1.93 (0.88, 4.21)	0.10
Quartile 2	(reference)		(reference)		(reference)	
Quartile 3	0.97 (0.43, 2.2)	0.95	0.84 (0.58, 1.23)	0.37	1.39 (0.59, 3.26)	0.45
Quartile 4	1.38 (0.68, 2.78)	0.38	0.71 (0.48, 1.05)	0.08	1.42 (0.63, 3.21)	0.40
TNFR-2						
Per 10% reduction	0.92 (0.87, 0.98)	0.01	1.04 (0.95, 1.14)	0.35	0.97 (0.82, 1.16)	0.75
Quartile 1	0.57 (0.23, 1.44)	0.23	0.93 (0.65, 1.34)	0.71	2.27 (1.00, 5.17)	0.05
Quartile 2	(reference)		(reference)		(reference)	
Quartile 3	1.15 (0.50, 2.65)	0.74	0.86 (0.60, 1.25)	0.44	1.19 (0.47, 3.03)	0.72
Quartile 4	2.07 (0.99, 4.33)	0.06	0.80 (0.55, 1.17)	0.25	2.02 (0.85, 4.78)	0.11

KIM-1

Per 10% reduction	0.94 (0.89, 1.02)	0.16	1.00 (0.95, 1.05)	0.99	0.96 (0.87, 1.06)	0.43
Quartile 1	1.23 (0.58, 2.59)	0.59	0.81 (0.56, 1.16)	0.25	0.73 (0.36, 1.48)	0.38
Quartile 2	(reference)		(reference)		(reference)	
Quartile 3	1.63 (0.74, 3.58)	0.22	0.92 (0.64, 1.32)	0.66	1.15 (0.58, 2.28)	0.69
Quartile 4	1.06 (0.42, 2.65)	0.91	0.92 (0.62, 1.36)	0.67	0.56 (0.22, 1.46)	0.24

NOTE: Interaction p values for TNFR-1 and TNFR-2 with treatment assignment for the kidney outcome were not statically significant ($p = 0.60$ and $p = 0.20$) indicating that the association between 1-year changes from baseline in TNFR-1 and TNFR-2 were consistent in the canagliflozin and placebo group.

Models are adjusted for the following covariates. Model 1: baseline biomarker (TNFR-1, TNFR-2, or KIM-1), age, sex, race, and randomised treatment. Model 2: covariates of model 1 + change in eGFR from baseline to year 1 and baseline eGFR. Model 3: covariates of model 1 + change in UACR from baseline to year 1 and baseline UACR. Model 4: covariates of model 1 + change in eGFR and UACR from baseline to year 1 and baseline eGFR and UACR. Model 5: covariates of model 1 + history of CVD, current smoking, HbA_{1c}, systolic and diastolic BP, BMI, LDL cholesterol, eGFR, baseline UACR, and change in eGFR, UACR, systolic BP, BMI, and HbA_{1c} from baseline to year 1.

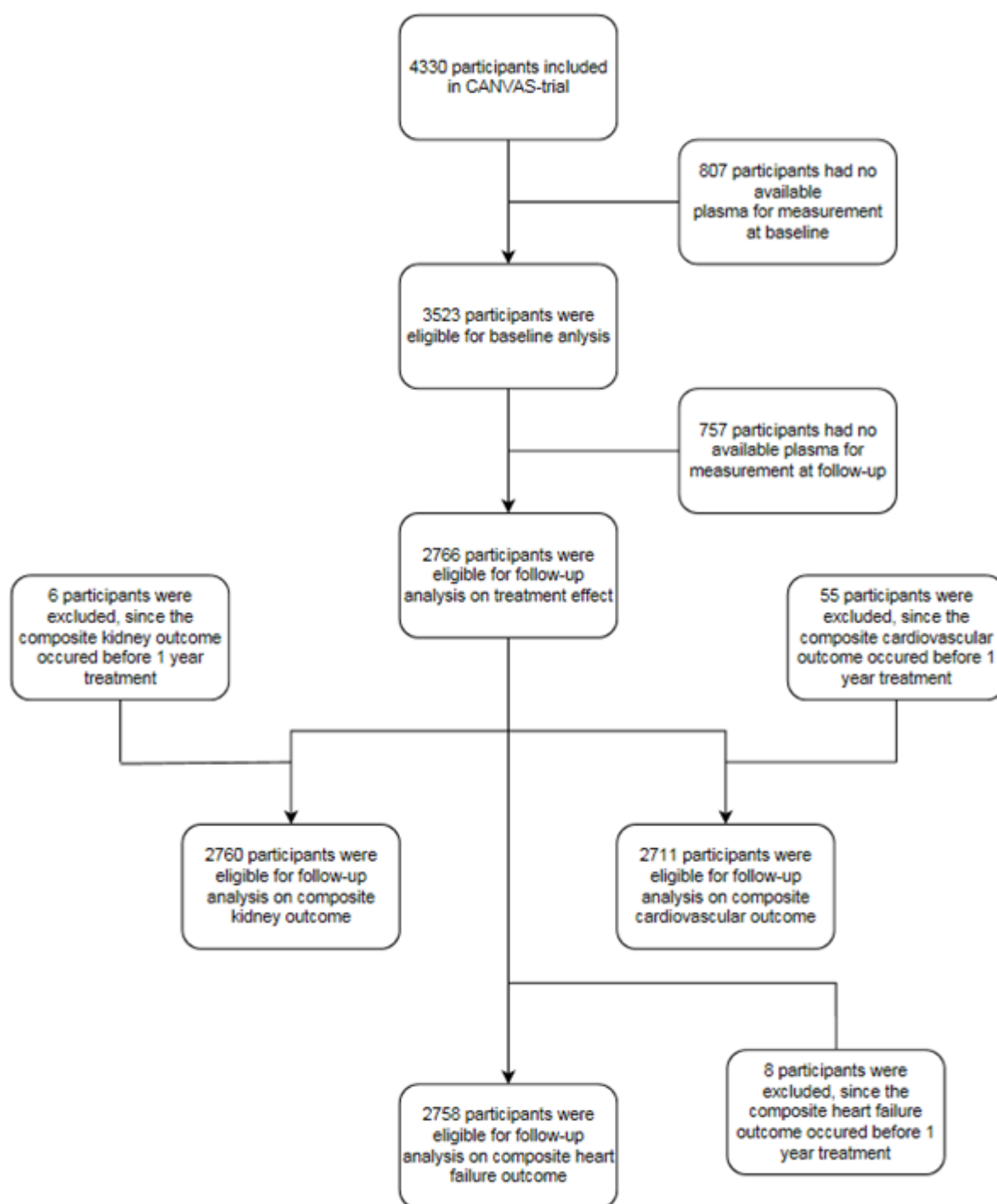
KIM-1, kidney injury molecule-1; TNFR-1, tumour necrosis factor receptor-1; TNFR-2, tumour necrosis factor receptor-2; UACR, urine albumin/creatinine ratio.

ESM Table 8. Proportion of treatment effects explained by changes in TNFR-1, TNFR-2, or KIM-1 from baseline to 1-year follow-up

	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Proportion explained (%)
Kidney outcome			
TNFR-1	0.56 (0.38, 0.81)	0.53 (0.36, 0.77)	−6.8
TNFR-2	0.56 (0.38, 0.81)	0.50 (0.34, 0.74)	−13.6
KIM-1	0.56 (0.38, 0.81)	0.58 (0.40, 0.86)	4.5
Cardiovascular outcome			
TNFR-1	0.92 (0.73, 1.15)	0.91 (0.73, 1.14)	−12.5
TNFR-2	0.92 (0.73, 1.15)	0.91 (0.73, 1.14)	−12.5
KIM-1	0.92 (0.73, 1.15)	0.97 (0.77, 1.22)	62.5
Heart failure outcome			
TNFR-1	0.82 (0.54, 1.25)	0.80 (0.53, 1.22)	−11.1
TNFR-2	0.82 (0.54, 1.25)	0.79 (0.52, 1.20)	−16.7
KIM-1	0.82 (0.54, 1.25)	0.89 (0.58, 1.37)	38.9

KIM-1, kidney injury molecule-1; TNFR-1, TNF receptor-1; TNFR-2, TNF receptor-2.

ESM Fig. 1 Flow diagram of study design and analysis.



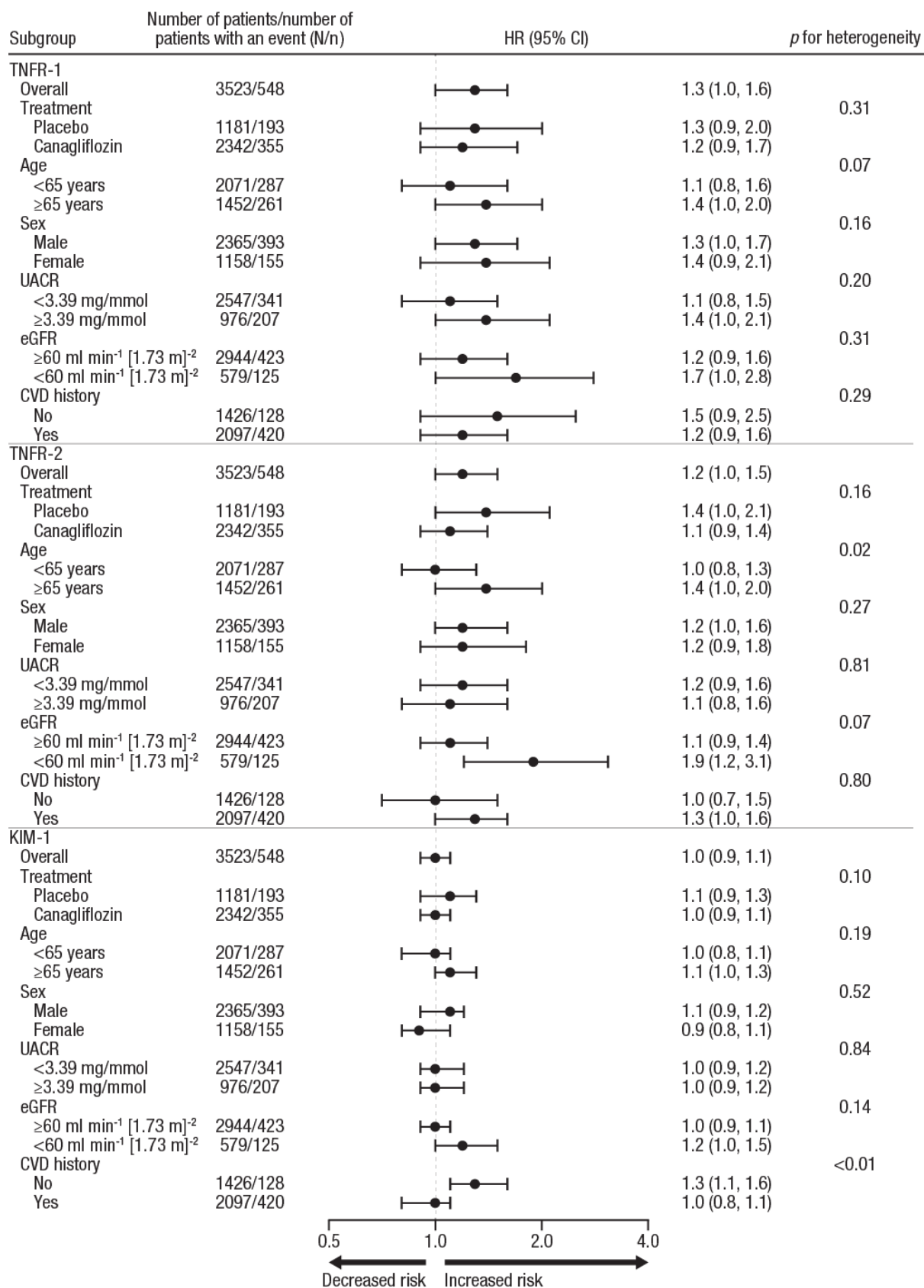
ESM Fig. 2 Pearson correlation test of each baseline biomarker with covariates used in the assessment of the association of each baseline biomarker with kidney and cardiovascular outcomes.



Age (years)	0.24	0.18	0.17
Sex (male/female)	-0.01	-0.04	-0.01
Race	0.01	-0.06	0.07
Treatment with canagliflozin (yes/no)	0.00	-0.01	-0.01
History of CVD	0.05	0.06	0.03
Current smoking	-0.10	-0.08	0.01
HbA _{1c}	0.06	0.07	0.14
Systolic BP	0.08	0.04	0.18
Diastolic BP	-0.13	-0.13	0.02
BMI	0.17	0.12	0.05
LDL cholesterol	-0.06	-0.07	0.10
eGFR	-0.54	-0.45	-0.26
UACR	0.29	0.26	0.47

TNFR-1 TNFR-2 KIM-1
KIM-1, kidney injury molecule-1; TNFR-1, tumour necrosis factor receptor-1; TNFR-2, tumour necrosis factor receptor-2; UACR, urine albumin/creatinine ratio.

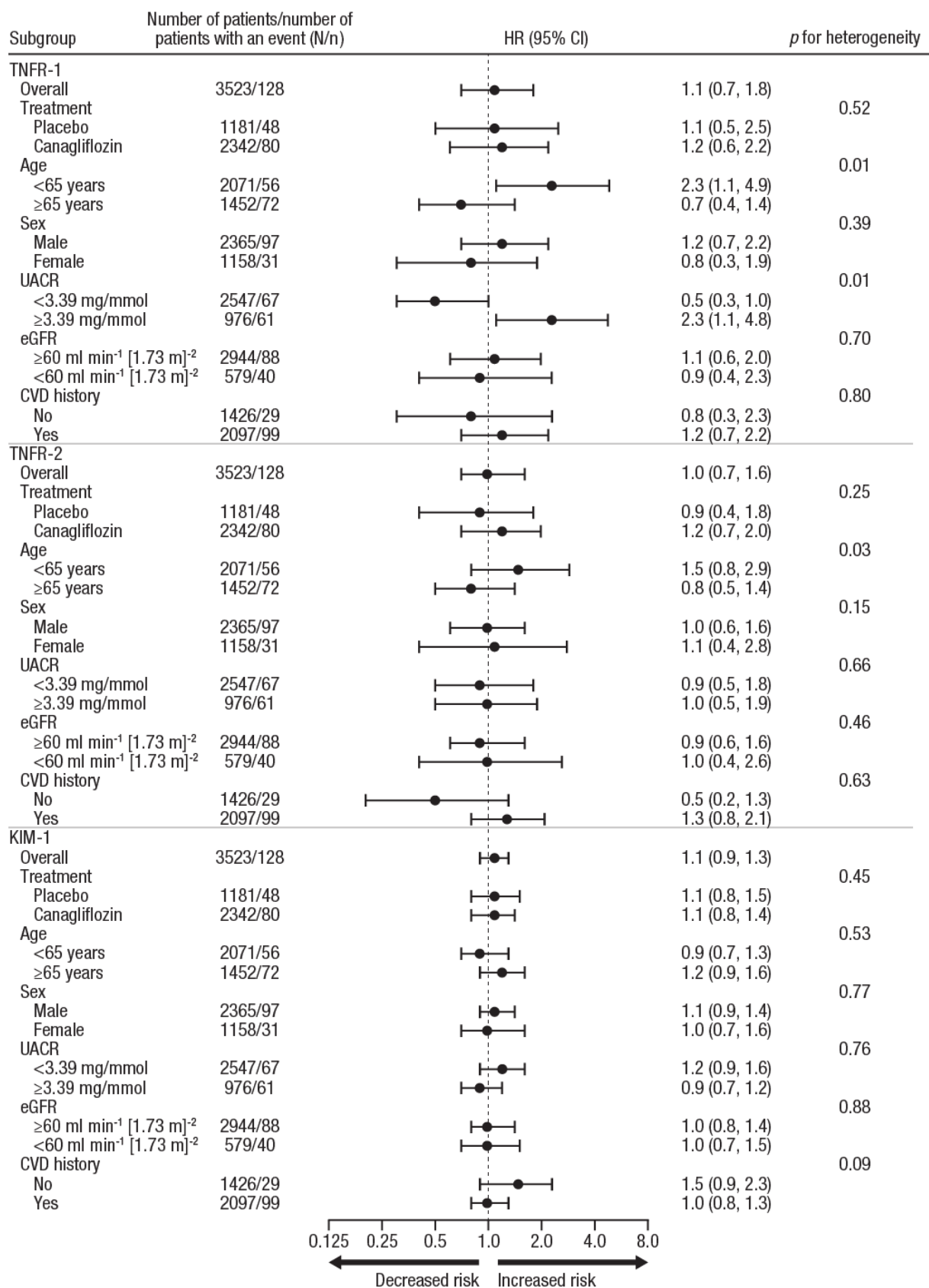
ESM Fig. 3 Associations of the doubling in each baseline biomarker with the cardiovascular outcome by subpopulations.



NOTE: Models are adjusted for the following covariates: age, sex, race, and randomised treatment, history of CVD, HbA_{1c}, current smoking, systolic and diastolic BP, BMI, and LDL cholesterol, baseline eGFR, log transformed baseline urine albumin/creatinine ratio.

KIM-1, kidney injury molecule-1; TNFR-1, tumour necrosis factor receptor-1; TNFR-2, tumour necrosis factor receptor-2; UACR, urine albumin/creatinine ratio.

ESM Fig. 4 Associations of the doubling in each baseline biomarker with the heart failure outcome by subpopulations.

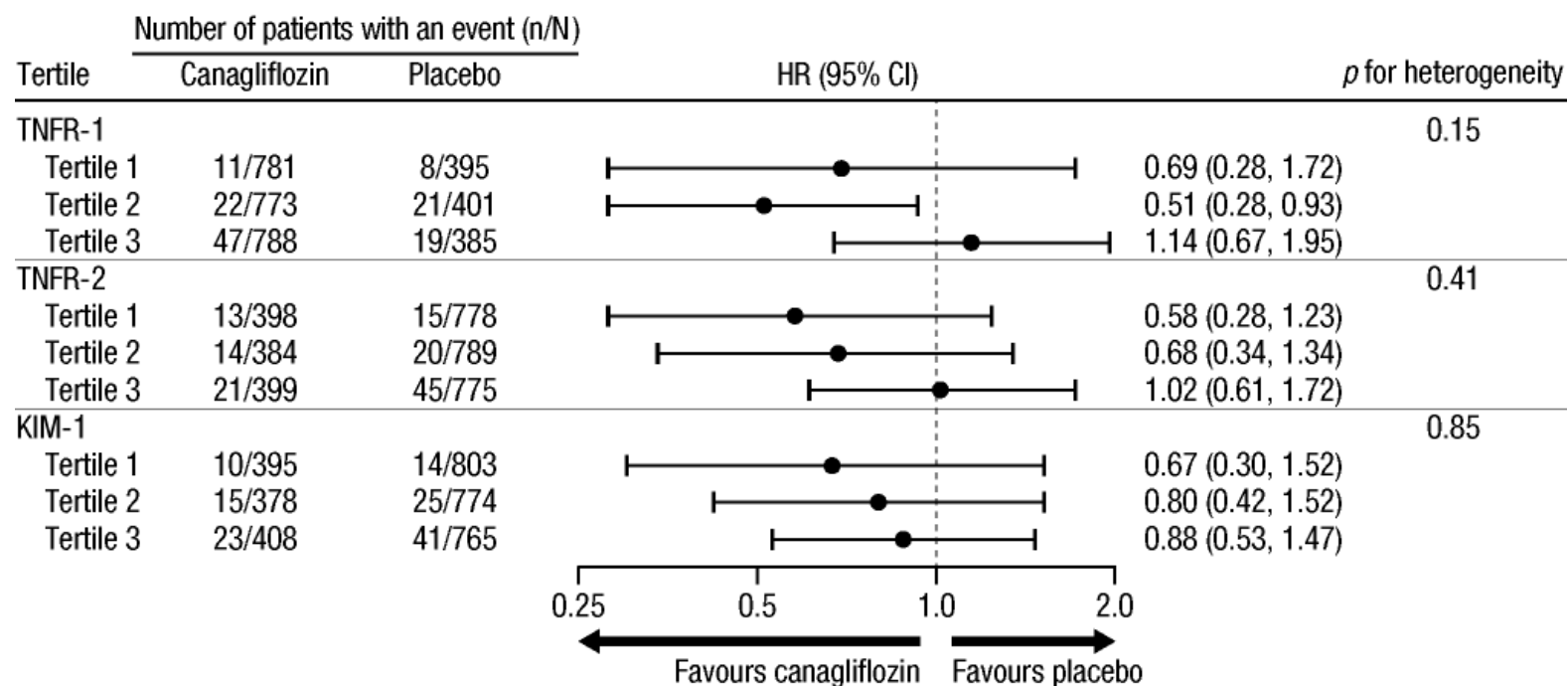


NOTE: Models are adjusted for the following covariates: age, sex, race, and randomised treatment, history of CVD, HbA_{1c}, current smoking, systolic and diastolic BP, BMI, and LDL cholesterol, baseline eGFR, log transformed baseline urine albumin/creatinine ratio.

When UACR was fitted as dichotomous variable the *p* value for heterogeneity between UACR-categories and TNFR-1 was 0.02.

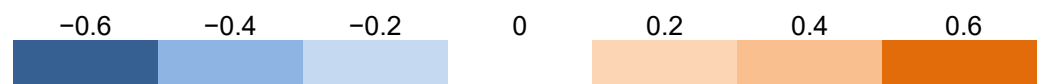
KIM-1, kidney injury molecule-1; TNFR-1, tumour necrosis factor receptor-1; TNFR-2, tumour necrosis factor receptor-2; UACR, urine albumin/creatinine ratio.

ESM Fig. 5 Forest plot of the effect of canagliflozin on heart failure outcome by baseline TNFR-1, TNFR-2, and KIM-1 divided in tertiles.



KIM-1, kidney injury molecule-1; TNFR-1, tumour necrosis factor receptor-1; TNFR-2, tumour necrosis factor receptor-2.

ESM Fig. 6 Pearson correlation test of each change in biomarker from baseline to year 1 with covariates used in the assessment of the association of each change in biomarker from baseline to year 1 with kidney and cardiovascular outcomes.



Baseline biomarker (TNFR-1, TNFR-2, or KIM-1)	-0.13	-0.15	-0.30
Treatment with canagliflozin (yes/no)	-0.02	0.01	-0.22
Age	0.05	0.06	-0.05
Sex	-0.04	-0.01	0.04
Race	0.00	0.02	0.04
History of CVD	-0.01	-0.02	0.03
Current smoking	-0.02	-0.03	0.03
HbA _{1c}	0.05	0.03	0.15
Systolic BP	-0.07	-0.06	0.06
Diastolic BP	-0.08	-0.09	0.05
BMI	0.02	0.01	0.02
LDL cholesterol	0.05	0.02	0.10
eGFR	-0.12	-0.11	0.08
Change in UACR from baseline	-0.05	-0.08	0.20
Change in systolic BP	-0.13	-0.13	0.13
Change in diastolic BP	0.07	0.02	0.10
Change in HbA _{1c}	0.04	0.03	0.23
Baseline UACR	0.08	0.06	-0.09
Change in eGFR	-0.23	-0.17	0.02

	Change in TNFR-1	Change in TNFR-2	Change in KIM-1
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KIM-1, kidney injury molecule-1; TNFR-1, tumour necrosis factor receptor-1; TNFR-2, tumour necrosis factor receptor-2; UACR, urine albumin/creatinine ratio