Supplemental Material

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Supplemental Figure 1. Mean serum potassium according to short-term changes in serum potassium after initiating ACE inhibitor-based therapy.

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Supplemental Figure 4. Sensitivity analyses: Modification of randomized treatment effects of ACE inhibitor-based therapy on the risk of major clinical outcomes, by thirds of serum potassium after treatment initiation.

Supplemental Table 1:
Baseline characteristics of the ADVANCE trial participants according to serum potassium at registration.

Variable	Serum potassium at registration		
	Hypokalemia (<3.5 mEq/l)	Normokalemia (3.5-5.0 mEq/l)	Hyperkalemia (≥5.0 mEq/l)
Number of participants	178	9694	1162
Demographic factors			
Age (years)	66 (6)	66 (6)	67 (6)
Female (%)	71 (40)	4149 (43)	471 (41)
Residence in Asia (%)	76 (43)	3624 (37)	433 (37)
Medical and Lifestyle history			
Duration of diabetes mellitus (years)	6.4 (5.8)	7.8 (6.3)	9.2 (6.8)
History of macrovascular disease at baseline (%)	60 (34)	3078 (32)	413 (36)
Current smoking (%)	22 (12)	1493 (15)	150 (13)
Current alcohol drinking (%)	59 (33)	2978 (31)	313 (27)
Risk factors			
Systolic BP (mmHg)	148 (23)	145 (21)	145 (22)
Diastolic BP (mmHg)	82 (12)	81 (11)	80 (11)
HbA_{1c} (%)	7.3 (1.3)	7.5 (1.5)	7.7 (1.7)
Total cholesterol (mg/dl)	195 (45)	201 (46)	202 (48)
Triglycerides (mg/dl)	142 (106-212)	143 (106-204)	142 (102-204)
Body mass index (kg/m^2)	28.6 (5.4)	28.4 (5.2)	27.8 (5.2)
eGFR ($ml/min/1.73m^2$)	73 (18)	75 (17)	70 (19)
Decreased eGFR (<60 $ml/min/1.73m^2$) (%)	45 (25)	1951 (20)	383 (33)
UACR (μg/mg)	18 (9-44)	15 (7-39)	17 (8-48)
Randomized treatments			
Perindopril-indapamide (%)	96 (54)	4848 (50)	567 (49)
Intensive blood glucose control (%)	77 (43)	4858 (50)	583 (50)
Blood glucose-lowering treatments			
Oral hypoglycemic agents^ (%)	159 (89)	8791 (91)	1083 (93)
Insulin (%)	3 (2)	143 (1)	12 (1)
BP-lowering treatments			
β-blocker (%)	47 (26)	2339 (24)	314 (27)

Calcium-channel blocker (%)	95 (53)	2978 (31)	325 (28)
Diuretics† (%)	93 (52)	2253 (23)	256 (22)
Angiotensin-converting enzyme inhibitors† (%)	87 (49)	4088 (42)	556 (48)
Angiotensin II receptor blockers (%)	12 (7)	528 (5)	63 (5)
Renin angiotensin system inhibitors (%)	98 (55)	4541 (47)	608 (52)
Other antihypertensive agents (%)	29 (16)	1193 (12)	148 (13)
Any BP-lowering agents† (%)	161 (90)	7728 (75)	895 (77)
Changes in serum potassium			
Potassium at registration (mEq/l)	3.30 (3.20-3.40)	4.30 (4.07-4.57)	5.16 (5.00-5.30)
Potassium after 3 weeks during the run-in period (mEq/l)	3.70 (3.50-3.95)	4.30 (4.00-4.52)	4.80 (4.40-5.10)

For continuous variables, mean values and their corresponding standard deviations (SDs) are presented except that median values (interquartile interval) are presented for triglycerides, UACR, and potassium. Linear trends of triglycerides and UACR across categories were tested after log-transformation. Categorical variables are presented as number (%).
^Randomized treatment with gliclazide was not included
†Randomized treatment with perindopril-indapamide was not included.
Renin angiotensin system inhibitors were defined as either angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers.
Abbreviations: BP, blood pressure; eGFR, estimated glomerular filtration rate, UACR, urine albumin-creatinine-ratio.

Supplementary Table 2:
Sensitivity analyses: The association between short-term changes in serum potassium after initiating ACE inhibitor-based therapy and subsequent risk of major clinical outcomes, using a cut-off value of hyperkalemia of 5.5 mEq/l instead of 5.0 mEq/l.

Short-term changes in serum potassium	N events / N subjects	HR (95% CI)	P for trend
Combined major macrovascular and microvascular events			
Hypokalemia	17/96	1.15 (0.71, 1.86)	
Normokalemia	1393/9039	1.00 (reference)	0.78
Hyperkalemia	10/55	1.09 (0.58, 2.04)	
All-cause death			
Hypokalemia	4/96	0.64 (0.24, 1.70)	
Normokalemia	662/9039	1.00 (reference)	0.73
Hyperkalemia	3/55	0.72 (0.23, 2.24)	
Cardiovascular death			
Hypokalemia	2/96	0.62 (0.15, 2.50)	
Normokalemia	344/9039	1.00 (reference)	0.63
Hyperkalemia	2/55	0.94 (0.23, 3.80)	
Major macrovascular events			
Hypokalemia	6/96	0.77 (0.34, 1.72)	
Normokalemia	762/9039	1.00 (reference)	0.53
Hyperkalemia	5/55	1.09 (0.45, 2.64)	
Major coronary events			
Hypokalemia	2/96	0.51 (0.13, 2.03)	
Normokalemia	420/9039	1.00 (reference)	0.61
Hyperkalemia	2/55	0.76 (0.19, 3.04)	
Major cerebrovascular events			
Hypokalemia	3/96	0.78 (0.25, 2.44)	
Normokalemia	338/9039	1.00 (reference)	0.42
Hyperkalemia	3/55	1.56 (0.50, 4.88)	
Major microvascular events			
Hypokalemia	13/96	1.56 (0.90, 2.70)	
Normokalemia	713/9039	1.00 (reference)	0.19
Hyperkalemia	5/55	0.95 (0.39, 2.31)	
New or worsening nephropathy			
Hypokalemia	7/96	1.82 (0.85, 3.87)	
Normokalemia	295/9039	1.00 (reference)	0.16
Hyperkalemia	2/55	0.84 (0.21, 3.44)	
New or worsening retinopathy			
Hypokalemia	7/96	1.38 (0.65, 2.92)	
Normokalemia	454/9039	1.00 (reference)	0.45
Hyperkalemia	3/55	0.93 (0.30, 2.89)	

Short-term changes in serum potassium was defined based on the measurement made 3 weeks after initiating ACE inhibitor-based therapy.
Models were adjusted for age, sex, region of residence, duration of diabetes mellitus, history of macrovascular diseases, smoking habit, alcohol drinking habit, body mass index, hemoglobin A_{1c}, total

cholesterol, log-transformed triglyceride, systolic blood pressure, estimated glomerular filtration rate, log-transformed urine albumin-to-creatinine ratio, randomized blood pressure–lowering intervention, and randomized glucose control intervention (n=9,190).
Abbreviations: CI, confidence interval; HR, hazard ratio.

Supplementary Table 3:
Competing risk analysis: The association between short-term changes in serum potassium after initiating ACE inhibitor-based therapy and subsequent risk of major clinical outcomes, accounting for the competing risk of death.

Short-term changes in serum potassium	N			Sub distribution HRs (95%CI)	P for trend
	Event	Censored	Competing event		
Combined major macrovascular and microvascular events					
Hypokalemia	17	77	2	1.17 (0.74, 1.87)	
Normokalemia	1296	7020	261	1.00 (reference)	0.32
Hyperkalemia	107	397	13	1.15 (0.94, 1.41)	
Cardiovascular death					
Hypokalemia	2	92	2	0.64 (0.17, 2.39)	
Normokalemia	321	7954	302	1.00 (reference)	0.74
Hyperkalemia	25	475	17	1.02 (0.68, 1.52)	
Major macrovascular events					
Hypokalemia	6	88	2	0.78 (0.36, 1.73)	
Normokalemia	711	7581	285	1.00 (reference)	0.29
Hyperkalemia	56	445	16	1.13 (0.86, 1.49)	
Major coronary events					
Hypokalemia	2	91	3	0.50 (0.13, 1.97)	
Normokalemia	395	7795	387	1.00 (reference)	0.86
Hyperkalemia	27	469	21	0.96 (0.65, 1.41)	
Major cerebrovascular events					
Hypokalemia	3	89	4	0.80 (0.26, 2.44)	
Normokalemia	311	7730	536	1.00 (reference)	0.058
Hyperkalemia	30	451	36	1.45 (0.99, 2.12)	
Major microvascular events					
Hypokalemia	13	80	3	1.62 (0.94, 2.78)	
Normokalemia	659	7352	566	1.00 (reference)	0.76
Hyperkalemia	59	424	34	1.16 (0.89, 1.53)	
New or worsening nephropathy					
Hypokalemia	7	86	3	1.98 (0.89, 4.44)	
Normokalemia	263	7728	586	1.00 (reference)	0.37
Hyperkalemia	34	447	36	1.42 (0.97, 2.09)	
New or worsening retinopathy					
Hypokalemia	7	85	4	1.41 (0.69, 2.90)	
Normokalemia	426	7552	599	1.00 (reference)	0.75
Hyperkalemia	31	447	39	1.01 (0.70, 1.45)	

Short-term changes in serum potassium was defined based on the measurement made 3 weeks after initiating ACE inhibitor-based therapy.
Models were adjusted for age, sex, region of residence, duration of diabetes mellitus, history of macrovascular diseases, smoking habit, alcohol drinking habit, body mass index, hemoglobin A_{1c}, total cholesterol, log-transformed triglyceride, systolic blood pressure, estimated glomerular filtration rate, log-

transformed urine albumin-to-creatinine ratio, randomized blood pressure–lowering intervention, and randomized glucose control intervention (n=9,190).
Abbreviations: CI, confidence interval; HR, hazard ratio.

Supplementary Table 4:
Sensitivity analyses: Modification of randomized treatment effects of ACE inhibitor-based therapy on the risk of major clinical outcomes by short-term changes in serum potassium after treatment initiation, using a cut-off value of hyperkalemia of 5.5 mEq/l instead of 5.0 mEq/l.

Short-term changes in serum potassium	N events (%)		HR (95% CI)	P for heterogeneity
	Active	Placebo		
Combined major macrovascular and microvascular events				
Hypokalemia	9 (20)	8 (15)	1.38 (0.53, 3.59)	
Normokalemia	712 (15)	766 (16)	0.92 (0.83, 1.02)	0.69
Hyperkalemia	7 (18)	3 (16)	1.10 (0.28, 4.26)	
All-cause death				
Hypokalemia	1 (2)	3 (6)	0.40 (0.04, 3.82)	
Normokalemia	334 (7)	386 (8)	0.86 (0.74, 1.00)	0.48
Hyperkalemia	1 (3)	2 (11)	0.24 (0.02, 2.68)	
Cardiovascular death				
Hypokalemia	1 (2)	1 (2)	1.19 (0.07, 19.01)	
Normokalemia	160 (3)	212 (4)	0.75 (0.61, 0.92)	0.91
Hyperkalemia	1 (3)	1 (5)	0.49 (0.03, 7.89)	
Major macrovascular events				
Hypokalemia	3 (7)	3 (6)	1.21 (0.24, 6.00)	
Normokalemia	386 (8)	430 (9)	0.89 (0.78, 1.02)	0.73
Hyperkalemia	4 (10)	1 (5)	1.97 (0.22, 17.60)	
Major coronary events				
Hypokalemia	2 (4)	0 (0)	NA	
Normokalemia	212 (4)	237 (5)	0.89 (0.74, 1.07)	0.68
Hyperkalemia	1 (3)	1 (5)	0.49 (0.03, 7.89)	
Major cerebrovascular events				
Hypokalemia	1 (2)	2 (4)	0.58 (0.05, 6.41)	
Normokalemia	174 (4)	186 (4)	0.93 (0.76, 1.14)	0.70
Hyperkalemia	3 (8)	0 (0)	NA	
Major microvascular events				
Hypokalemia	7 (16)	6 (11)	1.36 (0.46, 4.06)	
Normokalemia	368 (8)	382 (8)	0.96 (0.83, 1.10)	0.75
Hyperkalemia	3 (8)	2 (11)	0.65 (0.11, 3.88)	
New or worsening nephropathy				
Hypokalemia	5 (11)	2 (4)	2.99 (0.58, 15.43)	
Normokalemia	148 (3)	165 (3)	0.89 (0.71, 1.11)	0.31
Hyperkalemia	1 (3)	1 (5)	0.43 (0.03, 6.94)	
New or worsening retinopathy				
Hypokalemia	2 (4)	5 (9)	0.45 (0.09, 2.32)	
Normokalemia	243 (5)	236 (5)	1.03 (0.86, 1.23)	0.61
Hyperkalemia	2 (5)	1 (5)	0.89 (0.08, 9.85)	

Short-term changes in serum potassium was defined based on the measurement made 3 weeks after initiating ACE inhibitor-based therapy.
Abbreviations: CI, confidence interval; HR, hazard ratio; NA, not available.

Active: perindopril-indapamide.
In the active group 45 participants were in the Hypokalemia group, 4764 Normokalemia, and 39 Hyperkalemia, corresponding numbers for the placebo group were 54, 4773 and 19.

Supplementary Table 5:
Competing risk analysis: Modification of randomized treatment effects of ACE inhibitor-based therapy on the risk of major clinical outcomes by short-term changes in serum potassium after treatment initiation, accounting for the competing risk of death.

Short-term changes in serum potassium	N						Sub distribution HRs (95%CI)	P for heterogeneity
	Active			Placebo				
	Event	Censored	Competing event	Event	Censored	Competing event		
Combined major macrovascular and microvascular events								
Hypokalemia	9	36	0	8	44	2	1.41 (0.55, 3.65)	
Normokalemia	659	3716	136	715	3668	145	0.92 (0.83, 1.02)	0.64
Hyperkalemia	60	224	8	54	202	8	0.99 (0.69, 1.43)	
Cardiovascular death								
Hypokalemia	1	44	0	1	51	2	1.19 (0.08, 18.48)	
Normokalemia	149	4199	163	198	4165	165	0.75 (0.61, 0.93)	0.94
Hyperkalemia	12	269	11	15	239	10	0.72 (0.34, 1.53)	
Major macrovascular events								
Hypokalemia	3	42	0	3	49	2	1.22 (0.25, 6.01)	
Normokalemia	355	4002	154	407	3967	154	0.87 (0.75, 1.00)	0.27
Hyperkalemia	35	247	10	24	230	10	1.34 (0.79, 2.25)	
Major coronary events								
Hypokalemia	2	43	0	0	51	3	NA	
Normokalemia	198	4115	198	225	4082	221	0.88 (0.73, 1.06)	0.67
Hyperkalemia	15	264	13	13	237	14	1.04 (0.50, 2.20)	
Major cerebrovascular events								
Hypokalemia	1	43	1	2	49	3	0.59 (0.05, 6.57)	
Normokalemia	157	4079	275	175	4046	307	0.90 (0.72, 1.11)	0.27
Hyperkalemia	20	252	20	11	232	21	1.66 (0.80, 3.47)	
Major microvascular events								

Hypokalemia	7	38	0	6	45	3	1.43 (0.48, 4.20)	
Normokalemia	341	3891	279	350	3845	333	0.98 (0.84, 1.14)	0.54
Hyperkalemia	30	244	18	34	210	20	0.78 (0.47, 1.27)	
New or worsening nephropathy								
Hypokalemia	5	40	0	2	49	3	3.11 (0.61, 15.82)	
Normokalemia	131	4089	291	145	4041	342	0.90 (0.71, 1.14)	0.29
Hyperkalemia	18	254	20	21	223	20	0.76 (0.40, 1.43)	
New or worsening retinopathy								
Hypokalemia	2	42	1	5	46	3	0.46 (0.09, 2.33)	
Normokalemia	230	3985	296	221	3956	351	1.05 (0.87, 1.26)	0.52
Hyperkalemia	15	257	20	16	223	25	0.84 (0.42, 1.70)	

Short-term changes in serum potassium was defined based on the measurement made 3 weeks after initiating ACE inhibitor-based therapy.
Abbreviations: CI, confidence interval; HR, hazard ratio; NA, not available.
Active: perindopril-indapamide.

Supplemental Table 6: Rate reductions for major clinical outcomes according to short-term changes in serum potassium after initiating ACE inhibitor-based therapy.

Short-term changes in serum potassium	Incidence rate (per 1000 PYs)			Rate reductions over 5 years per 1000 PYs	NNT to prevent one event over 5
	Overall	Active	Placebo		
Combined major macrovascular and microvascular events					
Hypokalemia	41.8 (21.9, 61.6)	49.2 (17.1, 81.3)	35.7 (11.0, 60.5)	-67.5 (-209.0, 74.2)	-15
Normokalemia	37.5 (35.5, 39.5)	35.9 (33.2, 38.6)	39.1 (36.3,42.0)	16.2 (2.1, 30.2)	62
Hyperkalemia	52.1 (42.6, 61.7)	52.0 (38.8, 65.1)	52.3 (38.3,66.2)	1.4 (-66.3, 69.0)	736
Overall	40.0 (38.2, 41.9)	38.1 (35.6, 40.7)	42.0 (39.3, 44.7)	19.2 (6.1, 32.3)	52
All-cause death					
Hypokalemia	9.2 (0.2, 18.3)	5.1 (0, 15.0)	12.8 (0, 27.2)	38.5 (-24.5, 101.5)	26
Normokalemia	17.3 (16.0, 18.7)	16.0 (14.2, 17.8)	18.7 (16.8, 20.6)	13.4 (4.1, 22.6)	75
Hyperkalemia	20.2 (14.5,26.0)	18.4 (10.9, 25.9)	22.3 (13.6, 31.1)	19.6 (-21.0, 60.2)	51
Overall	18.4 (17.2, 19.6)	17.0 (15.3, 18.6)	19.8 (18.0, 21.5)	13.8 (5.2, 22.4)	73
Cardiovascular death					
Hypokalemia	4.6 (0, 11.1)	5.1 (0, 15.0)	4.3 (0, 12.7)	-3.9 (-49.5, 41.7)	-257
Normokalemia	8.9 (8.0, 9.9)	7.7 (6.4, 8.9)	10.2 (8.8, 11.6)	12.8 (6.1, 19.4)	78
Hyperkalemia	11.4 (7.1, 15.7)	9.6 (4.2, 15.0)	13.4 (6.6, 20.2)	19.2 (-11.4, 49.7)	52
Overall	9.8 (8.9, 10.7)	8.8 (7.6, 10.0)	10.8 (9.5, 12.1)	10.0 (3.7, 16.2)	100
Major macrovascular events					
Hypokalemia	14.2 (2.8, 25.6)	15.9 (0, 33.8)	12.9 (0, 27.5)	-14.7 (-95.8, 66.3)	-68
Normokalemia	20.1 (18.7, 21.6)	18.7 (16.8, 20.7)	21.6 (19.5, 23.7)	14.3 (4.2, 24.4)	70
Hyperkalemia	25.8 (19.2, 32.3)	29.3 (19.6, 38.9)	22.0 (13.2, 30.7)	-36.5 (-82.9, 9.9)	-27
Overall	21.5 (20.2, 22.9)	20.6 (18.7, 22.4)	22.5 (20.5, 24.4)	9.5 (0.1, 18.9)	105
Major coronary events					
Hypokalemia	4.7 (0, 11.2)	10.4 (0, 24.7)	NA	NA	NA
Normokalemia	11.0 (10.0, 12.1)	10.3 (8.9, 11.7)	11.7 (10.2, 13.3)	7.3 (-0.2, 14.7)	138
Hyperkalemia	11.9 (7.5, 16.3)	12.1 (6.0, 18.3)	11.7 (5.3, 18.0)	-2.2 (-33.4, 29.0)	-458
Overall	11.8 (10.9, 12.8)	11.2 (9.8, 12.5)	12.5 (11.1, 13.9)	6.6 (-0.3, 13.6)	151
Major cerebrovascular events					
Hypokalemia	7.0 (0, 15.0)	5.2 (0, 15.3)	8.6 (0, 20.6)	17.2 (-38.5, 73.0)	58
Normokalemia	8.7 (7.7, 9.6)	8.2 (6.9, 9.5)	9.2 (7.8, 10.5)	4.9 (-1.7, 11.5)	205
Hyperkalemia	13.4 (8.7, 18.2)	16.5 (9.3, 23.8)	10.0 (4.1, 15.9)	-32.6 (-65.8, 0.7)	-31
Overall	9.2 (8.3, 10.1)	9.1 (7.9, 10.3)	9.3 (8.1, 10.5)	0.9 (-5.2, 7.1)	1063
Major microvascular events					
Hypokalemia	31.3 (14.3, 48.3)	36.6 (9.5, 63.7)	26.7 (5.3, 48.1)	-49.1 (-169.8, 71.6)	-20
Normokalemia	18.4 (17.0, 19.8)	18.1 (16.2, 20.1)	18.7 (16.7, 20.6)	2.6 (-7.1, 12.3)	385
Hyperkalemia	28.3 (21.4, 35.2)	24.9 (16.0, 33.7)	32.2 (21.4, 43.1)	36.9 (-12.4, 86.2)	27
Overall	19.9 (18.6, 21.1)	18.9 (17.2, 20.7)	20.8 (18.9, 22.6)	9.1 (0.0, 18.2)	110

New or worsening nephropathy					
Hypokalemia	16.6 (4.3, 29.0)	26.0 (3.2, 48.8)	8.7 (0, 20.9)	-86.3 (-175.3, 2.6)	-12
Normokalemia	7.2 (6.3, 8.0)	6.8 (5.6, 8.0)	7.6 (6.3, 8.8)	3.8 (-2.2, 9.8)	262
Hyperkalemia	16.8 (11.5, 22.1)	14.6 (7.8, 21.3)	19,3 (11.1, 27.6)	23.7 (-13.8, 61.2)	42
Overall	8.4 (7.6, 9.2)	7.6 (6.5, 8.7)	9.2 (8.0, 10.4)	7.8 (2.0, 13.7)	128
New or worsening retinopathy					
Hypokalemia	16.5 (4.3, 28.7)	10.2 (0, 24.2)	22.0 (2.7, 41.3)	59.3 (-26.4, 144.9)	17
Normokalemia	11.9 (10.8, 13.0)	12.1 (10.6, 13.7)	11.7 (10.1, 13.2)	-2.4 (-10.1, 5.4)	-421
Hyperkalemia	13.5 (8.7, 18.2)	12.3 (6.1, 18.5)	14.8 (7.5, 22.0)	12.5 (-21.1, 46.1)	80
Overall	12.3 (11.3, 1.34)	12.4 (11.0, 13.8)	12.3 (10.9, 13.7)	-0.3 (-7.5, 6.8)	-3189

Short-term change in serum potassium was defined based on the measurement made 3 weeks after initiating ACE inhibitor-based therapy.
Abbreviations: NA, not available; NNT, number needed to treat; PYs, person-years.

Figure legends

Supplemental Figure 1. Mean serum potassium according to short-term changes in serum potassium after initiating ACE inhibitor-based therapy.

Change in serum potassium was defined based on the measurement made 3 weeks after initiating ACE inhibitor-based therapy.

Supplemental Figure 2. Sensitivity analyses: The association between short-term changes in serum potassium after initiating ACE inhibitor-based therapy and subsequent risk of major clinical outcomes, according to thirds of serum potassium after treatment initiation.

Short-term changes in serum potassium were defined based on the measurement made 3 weeks after initiating ACE inhibitor-based therapy, and was subgrouped into 3 groups according to thirds (lowest third: ≤4.10 mEq/l, middle third: 4.11-4.44 mEq/l, highest third: ≥4.45 mEq/l).

Models were adjusted for age, sex, region of residence, duration of diabetes mellitus, history of macrovascular diseases, smoking habit, alcohol drinking habit, body mass index, hemoglobin A_{1c}, total cholesterol, log-transformed triglyceride, systolic blood pressure, estimated glomerular filtration rate, log-transformed urine albumin-to-creatinine ratio, randomized blood pressure–lowering intervention, and randomized glucose control intervention (n=9,190).

Abbreviations: CI, confidence interval; HR, hazard ratio.

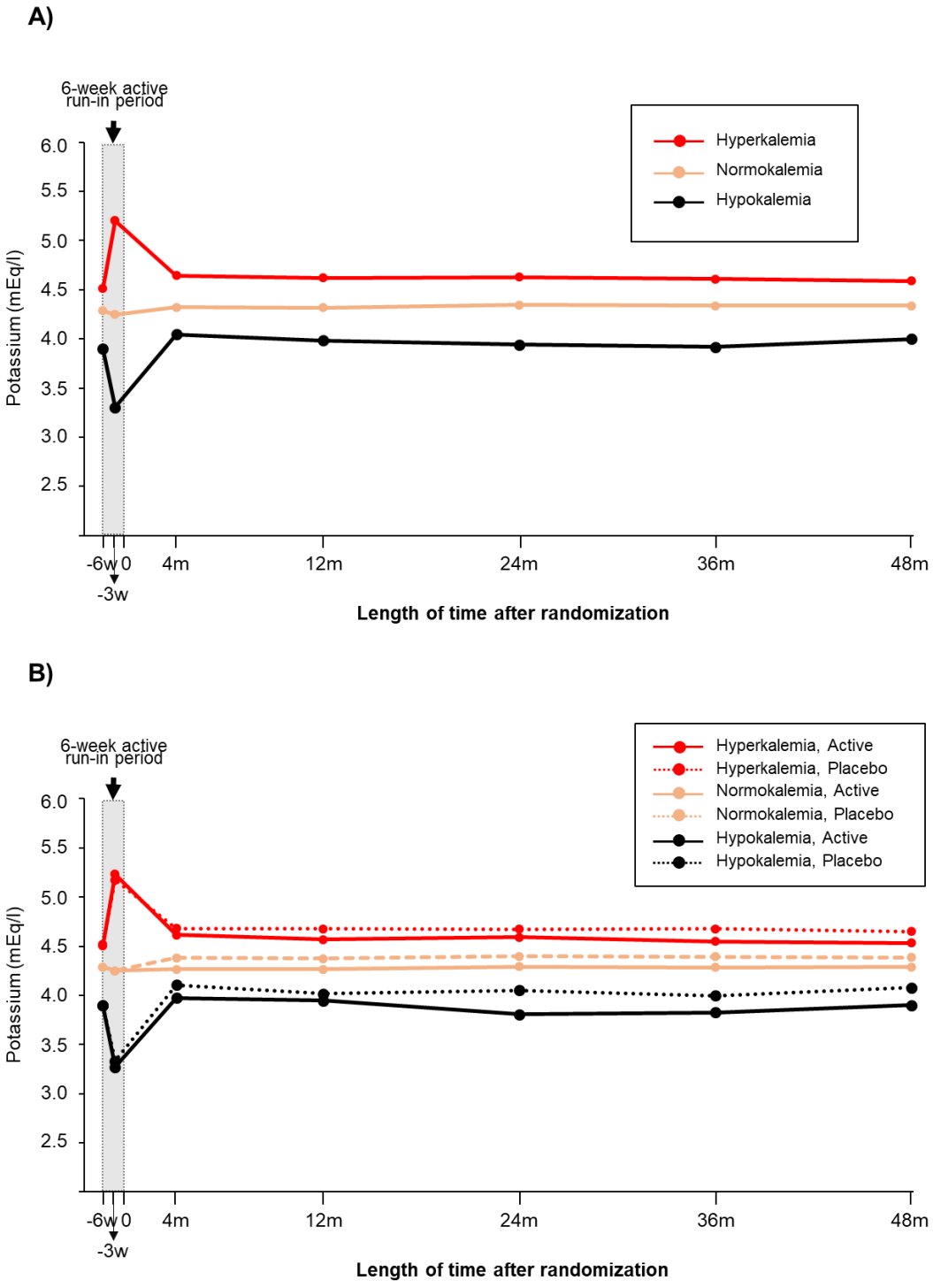
Supplemental Figure 3. Subgroup analyses: Modification of randomized treatment effects of ACE inhibitor-based therapy on the risk of composite of major macrovascular and microvascular events according to short-term changes in serum potassium after treatment initiation, stratified by eGFR level at registration and RASI use at registration.

Short-term changes in serum potassium were defined based on the measurement made 3 weeks after initiating ACE inhibitor-based therapy

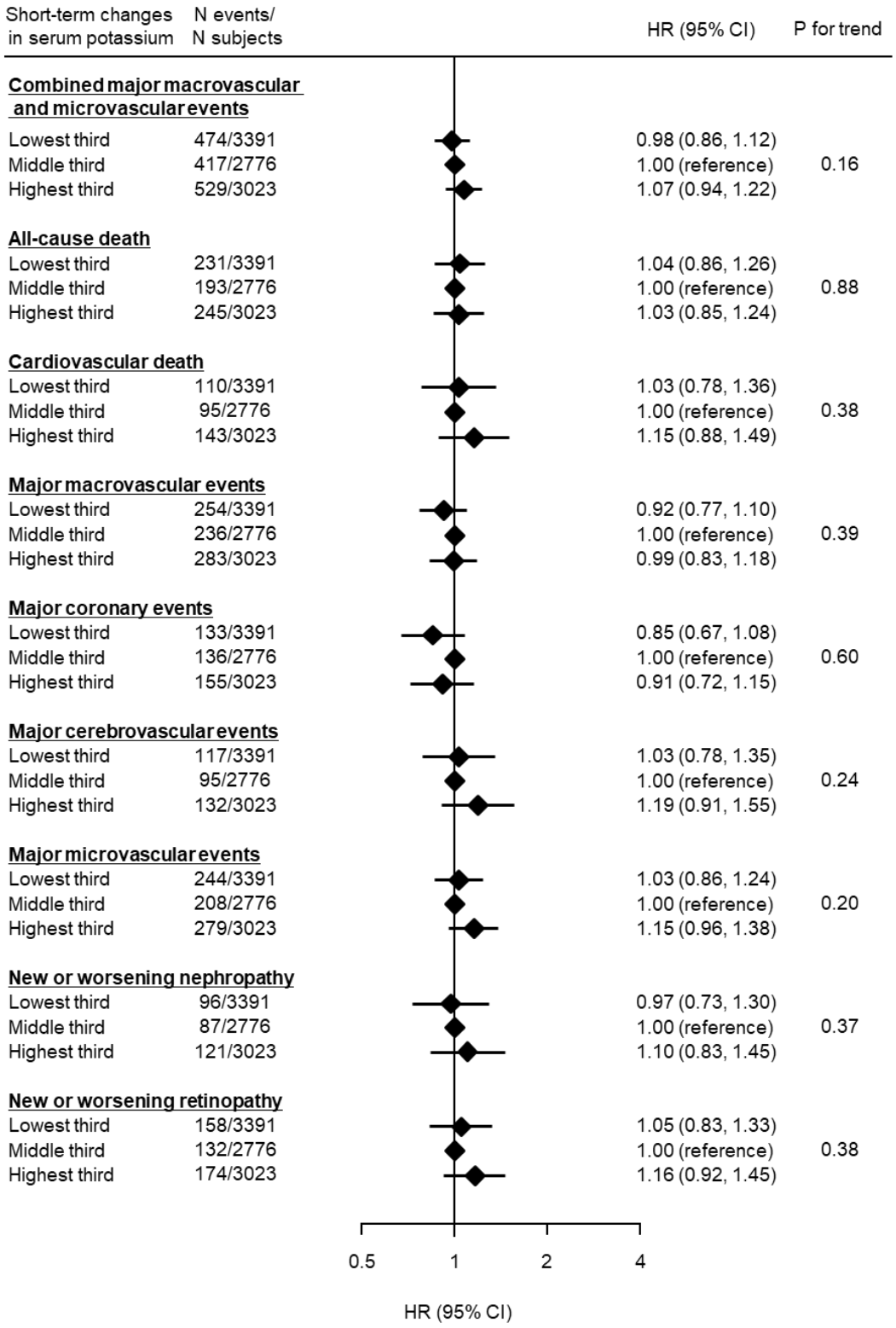
White diamonds indicate the HRs for subgroups defined by acute change in serum potassium.
Black diamonds indicate the HRs of each subgroup among overall randomized participants of the ADVANCE trial.
Abbreviations: RASI, renin angiotensin system inhibitors; CI, confidence interval; HR, hazard ratio.

Supplemental Figure 4. Sensitivity analyses: Modification of randomized treatment effects of ACE inhibitor-based therapy on the risk of major clinical outcomes by thirds of serum potassium after treatment initiation.
Change in serum potassium was defined based on the measurement made 3 weeks after initiating ACE inhibitor-based therapy, and was subgrouped into 3 groups according to thirds (lowest third: ≤4.10 mEq/l, middle third: 4.11-4.44 mEq/l, highest third: ≥4.45 mEq/l).
White diamonds indicate the HRs for subgroups defined by acute change in serum potassium.
Black diamonds indicate the HRs of overall randomized participants of the ADVANCE trial (n=11,140).
Abbreviations: CI, confidence interval; HR, hazard ratio.
Active: perindopril-indapamide.

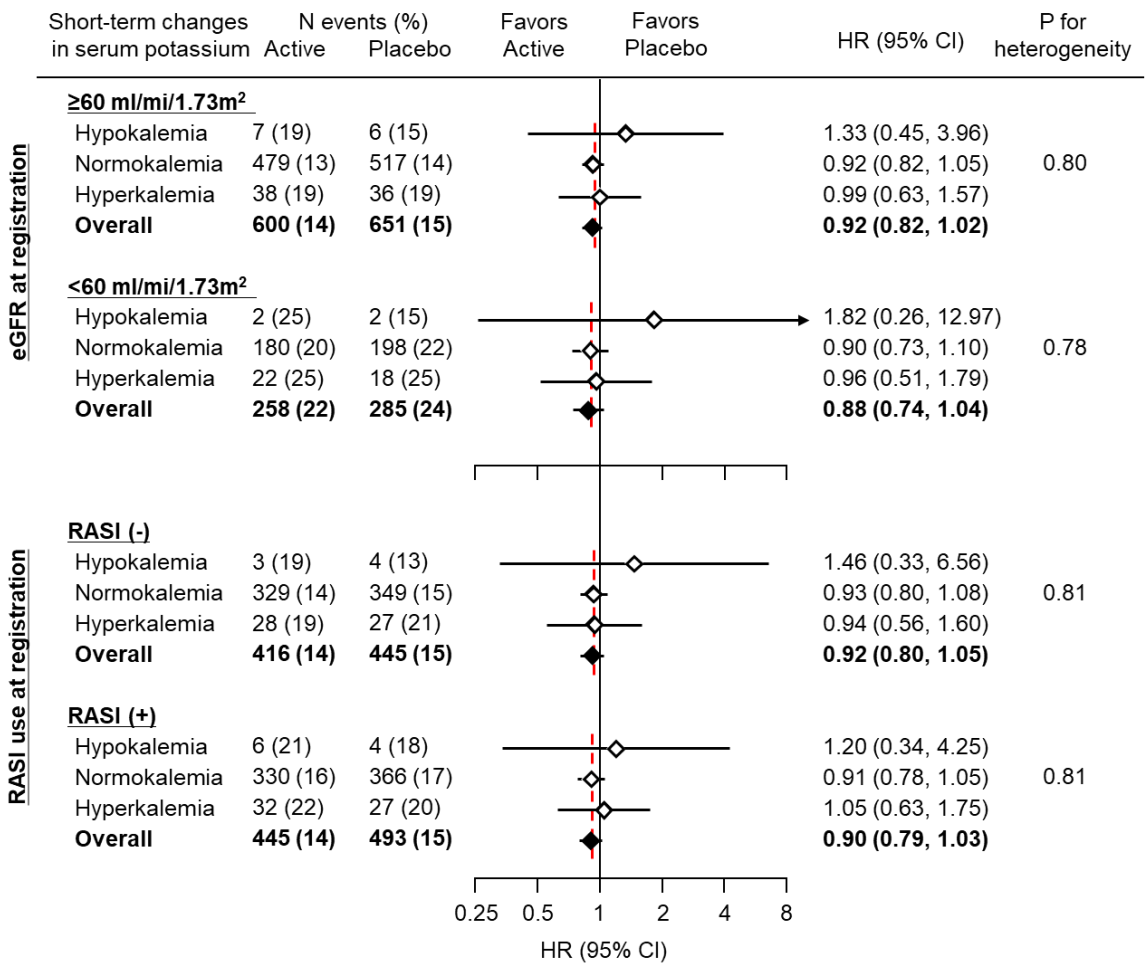
Supplemental Figure 1



Supplemental Figure 2



Supplemental Figure 3



Supplemental Figure 4