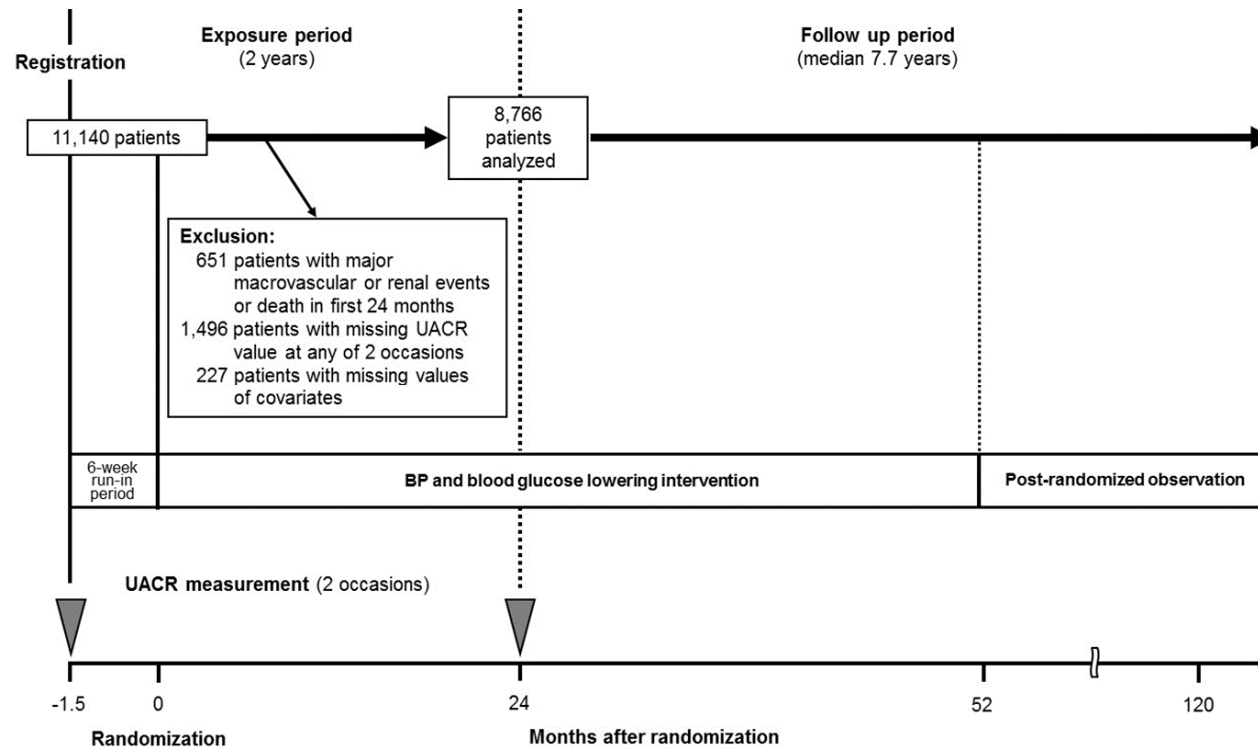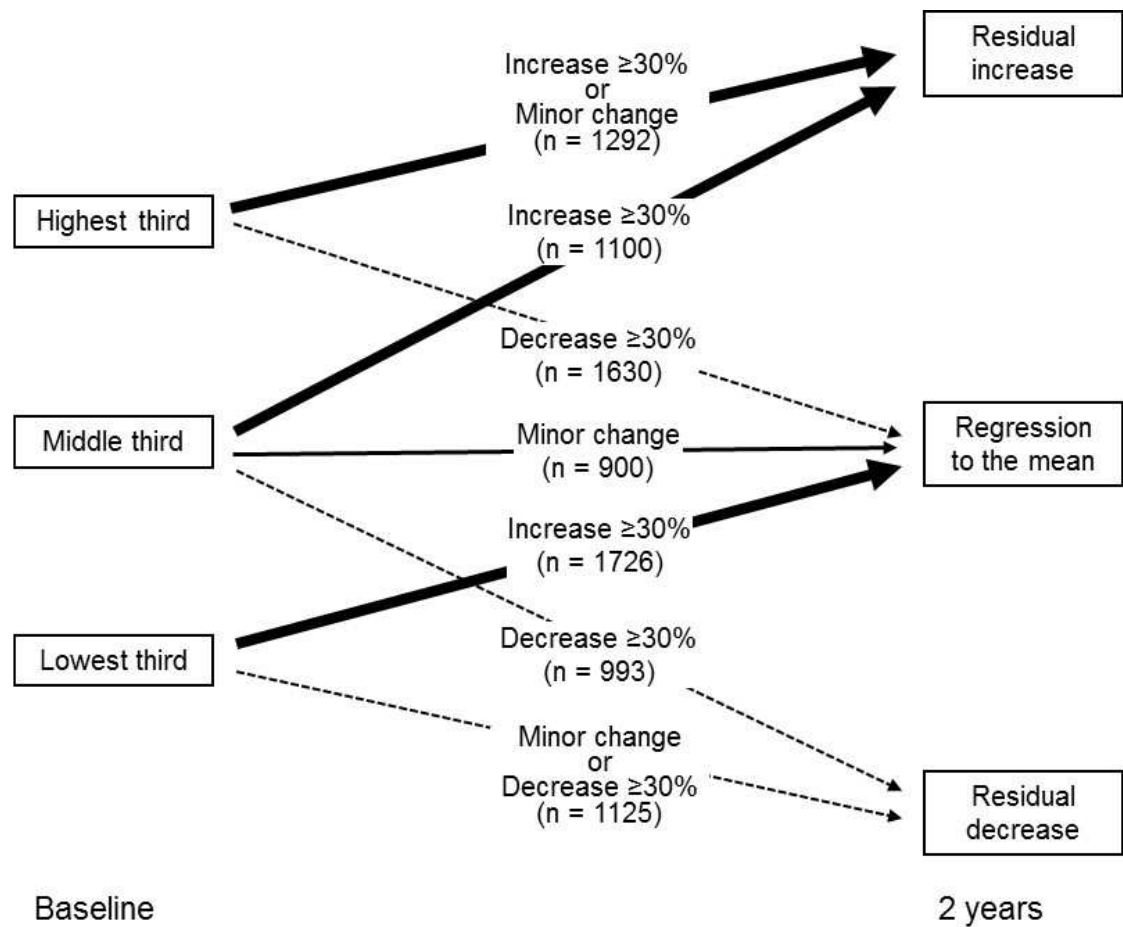SUPPLEMENTARY DATA

Supplementary Figure S1. Study design and identification of the study cohort

UACR=urine albumin-to-creatinine ratio; BP=blood pressure

SUPPLEMENTARY DATA

Supplementary Figure S2. Diagram showing the grouping of participants according to baseline and change in UACR to account for regression-to-the-mean

SUPPLEMENTARY DATA

Supplementary Figure S3. Adjusted† hazard ratios (HRs) and 95% confidence intervals (CIs) for study outcomes associated with UACR values at baseline^^; HRs (95% CIs) are shown for a one standard deviation increase before and after adjusting for regression to the mean
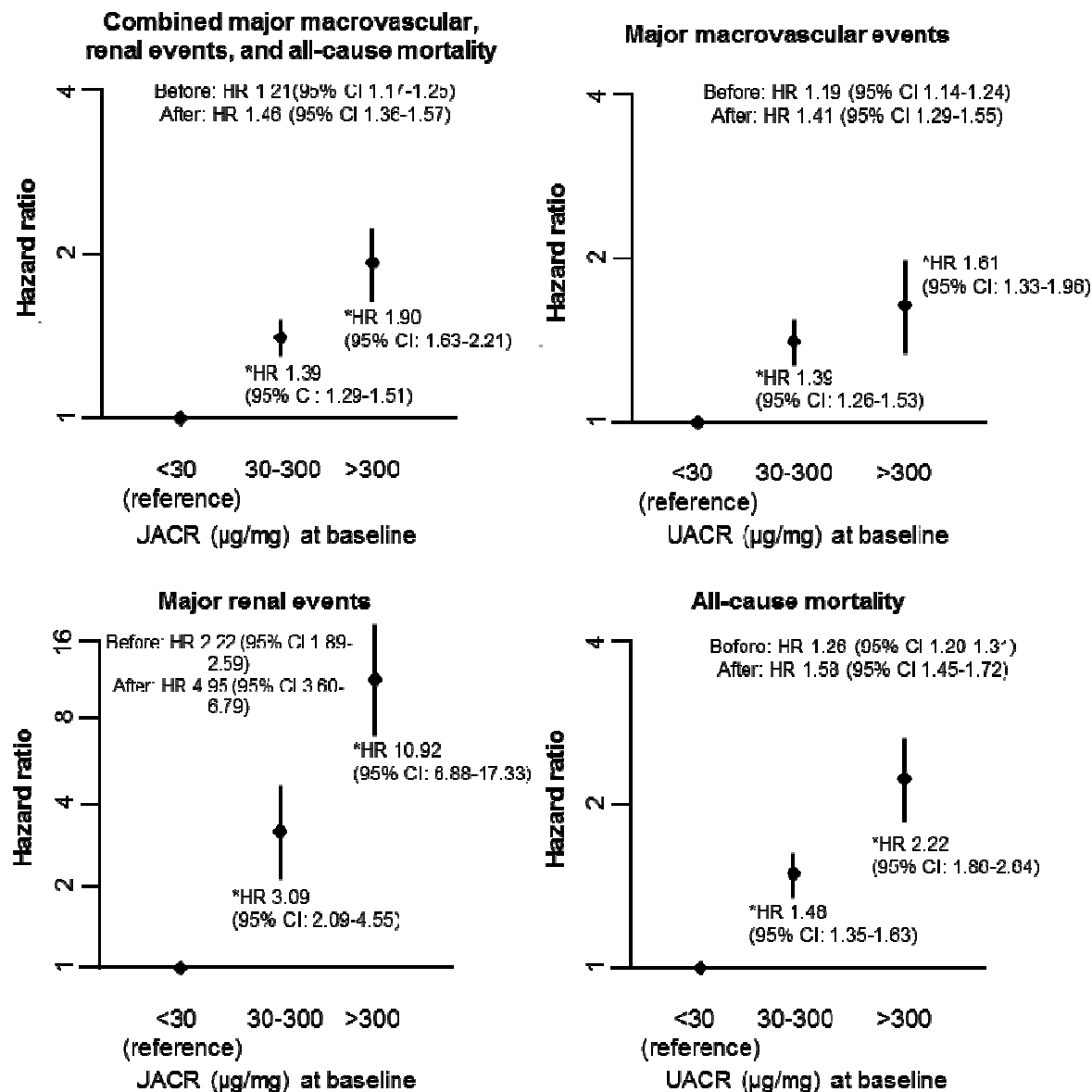
†^Adjusted for age, sex, region of residence, duration of diabetes, history of macrovascular diseases, smoking habit, drinking habit, body mass index, HbA1c, total cholesterol, log-transformed triglycerides, estimated glomerular filtration rate (eGFR) systolic blood pressure (BP) and ADVANCE trial treatment allocation (randomized blood pressure lowering and glucose control); *HRs and 95% CIs indicate the association between baseline UACR level (30-300 and >300 µg/mg) and outcomes compared with the reference group (<30 µg/mg); adjustments as for analysis showing one standard deviation increase of UACR

Supplementary Figure S4. The relationship between baseline and two-year UACR values (on the natural log scale) according to tenths of baseline UACR
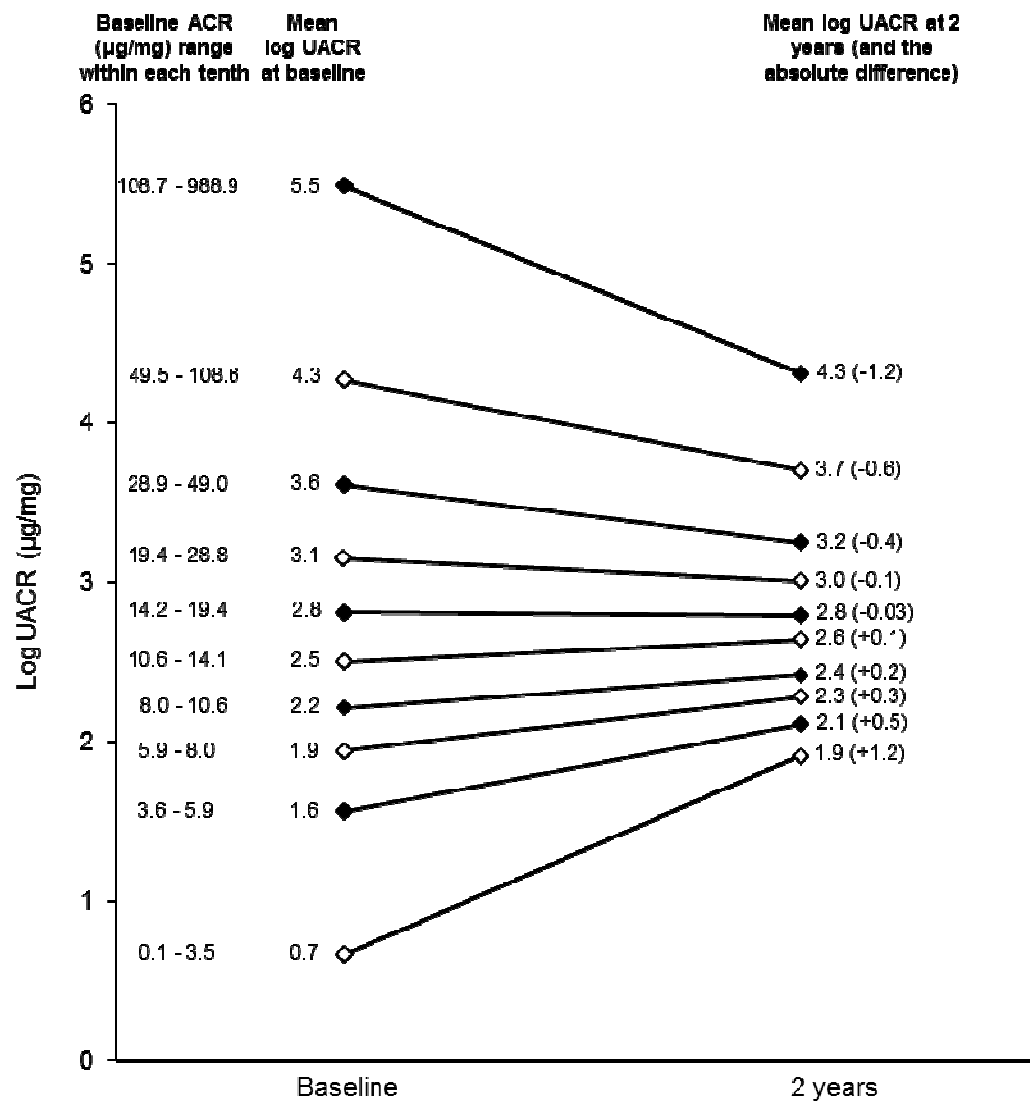
UACR=urine albumin-to-creatinine ratio

SUPPLEMENTARY DATA

Supplementary Figure S5. Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for major macrovascular events according to baseline eGFR and systolic BP*
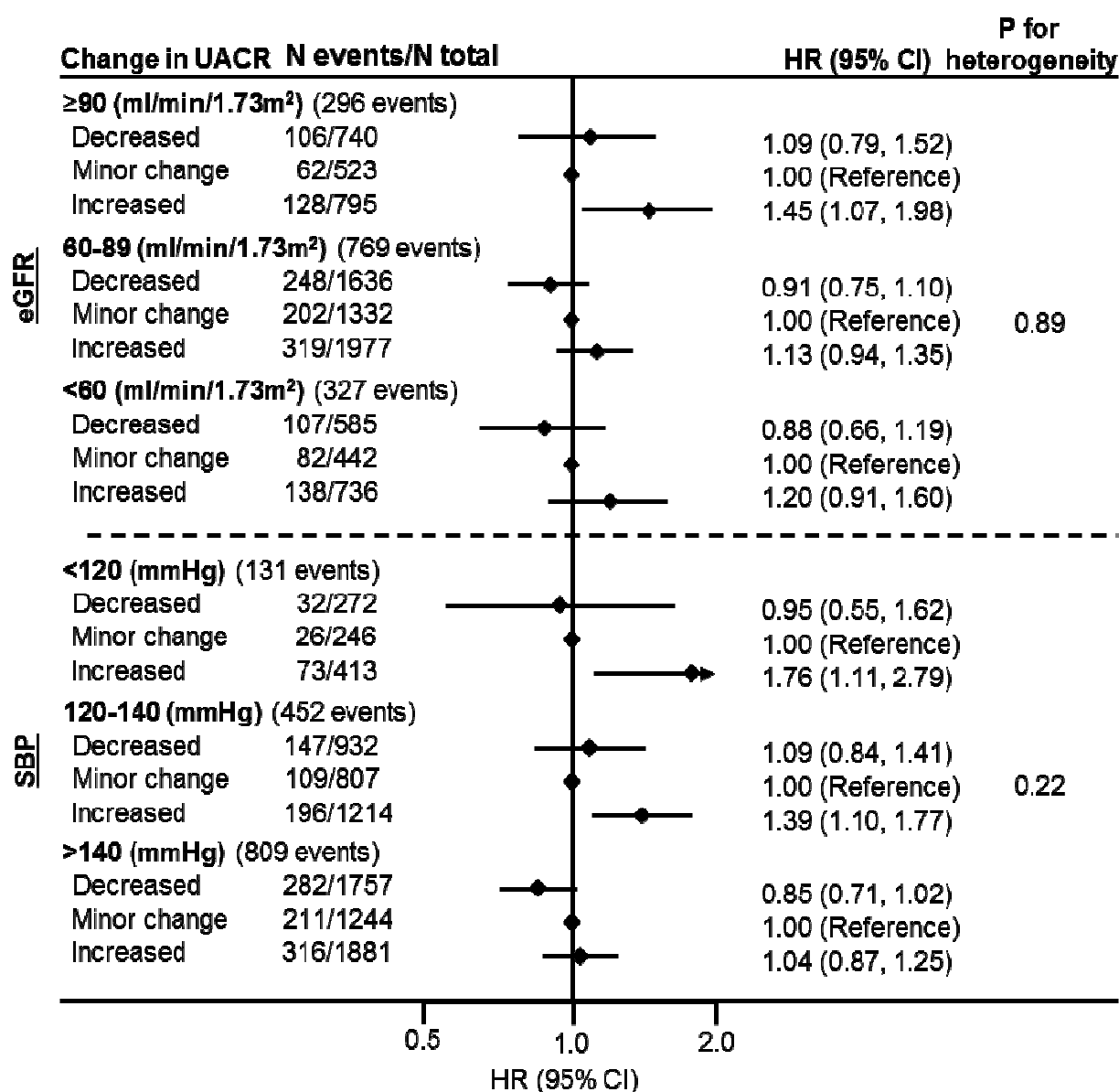
Change in UACR	N events/N total	HR (95% CI)	P for heterogeneity
≥90 (ml/min/1.73m²) (296 events)			
Decreased	106/740	1.09 (0.79, 1.52)	
Minor change	62/523	1.00 (Reference)	
Increased	128/795	1.45 (1.07, 1.98)	
60-89 (ml/min/1.73m²) (769 events)			
Decreased	248/1636	0.91 (0.75, 1.10)	
Minor change	202/1332	1.00 (Reference)	0.89
Increased	319/1977	1.13 (0.94, 1.35)	
<60 (ml/min/1.73m²) (327 events)			
Decreased	107/585	0.88 (0.66, 1.19)	
Minor change	82/442	1.00 (Reference)	
Increased	138/736	1.20 (0.91, 1.60)	
<120 (mmHg) (131 events)			
Decreased	32/272	0.95 (0.55, 1.62)	
Minor change	26/246	1.00 (Reference)	
Increased	73/413	1.76 (1.11, 2.79)	
120-140 (mmHg) (452 events)			
Decreased	147/932	1.09 (0.84, 1.41)	
Minor change	109/807	1.00 (Reference)	0.22
Increased	196/1214	1.39 (1.10, 1.77)	
>140 (mmHg) (809 events)			
Decreased	282/1757	0.85 (0.71, 1.02)	
Minor change	211/1244	1.00 (Reference)	
Increased	316/1881	1.04 (0.87, 1.25)	

eGFR / SBP

HR (95% CI): 0.5   1.0   2.0

*Adjusted for age, sex, region of residence, duration of diabetes, history of macrovascular diseases, smoking habit, drinking habit, body mass index, HbA1c, total cholesterol, log-transformed triglycerides, estimated glomerular filtration rate (eGFR), systolic blood pressure (BP), log-transformed baseline urine albumin-to-creatinine ratio (UACR), change in systolic BP, change in eGFR and ADVANCE trial treatment allocation (randomized blood pressure lowering and glucose control)

SUPPLEMENTARY DATA

Supplementary Figure S6. Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for major macrovascular events according to sociodemographic information and comorbidities*

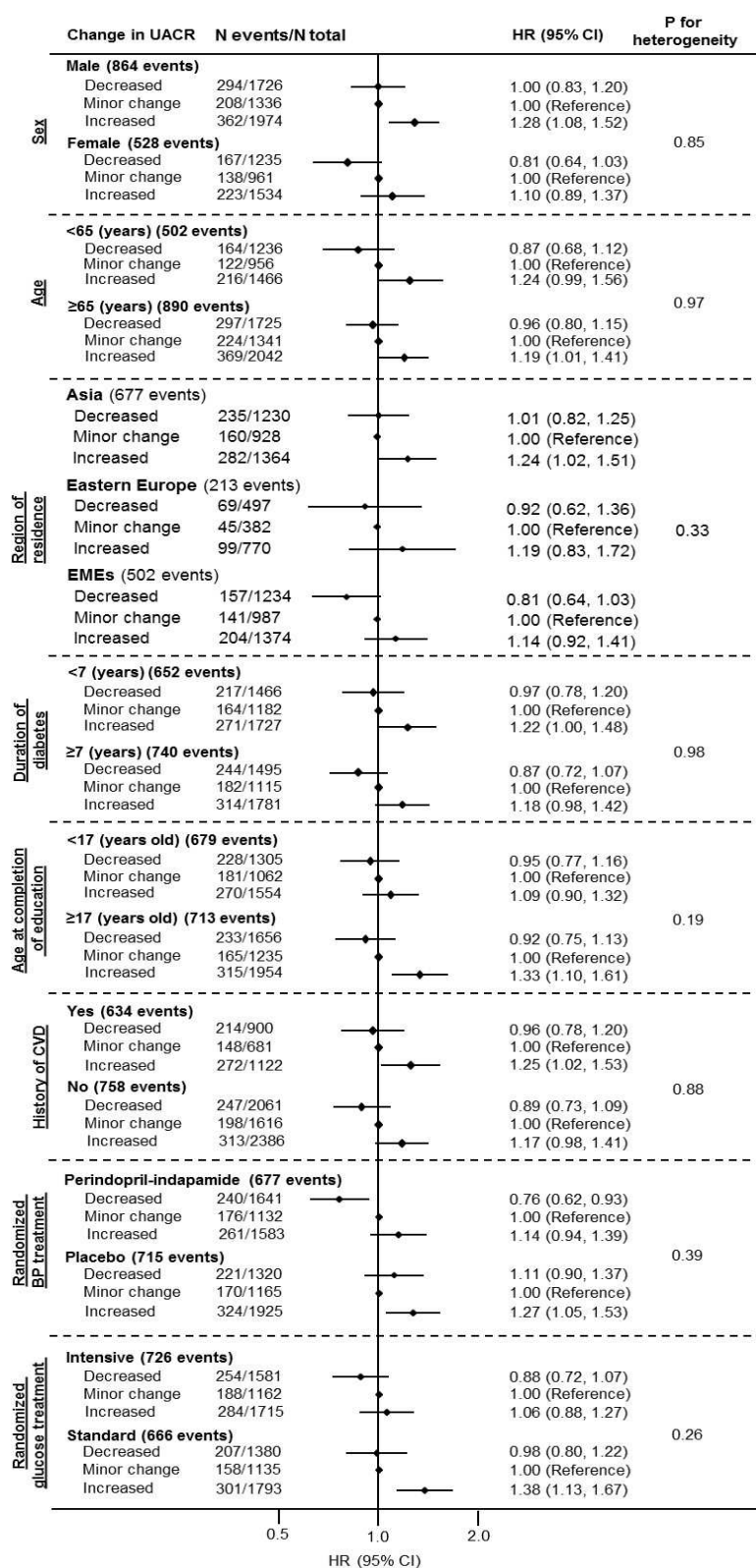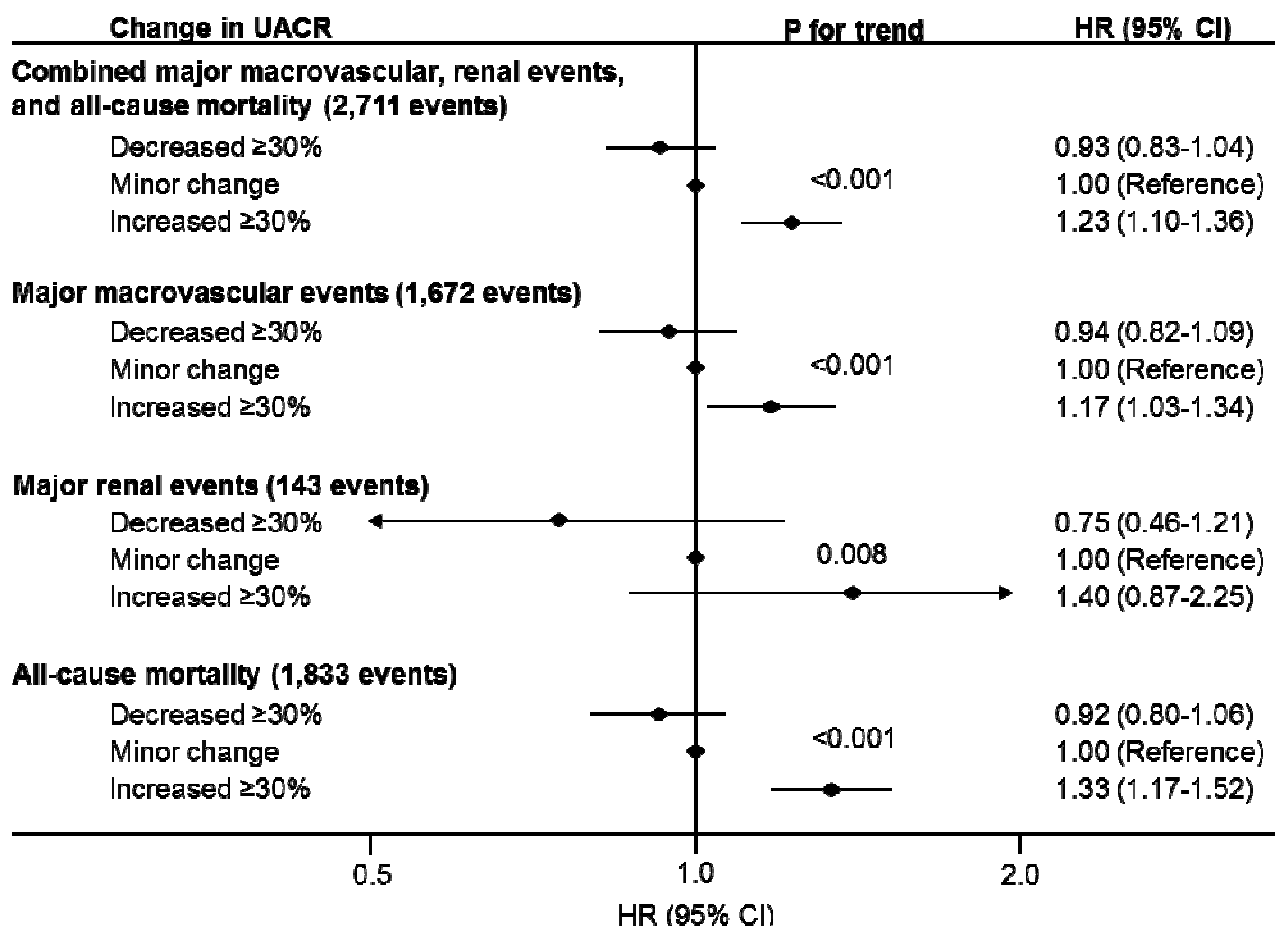|	Change in UACR	N events/N total	HR (95% CI)	P for heterogeneity
Sex	**Male (864 events)**			
	Decreased	294/1726	1.00 (0.83, 1.20)	
	Minor change	208/1336	1.00 (Reference)	
	Increased	362/1974	1.28 (1.08, 1.52)	
	Female (528 events)			0.85
	Decreased	167/1235	0.81 (0.64, 1.03)	
	Minor change	138/961	1.00 (Reference)	
	Increased	223/1534	1.10 (0.89, 1.37)	
Age	**<65 (years) (502 events)**			
	Decreased	164/1236	0.87 (0.68, 1.12)	
	Minor change	122/956	1.00 (Reference)	
	Increased	216/1466	1.24 (0.99, 1.56)	
	≥65 (years) (890 events)			0.97
	Decreased	297/1725	0.96 (0.80, 1.15)	
	Minor change	224/1341	1.00 (Reference)	
	Increased	369/2042	1.19 (1.01, 1.41)	
Region of residence	**Asia (677 events)**			
	Decreased	235/1230	1.01 (0.82, 1.25)	
	Minor change	160/928	1.00 (Reference)	
	Increased	282/1364	1.24 (1.02, 1.51)	
	Eastern Europe (213 events)			
	Decreased	69/497	0.92 (0.62, 1.36)	
	Minor change	45/382	1.00 (Reference)	0.33
	Increased	99/770	1.19 (0.83, 1.72)	
	EMEs (502 events)			
	Decreased	157/1234	0.81 (0.64, 1.03)	
	Minor change	141/987	1.00 (Reference)	
	Increased	204/1374	1.14 (0.92, 1.41)	
Duration of diabetes	**<7 (years) (652 events)**			
	Decreased	217/1466	0.97 (0.78, 1.20)	
	Minor change	164/1182	1.00 (Reference)	
	Increased	271/1727	1.22 (1.00, 1.48)	
	≥7 (years) (740 events)			0.98
	Decreased	244/1495	0.87 (0.72, 1.07)	
	Minor change	182/1115	1.00 (Reference)	
	Increased	314/1781	1.18 (0.98, 1.42)	
Age at completion of education	**<17 (years old) (679 events)**			
	Decreased	228/1305	0.95 (0.77, 1.16)	
	Minor change	181/1062	1.00 (Reference)	
	Increased	270/1554	1.09 (0.90, 1.32)	
	≥17 (years old) (713 events)			0.19
	Decreased	233/1656	0.92 (0.75, 1.13)	
	Minor change	165/1235	1.00 (Reference)	
	Increased	315/1954	1.33 (1.10, 1.61)	
History of CVD	**Yes (634 events)**			
	Decreased	214/900	0.96 (0.78, 1.20)	
	Minor change	148/681	1.00 (Reference)	
	Increased	272/1122	1.25 (1.02, 1.53)	
	No (758 events)			0.88
	Decreased	247/2061	0.89 (0.73, 1.09)	
	Minor change	198/1616	1.00 (Reference)	
	Increased	313/2386	1.17 (0.98, 1.41)	
Randomized BP treatment	**Perindopril-indapamide (677 events)**			
	Decreased	240/1641	0.76 (0.62, 0.93)	
	Minor change	176/1132	1.00 (Reference)	
	Increased	261/1583	1.14 (0.94, 1.39)	
	Placebo (715 events)			0.39
	Decreased	221/1320	1.11 (0.90, 1.37)	
	Minor change	170/1165	1.00 (Reference)	
	Increased	324/1925	1.27 (1.05, 1.53)	
Randomized glucose treatment	**Intensive (726 events)**			
	Decreased	254/1581	0.88 (0.72, 1.07)	
	Minor change	188/1162	1.00 (Reference)	
	Increased	284/1715	1.06 (0.88, 1.27)	
	Standard (666 events)			0.26
	Decreased	207/1380	0.98 (0.80, 1.22)	
	Minor change	158/1135	1.00 (Reference)	
	Increased	301/1793	1.38 (1.13, 1.67)	

HR (95% CI)   0.5   1.0   2.0

*Adjusted for age, sex, region of residence, duration of diabetes, history of macrovascular diseases, smoking habit, drinking habit, body mass index, HbA1c, total cholesterol, log-transformed triglycerides, estimated glomerular filtration rate (eGFR), systolic blood pressure (BP), log-transformed baseline urine albumin-to-creatinine ratio (UACR), change in systolic BP, change in eGFR and ADVANCE trial treatment allocation (randomized blood pressure lowering and glucose control)

Supplemental Figure S7. Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for study outcomes according to categorical change after multiple imputation of missing UACR and covariate information for patients initially excluded from the study cohort*

Change in UACR	P for trend	HR (95% CI)
Combined major macrovascular, renal events, and all-cause mortality (2,711 events)		
Decreased ≥30%		0.93 (0.83-1.04)
Minor change	<0.001	1.00 (Reference)
Increased ≥30%		1.23 (1.10-1.36)
Major macrovascular events (1,672 events)		
Decreased ≥30%		0.94 (0.82-1.09)
Minor change	<0.001	1.00 (Reference)
Increased ≥30%		1.17 (1.03-1.34)
Major renal events (143 events)		
Decreased ≥30%		0.75 (0.46-1.21)
Minor change	0.008	1.00 (Reference)
Increased ≥30%		1.40 (0.87-2.25)
All-cause mortality (1,833 events)		
Decreased ≥30%		0.92 (0.80-1.06)
Minor change	<0.001	1.00 (Reference)
Increased ≥30%		1.33 (1.17-1.52)

HR (95% CI) axis: 0.5 — 1.0 — 2.0

*Adjusted for age, sex, region of residence, duration of diabetes, history of macrovascular diseases, smoking habit, drinking habit, body mass index, HbA1c, total cholesterol, log-transformed triglycerides, estimated glomerular filtration rate (eGFR), systolic blood pressure (BP), log-transformed baseline urine albumin-to-creatinine ratio (UACR), change in systolic BP, change in eGFR and ADVANCE trial treatment allocation (randomized blood pressure lowering and glucose control)