Supplementary appendix [posted as supplied by author]

Supplement to the study "Blood Pressure and Complications in Individuals with Type 2 Diabetes and No Previous Cardiovascular Disease: national population based cohort study"

Table of contents

Table A. Baseline characteristics of the total population including individuals with previous diseases, n=265,638

Characteristics	110-119 mmHg (n=19 254)	120-129 mmHg (n=52 597)	130-139 mmHg (n=69 949)	140-149 mmHg (n=61 445)	150-159 mmHg (n=30 249)	>=160 mmHg (n=32 144)	Missing
Systolic blood pressure, mmHg	112.9 (3.0)	122.6 (2.9)	132.3 (2.8)	141.8 (2.6)	151.7 (2.6)	168.1 (10.7)	
Male	10959 (56.9%)	31719 (60.3%)	42604 (60.9%)	36771 (59.8%)	17998 (59.5%)	18479 (57.5%)	
Age	57.6 (11.3)	59.7 (10.1)	61.7 (9.2)	63.0 (8.4)	63.7 (8.1)	64.6 (7.7)	
Duration of diabetes, years	5.3 (6.0)	5.5 (6.1)	5.9 (6.2)	6.3 (6.4)	6.6 (6.5)	7.1 (6.8)	
HbA1c, mmol/mol	52.0 (13.5)	52.5 (13.3)	52.8 (12.9)	53.6 (13.3)	54.2 (13.6)	55.3 (14.5)	12660 (4.8%)
Diet treatment only	5912 (30.7%)	15154 (28.8%)	20109 (28.7%)	17238 (28.1%)	8352 (27.6%)	8337 (25.9%)	
Tablet treatment only	8965 (46.6%)	25603 (48.7%)	33896 (48.5%)	29358 (47.8%)	14193 (46.9%)	14833 (46.1%)	
Insulin treatment	2268 (11.8%)	5605 (10.7%)	6958 (9.9%)	6009 (9.8%)	3118 (10.3%)	3833 (11.9%)	
Insulin and tablet treatment	2109 (11.0%)	6235 (11.9%)	8986 (12.8%)	8840 (14.4%)	4586 (15.2%)	5141 (16.0%)	
BMI, kg/m^2	29.6 (5.5)	30.0 (5.4)	30.3 (5.3)	30.5 (5.4)	30.6 (5.4)	30.5 (5.4)	38760 (14.6%)
LDL, mmol/l	2.7 (0.9)	2.8 (0.9)	2.8 (0.9)	2.8 (0.9)	2.8 (0.9)	2.9 (1.0)	92192 (34.7%)
HDL, mmol/l	1.3 (0.4)	1.3 (0.4)	1.3 (0.4)	1.3 (0.4)	1.3 (0.4)	1.3 (0.4)	86207 (32.5%)
Cholesterol, mmol/l	4.8 (1.1)	4.8 (1.0)	4.9 (1.0)	4.9 (1.0)	5.0 (1.1)	5.1 (1.1)	63853 (24.0%)
Triglycerides, mmol/l	1.8 (1.2)	1.9 (1.2)	1.9 (1.2)	1.9 (1.2)	1.9 (1.2)	2.0 (1.2)	84096 (31.7%)
Microalbuminuria	1553 (12.0%)	4656 (12.9%)	6927 (14.3%)	6875 (16.4%)	3802 (18.3%)	4706 (21.7%)	83626 (31.5%)
Macroalbuminuria	725 (5.6%)	2035 (5.6%)	2954 (6.1%)	3049 (7.3%)	1897 (9.2%)	2558 (11.8%)	

Characteristics	110-119 mmHg (n=19 254)	120-129 mmHg (n=52 597)	130-139 mmHg (n=69 949)	140-149 mmHg (n=61 445)	150-159 mmHg (n=30 249)	>=160 mmHg (n=32 144)	Missing
eGFR, ml/min/1.73 m^2	86.6 (25.5)	86.5 (24.5)	85.3 (23.1)	84.6 (23.4)	84.0 (23.8)	82.9 (25.5)	45659 (17.2%)
Current smoker	3407 (20.6%)	8458 (18.6%)	10370 (17.2%)	8651 (16.5%)	4336 (16.9%)	4953 (18.2%)	38157 (14.4%)
Previous AMI	1737 (9.0%)	3908 (7.4%)	4447 (6.4%)	3597 (5.9%)	1649 (5.5%)	1765 (5.5%)	
Previous stroke	820 (4.3%)	2173 (4.1%)	2892 (4.1%)	2607 (4.2%)	1306 (4.3%)	1581 (4.9%)	
Previous CVD	2435 (12.6%)	5802 (11.0%)	7022 (10.0%)	5917 (9.6%)	2837 (9.4%)	3204 (10.0%)	
Previous CHD	3238 (16.8%)	7740 (14.7%)	9381 (13.4%)	7919 (12.9%)	3691 (12.2%)	4066 (12.6%)	
Previous amputation	53 (0.3%)	141 (0.3%)	169 (0.2%)	177 (0.3%)	98 (0.3%)	157 (0.5%)	
Previous heart failure	1421 (7.4%)	2456 (4.7%)	2434 (3.5%)	1974 (3.2%)	942 (3.1%)	992 (3.1%)	
Previous atrial fibrillation	1414 (7.3%)	2788 (5.3%)	3384 (4.8%)	2817 (4.6%)	1300 (4.3%)	1350 (4.2%)	
Previous renal disease	63 (0.3%)	130 (0.2%)	136 (0.2%)	100 (0.2%)	63 (0.2%)	62 (0.2%)	
Previous dementia	56 (0.3%)	96 (0.2%)	110 (0.2%)	87 (0.1%)	42 (0.1%)	49 (0.2%)	
Previous cancer	693 (3.6%)	1856 (3.5%)	2538 (3.6%)	2234 (3.6%)	1094 (3.6%)	1130 (3.5%)	
Thiazide diuretics	2500 (13.0%)	8847 (16.8%)	14281 (20.4%)	13876 (22.6%)	7251 (24.0%)	8155 (25.4%)	
Loop diuretics	2465 (12.8%)	5325 (10.1%)	6659 (9.5%)	6293 (10.2%)	3368 (11.1%)	3938 (12.3%)	
Calcium antagonists	2397 (12.4%)	8946 (17.0%)	14954 (21.4%)	15077 (24.5%)	8204 (27.1%)	9024 (28.1%)	
Spironolactone	1017 (5.3%)	1932 (3.7%)	2018 (2.9%)	1659 (2.7%)	799 (2.6%)	778 (2.4%)	
B-blockers	5781 (30.0%)	15995 (30.4%)	22529 (32.2%)	21376 (34.8%)	11317 (37.4%)	13460 (41.9%)	
RAAS-blockers	6770 (35.2%)	21368 (40.6%)	32807 (46.9%)	31424 (51.1%)	17042 (56.3%)	19514 (60.7%)	

Characteristics	110-119 mmHg (n=19 254)	120-129 mmHg (n=52 597)	130-139 mmHg (n=69 949)	140-149 mmHg (n=61 445)	150-159 mmHg (n=30 249)	>=160 mmHg (n=32 144)	Missing
Number of antihypertensive agents	1.1 (1.3)	1.2 (1.3)	1.4 (1.3)	1.5 (1.3)	1.6 (1.3)	1.8 (1.4)	
Medication for heart disease	2468 (12.8%)	5609 (10.7%)	6705 (9.6%)	5687 (9.3%)	2809 (9.3%)	2927 (9.1%)	
Statins	7972 (41.4%)	23281 (44.3%)	31748 (45.4%)	27171 (44.2%)	13019 (43.0%)	13407 (41.7%)	

Data are presented as mean (±SD) or count (%).

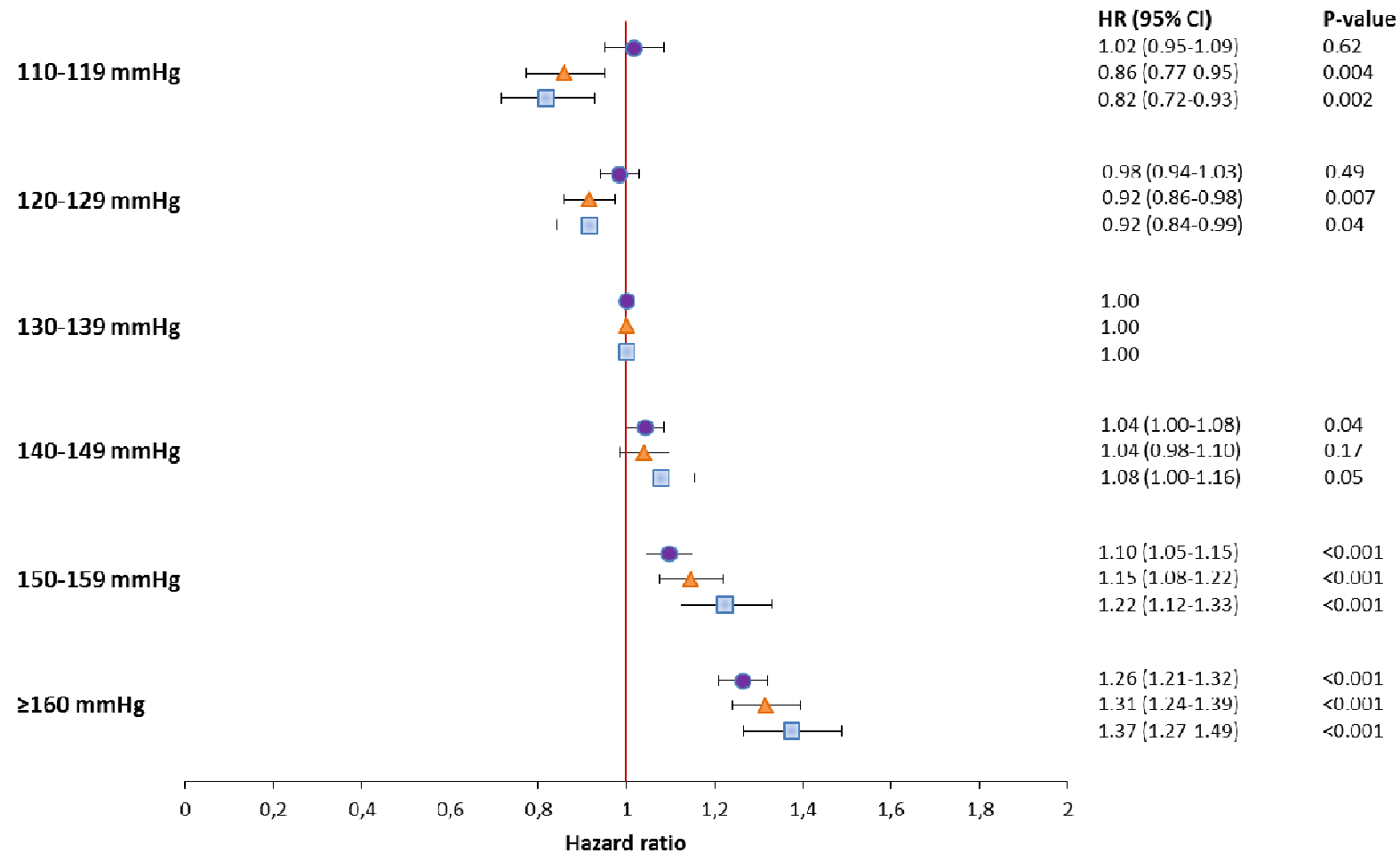## Results from Cox regression models for all studied endpoints

Three models were tested. The first model included all individuals, even those with previous diseases (n=265,638). The second and third models included only individuals who did not have a history of cancer, coronary heart disease (CHD), cardiovascular disease (CVD), heart failure, atrial fibrillation, end stage renal disease, amputation or dementia at baseline (n=187,106). The models were adjusted for the following variables: age, gender, diabetes duration, type of diabetes treatment, HbA1c, smoking status, LDL cholesterol, HDL cholesterol, triglycerides, microalbuminuria, and macroalbuminuria. BMI and eGFR were used as categorical variables because of their nonlinear relationship with mortality. The third model was also adjusted for thiazide diuretics, loop diuretics, calcium antagonists, spironolactone, β-blockers, and medication for heart disease. As a covariate of treatment intensity at the care unit, the percentage of patients receiving a combination of a thiazide diuretic, calcium antagonist and either a renin-angiotensin system inhibitor or angiotensin II blocker (RAAS blocking agent) was used. The following variables were entered as continuous variables: age, HbA1c, LDL-cholesterol, HDL-cholesterol, and triglycerides. The following variables were entered as categorical variables: systolic blood pressure, gender, smoking, microalbuminuria, macroalbuminuria, diabetes treatment, BMI, eGFR, loop diuretics, calcium antagonists, treatment intensity at the care unit. The following variables were included with an interaction term with systolic blood pressure: calcium antagonists, spironolactone, and β-blockers.

Table B. Hazard-ratios for covariates included in the fully adjusted regression model, endpoint: nonfatal cardiovascular disease (CVD)

Variable	Hazard ratio (95% confidence interval)	p-value
110-119 mmHg	0.82 (0.72 to 0.93)	0.002
120-129 mmHg	0.92 (0.84 to 0.99)	0.04
140-149 mmHg	1.08 (1.00 to 1.16)	0.05
150-159 mmHg	1.22 (1.12 to 1.33)	<0.001
≥160 mmHg	1.37 (1.27 to 1.49)	<0.001
Age (years)	1.06 (1.06 to 1.06)	<0.001
Male (vs. female)	1.51 (1.44 to 1.57)	<0.001
Diabetes duration, per year	1.02 (1.01 to 1.02)	<0.001
Smoking (yes vs. no)	1.58 (1.50 to 1.66)	<0.001
HbA1c, per mmol/mol	1.01 (1.01 to 1.01)	<0.001
LDL-cholesterol, per mmol/l	1.17 (1.14 to 1.19)	<0.001
HDL-cholesterol, per mmol/l	0.90 (0.85 to 0.96)	<0.001
Triglycerides, per mmol/l	1.08 (1.06 to 1.10)	<0.001
Microalbuminuria	1.23 (1.17 to 1.30)	<0.001
Macroalbuminuria	1.41 (1.31 to 1.52)	<0.001
Tablet diabetes treatment only (vs. diet treatment only)	1.14 (1.08 to 1.20)	<0.001
Insulin diabetes treatment only (vs. diet treatment only)	1.27 (1.18 to 1.36)	<0.001
Tablet & insulin treatment (vs. diet treatment only)	1.33 (1.25 to 1.42)	<0.001
BMI, 18.1-19 kg/m^2 (vs. BMI, 22.1-23 kg/m^2)	0.98 (0.67 to 1.44)	0.94
BMI, 19.1-20 kg/m^2 (vs. BMI, 22.1-23 kg/m^2)	1.06 (0.77 to 1.45)	0.73
BMI, 20.1-21 kg/m^2 (vs. BMI, 22.1-23 kg/m^2)	1.17 (0.93 to 1.48)	0.18
BMI, 21.1-22 kg/m^2 (vs. BMI, 22.1-23 kg/m^2)	0.91 (0.74 to 1.13)	0.41
BMI, 23.1-24 kg/m^2 (vs. BMI, 22.1-23 kg/m^2)	0.94 (0.80 to 1.11)	0.46
BMI, 24.1-25 kg/m^2 (vs. BMI, 22.1-23 kg/m^2)	0.92 (0.78 to 1.09)	0.34
BMI, 25.1-30 kg/m^2 (vs. BMI, 22.1-23 kg/m^2)	0.96 (0.83 to 1.11)	0.59
BMI, 30.1-35 kg/m^2 (vs. BMI, 22.1-23 kg/m^2)	0.94 (0.81 to 1.08)	0.37
BMI, >35 kg/m2 (vs. BMI, 22.1-23 kg/m^2)	0.91 (0.78 to 1.06)	0.22
GFR ≥50 ml/min/1.73 m2	1.29 (1.17 to 1.41)	<0.001
Thiazide diuretics (yes vs. no)	0.94 (0.85 to 1.04)	0.24
Loop diuretics (yes vs. no)	1.15 (1.08 to 1.22)	<0.001
Calcium channel blockers (yes vs. no)	1.28 (1.16 to 1.41)	<0.001
Spironolactone (yes vs. no)	1.26 (1.00 to 1.60)	0.05
Beta blockers (yes vs. no)	1.10 (1.01 to 1.21)	0.03
Treatment intensity at the care unit	0.87 (0.82 to 0.91)	<0.001

Variable	Hazard ratio (95% confidence interval)	p-value
Interaction term: systolic BP 110-119 x thiazide diuretics	1.31 (0.99 to 1.73)	0.06
Interaction term: systolic BP 120-129 x thiazide diuretics	0.98 (0.82 to 1.16)	0.77
Interaction term: systolic BP 140-149 x thiazide diuretics	1.00 (0.87 to 1.14)	0.95
Interaction term: systolic BP 150-159 x thiazide diuretics	0.97 (0.83 to 1.13)	0.69
Interaction term: systolic BP ≥160 x thiazide diuretics	0.96 (0.84 to 1.11)	0.61
Interaction term: systolic BP 110-119 x calcium antagonists	1.07 (0.80 to 1.43)	0.65
Interaction term: systolic BP 120-129 x calcium antagonists	1.07 (0.91 to 1.26)	0.39
Interaction term: systolic BP 140-149 x calcium antagonists	0.81 (0.71 to 0.92)	0.002
Interaction term: systolic BP 150-159 x calcium antagonists	0.84 (0.73 to 0.98)	0.02
Interaction term: systolic BP ≥160 x calcium antagonists	0.86 (0.75 to 0.98)	0.02
Interaction term: systolic BP 110-119 x spironolactone	1.22 (0.73 to 2.03)	0.45
Interaction term: systolic BP 120-129 x spironolactone	0.70 (0.47 to 1.04)	0.07
Interaction term: systolic BP 140-149 x spironolactone	0.94 (0.68 to 1.31)	0.72
Interaction term: systolic BP 150-159 x spironolactone	0.79 (0.53 to 1.17)	0.24
Interaction term: systolic BP ≥160 x spironolactone	0.83 (0.57 to 1.20)	0.32
Interaction term: systolic BP 110-119 x B-blockers	0.95 (0.73 to 1.23)	0.69
Interaction term: systolic BP 120-129 x B-blockers	1.00 (0.86 to 1.16)	0.99
Interaction term: systolic BP 140-149 x B-blockers	1.04 (0.92 to 1.17)	0.56
Interaction term: systolic BP 150-159 x B-blockers	0.94 (0.82 to 1.09)	0.43
Interaction term: systolic BP ≥160 x B-blockers	0.98 (0.86 to 1.12)	0.79
Medication for heart disease (yes vs. no)	1.65 (1.52 to 1.77)	<0.001

Figure A. Hazard ratios for different levels of baseline systolic blood pressure in relation to nonfatal CVD, i.e. a first event of nonfatal myocardial infarction or stroke.

	HR (95% CI)	P-value
110-119 mmHg	1.02 (0.95-1.09)	0.62
	0.86 (0.77 0.95)	0.004
	0.82 (0.72-0.93)	0.002
120-129 mmHg	0.98 (0.94-1.03)	0.49
	0.92 (0.86-0.98)	0.007
	0.92 (0.84-0.99)	0.04
130-139 mmHg	1.00	
	1.00	
	1.00	
140-149 mmHg	1.04 (1.00-1.08)	0.04
	1.04 (0.98-1.10)	0.17
	1.08 (1.00-1.16)	0.05
150-159 mmHg	1.10 (1.05-1.15)	<0.001
	1.15 (1.08-1.22)	<0.001
	1.22 (1.12-1.33)	<0.001
≥160 mmHg	1.26 (1.21-1.32)	<0.001
	1.31 (1.24-1.39)	<0.001
	1.37 (1.27 1.49)	<0.001

Light blue boxes represent the fully adjusted model including drug treatment covariates. Orange triangles represents the same analysis without drug treatment as covariates. Dark blue circles represent the model including individuals with previous diseases.

Figure B. Hazard ratios for different levels of baseline systolic blood pressure in relation to total CVD, i.e. a first event of nonfatal or fatal myocardial infarction or stroke.
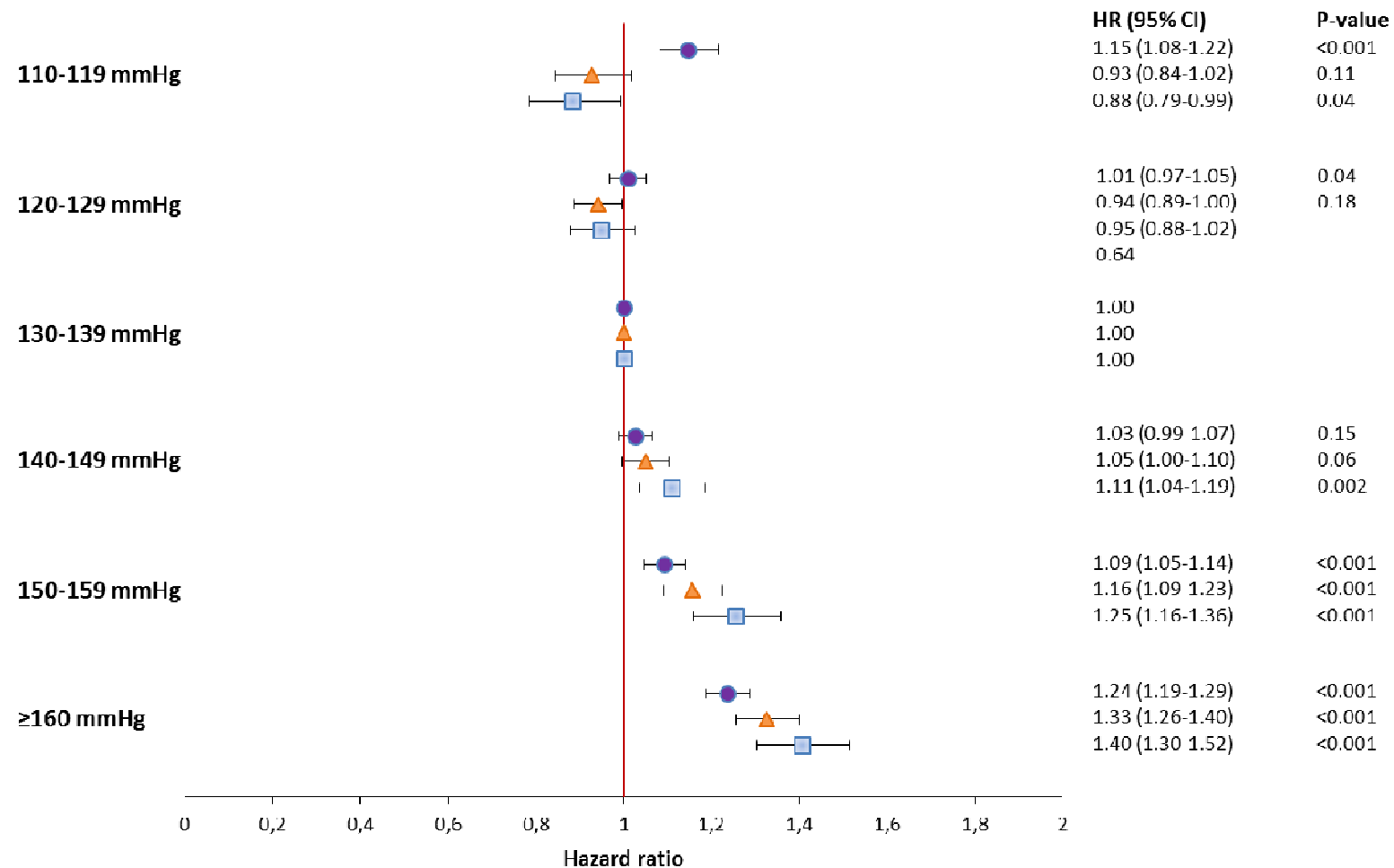
	HR (95% CI)	P-value
110-119 mmHg	1.15 (1.08-1.22)	<0.001
	0.93 (0.84-1.02)	0.11
	0.88 (0.79-0.99)	0.04
120-129 mmHg	1.01 (0.97-1.05)	0.04
	0.94 (0.89-1.00)	0.18
	0.95 (0.88-1.02)	
	0.64	
130-139 mmHg	1.00	
	1.00	
	1.00	
140-149 mmHg	1.03 (0.99 1.07)	0.15
	1.05 (1.00-1.10)	0.06
	1.11 (1.04-1.19)	0.002
150-159 mmHg	1.09 (1.05-1.14)	<0.001
	1.16 (1.09 1.23)	<0.001
	1.25 (1.16-1.36)	<0.001
≥160 mmHg	1.24 (1.19-1.29)	<0.001
	1.33 (1.26-1.40)	<0.001
	1.40 (1.30 1.52)	<0.001

Hazard ratio

Light blue boxes represent the fully adjusted model including drug treatment covariates. Orange triangles represents the same analysis without drug treatment as covariates. Dark blue circles represent the model including individuals with previous diseases.

Figure C. Hazard ratios for different levels of baseline systolic blood pressure in relation to nonfatal AMI

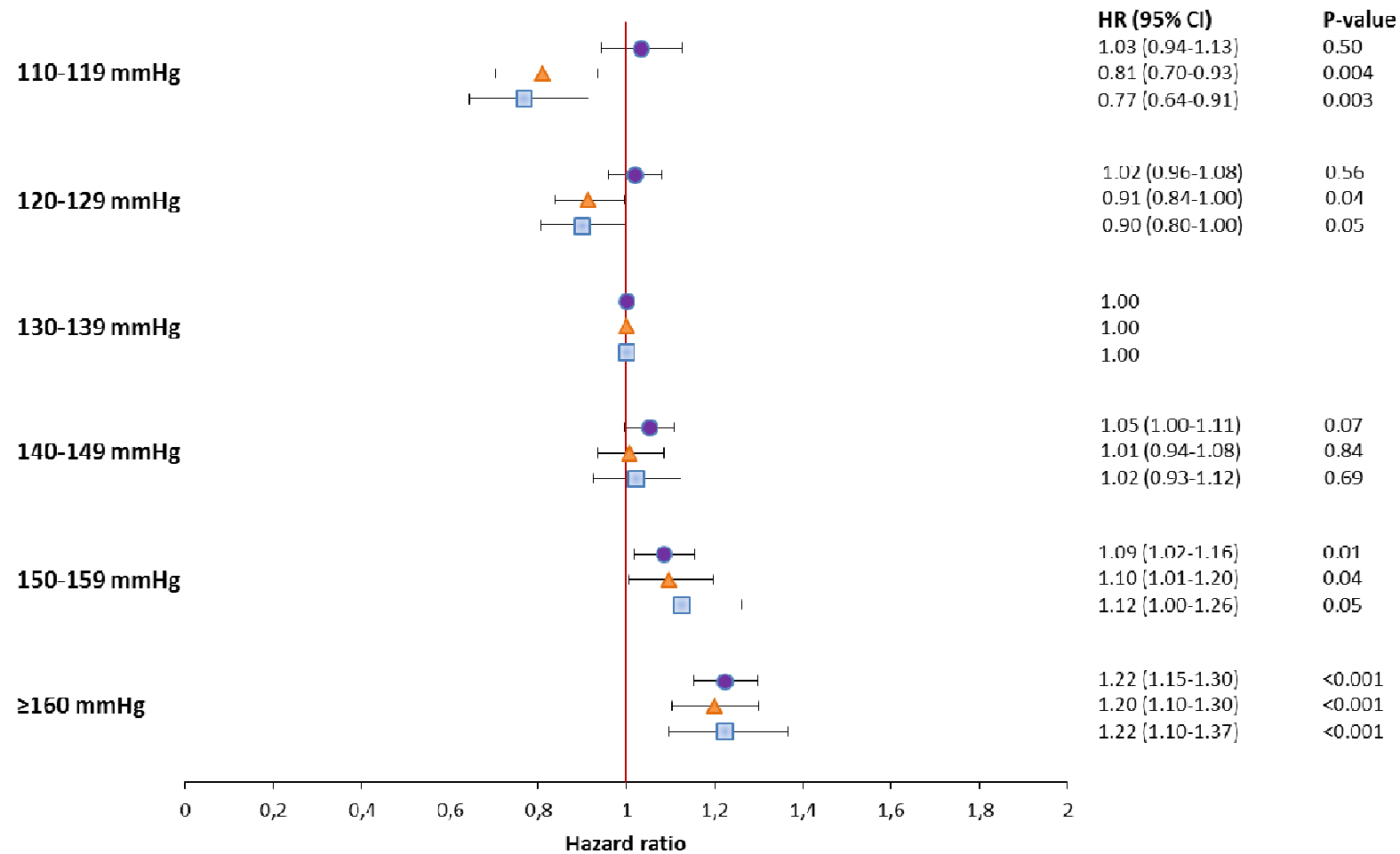|	HR (95% CI)	P-value
110-119 mmHg	1.03 (0.94-1.13)	0.50
	0.81 (0.70-0.93)	0.004
	0.77 (0.64-0.91)	0.003
120-129 mmHg	1.02 (0.96-1.08)	0.56
	0.91 (0.84-1.00)	0.04
	0.90 (0.80-1.00)	0.05
130-139 mmHg	1.00	
	1.00	
	1.00	
140-149 mmHg	1.05 (1.00-1.11)	0.07
	1.01 (0.94-1.08)	0.84
	1.02 (0.93-1.12)	0.69
150-159 mmHg	1.09 (1.02-1.16)	0.01
	1.10 (1.01-1.20)	0.04
	1.12 (1.00-1.26)	0.05
≥160 mmHg	1.22 (1.15-1.30)	<0.001
	1.20 (1.10-1.30)	<0.001
	1.22 (1.10-1.37)	<0.001

Light blue boxes represent the fully adjusted model including drug treatment covariates. Orange triangles represents the same analysis without drug treatment as covariates. Dark blue circles represent the model including individuals with previous diseases.

Figure D. Hazard ratios for different levels of baseline systolic blood pressure in relation to total AMI

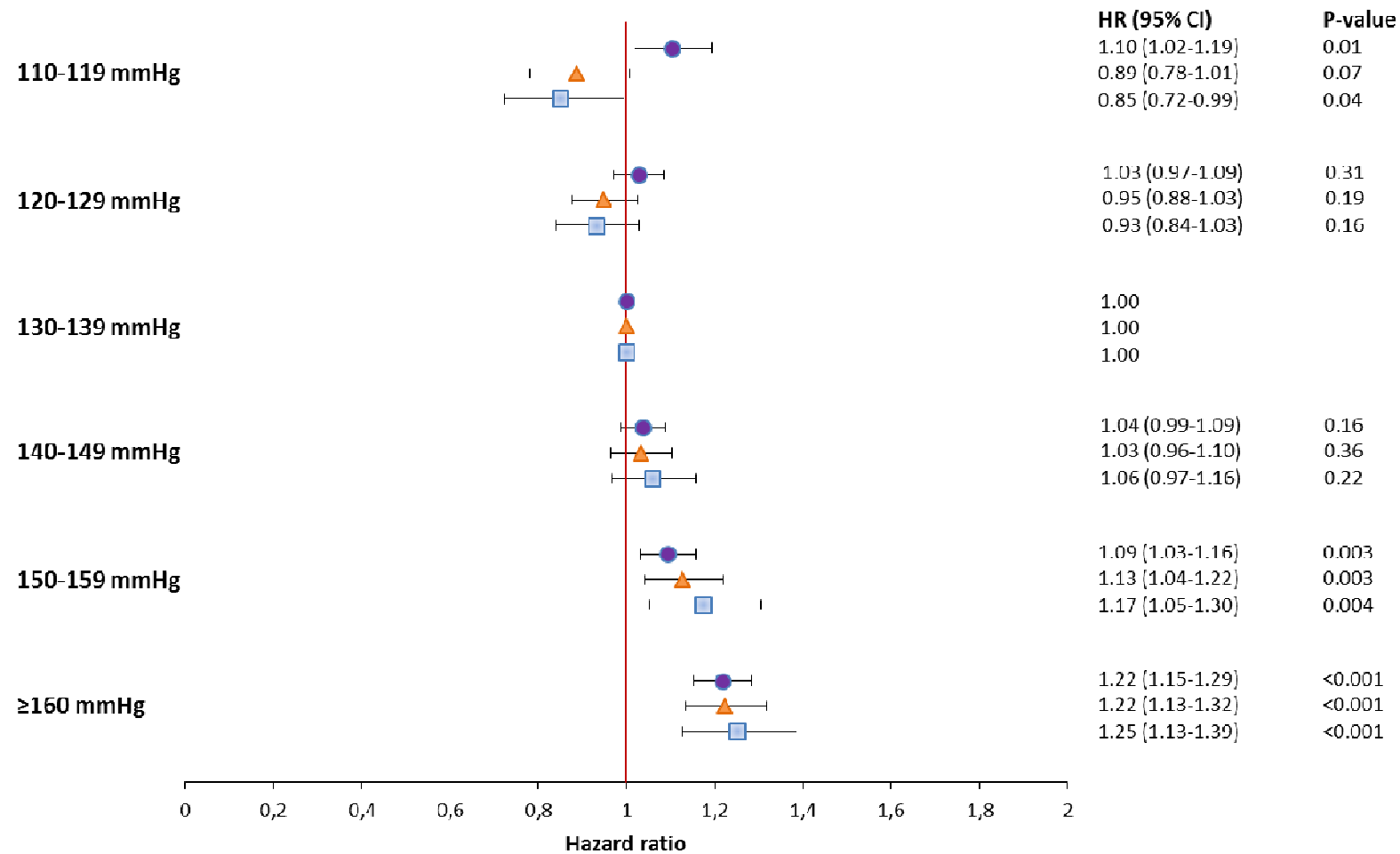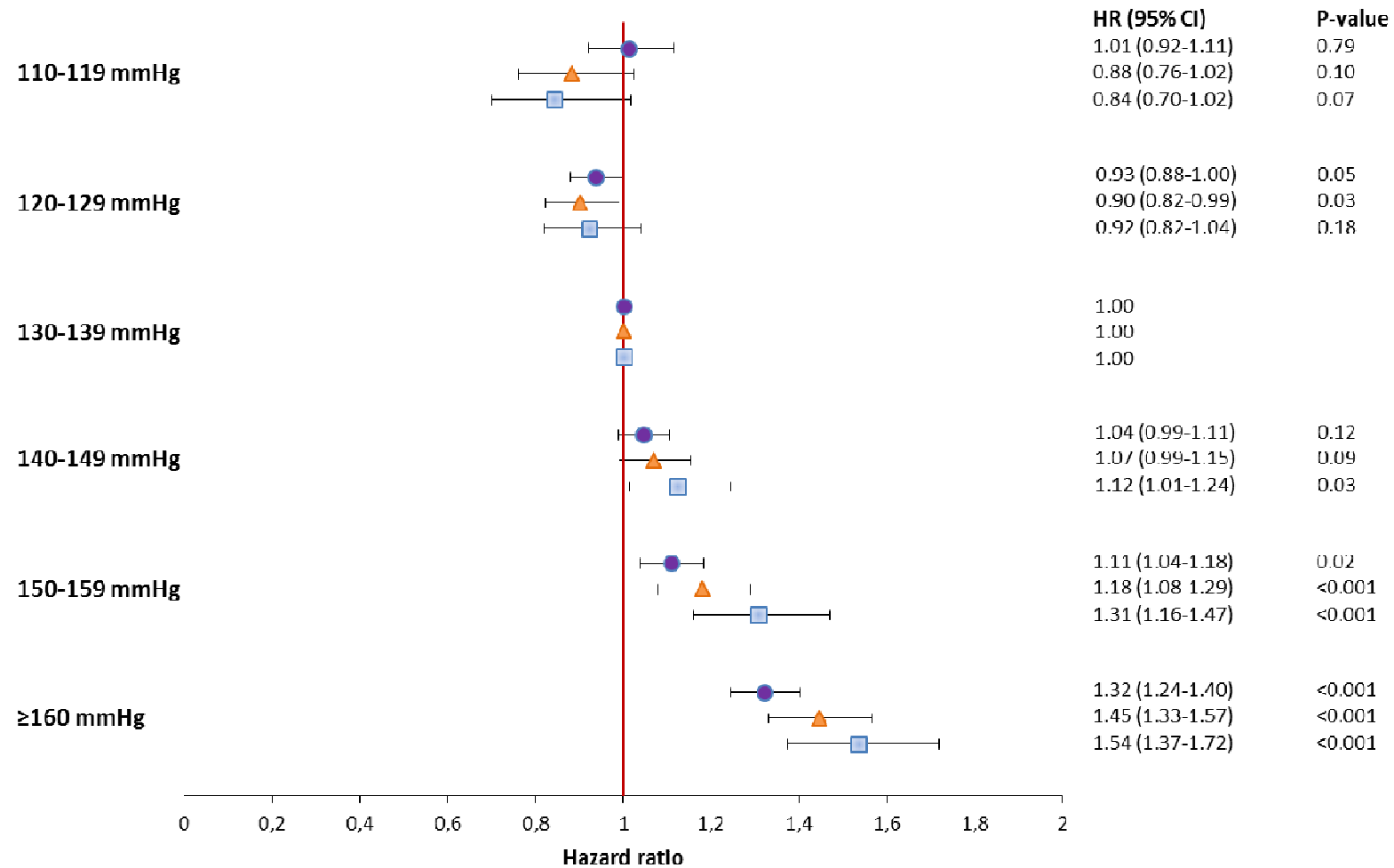|	HR (95% CI)	P-value
110-119 mmHg	1.10 (1.02-1.19)	0.01
	0.89 (0.78-1.01)	0.07
	0.85 (0.72-0.99)	0.04
120-129 mmHg	1.03 (0.97-1.09)	0.31
	0.95 (0.88-1.03)	0.19
	0.93 (0.84-1.03)	0.16
130-139 mmHg	1.00	
	1.00	
	1.00	
140-149 mmHg	1.04 (0.99-1.09)	0.16
	1.03 (0.96-1.10)	0.36
	1.06 (0.97-1.16)	0.22
150-159 mmHg	1.09 (1.03-1.16)	0.003
	1.13 (1.04-1.22)	0.003
	1.17 (1.05-1.30)	0.004
≥160 mmHg	1.22 (1.15-1.29)	<0.001
	1.22 (1.13-1.32)	<0.001
	1.25 (1.13-1.39)	<0.001

Light blue boxes represent the fully adjusted model including drug treatment covariates. Orange triangles represents the same analysis without drug treatment as covariates. Dark blue circles represent the model including individuals with previous diseases.

Figure E. Hazard ratios for different levels of baseline systolic blood pressure in relation to nonfatal stroke

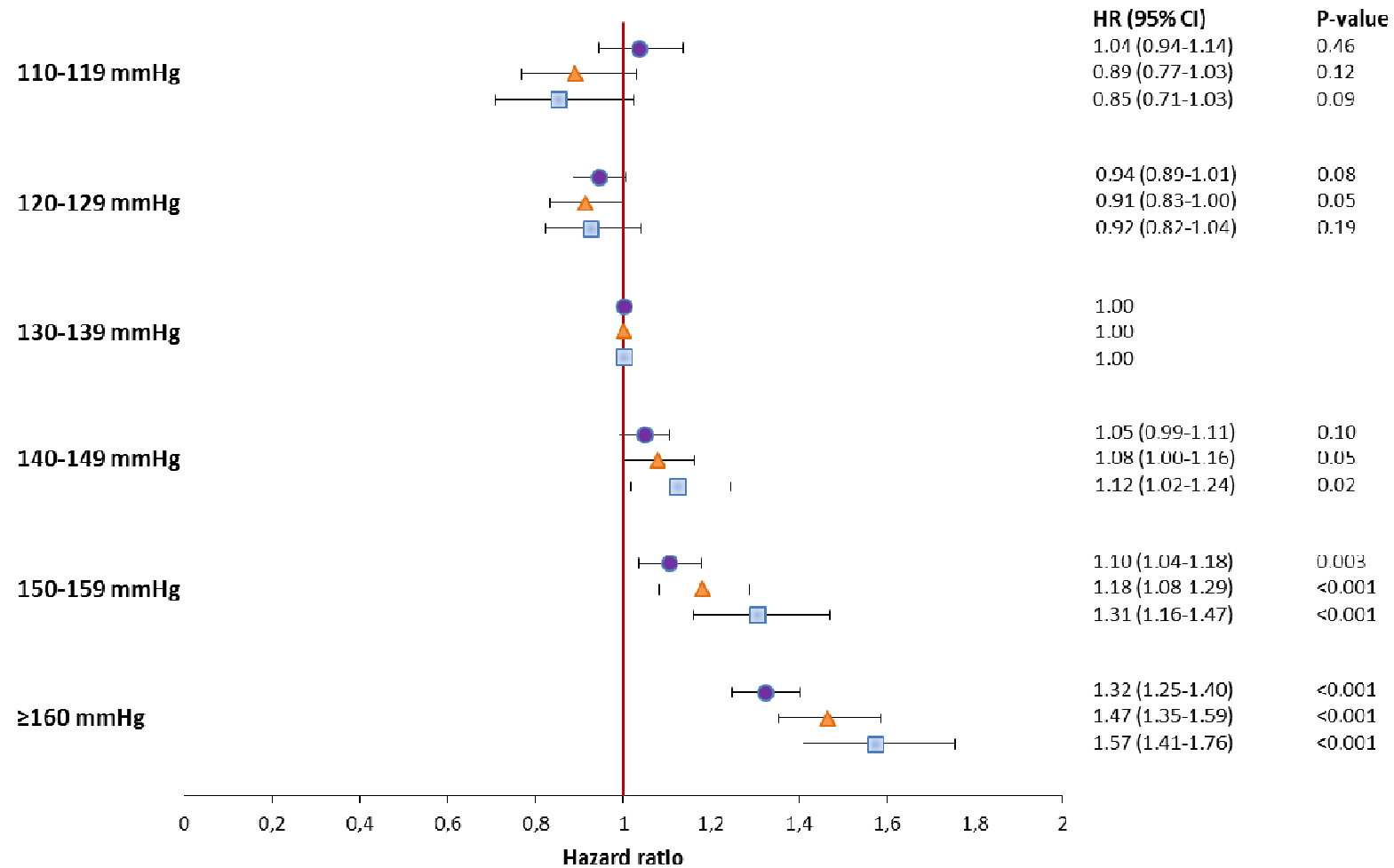|	HR (95% CI)	P-value
	1.01 (0.92-1.11)	0.79
110-119 mmHg	0.88 (0.76-1.02)	0.10
	0.84 (0.70-1.02)	0.07
	0.93 (0.88-1.00)	0.05
120-129 mmHg	0.90 (0.82-0.99)	0.03
	0.92 (0.82-1.04)	0.18
	1.00	
130-139 mmHg	1.00	
	1.00	
	1.04 (0.99-1.11)	0.12
140-149 mmHg	1.07 (0.99-1.15)	0.09
	1.12 (1.01-1.24)	0.03
	1.11 (1.04-1.18)	0.02
150-159 mmHg	1.18 (1.08-1.29)	<0.001
	1.31 (1.16-1.47)	<0.001
	1.32 (1.24-1.40)	<0.001
≥160 mmHg	1.45 (1.33-1.57)	<0.001
	1.54 (1.37-1.72)	<0.001

Light blue boxes represent the fully adjusted model including drug treatment covariates. Orange triangles represents the same analysis without drug treatment as covariates. Dark blue circles represent the model including individuals with previous diseases.

Figure F. Hazard ratios for different levels of baseline systolic blood pressure in relation to total stroke

|	HR (95% CI)	P-value
110-119 mmHg	1.04 (0.94-1.14)	0.46
	0.89 (0.77-1.03)	0.12
	0.85 (0.71-1.03)	0.09
120-129 mmHg	0.94 (0.89-1.01)	0.08
	0.91 (0.83-1.00)	0.05
	0.92 (0.82-1.04)	0.19
130-139 mmHg	1.00	
	1.00	
	1.00	
140-149 mmHg	1.05 (0.99-1.11)	0.10
	1.08 (1.00-1.16)	0.05
	1.12 (1.02-1.24)	0.02
150-159 mmHg	1.10 (1.04-1.18)	0.003
	1.18 (1.08 1.29)	<0.001
	1.31 (1.16-1.47)	<0.001
≥160 mmHg	1.32 (1.25-1.40)	<0.001
	1.47 (1.35-1.59)	<0.001
	1.57 (1.41-1.76)	<0.001

Light blue boxes represent the fully adjusted model including drug treatment covariates. Orange triangles represents the same analysis without drug treatment as covariates. Dark blue circles represent the model including individuals with previous diseases.

Figure G. Hazard ratios for different levels of baseline systolic blood pressure in relation to nonfatal coronary heart disease
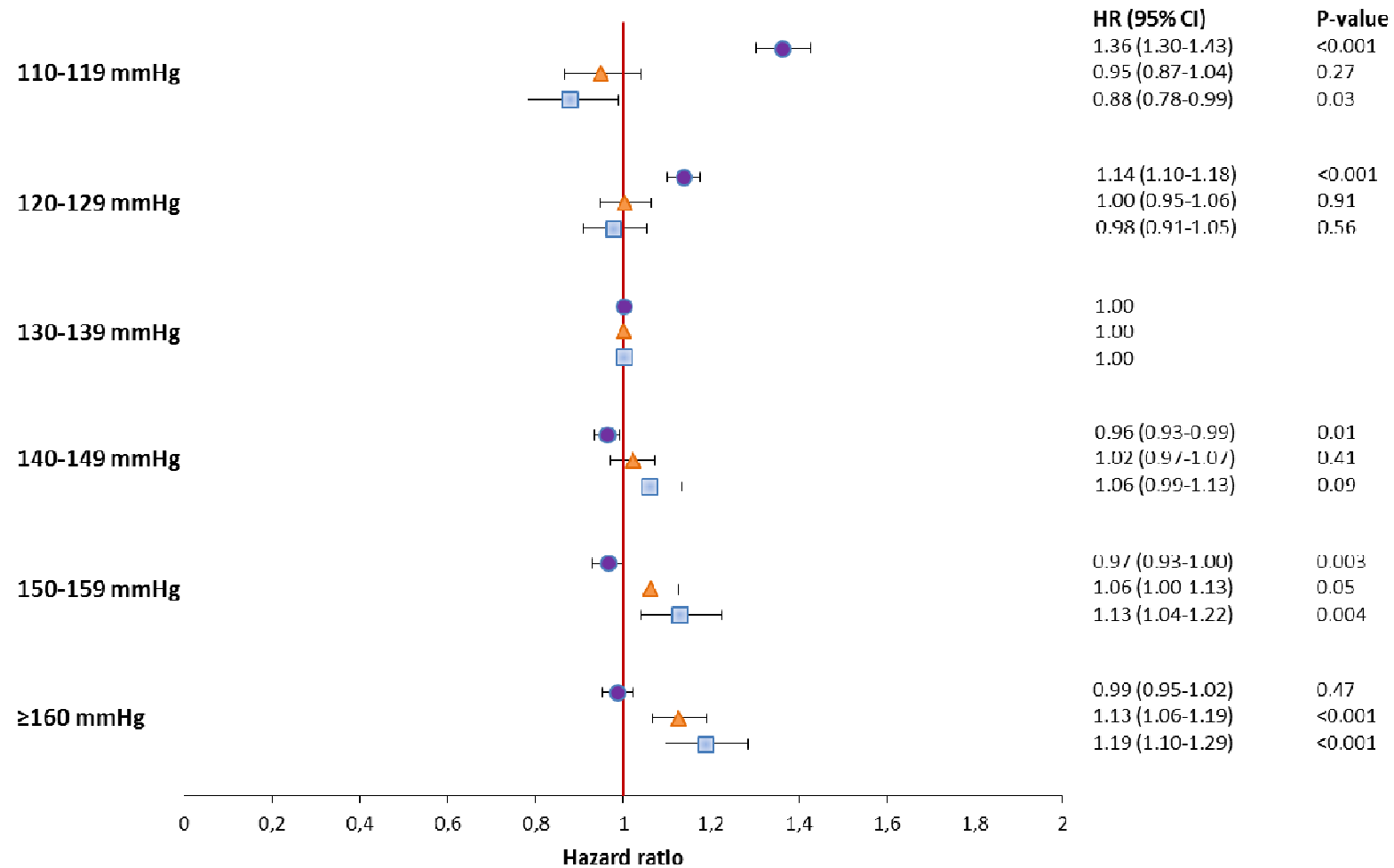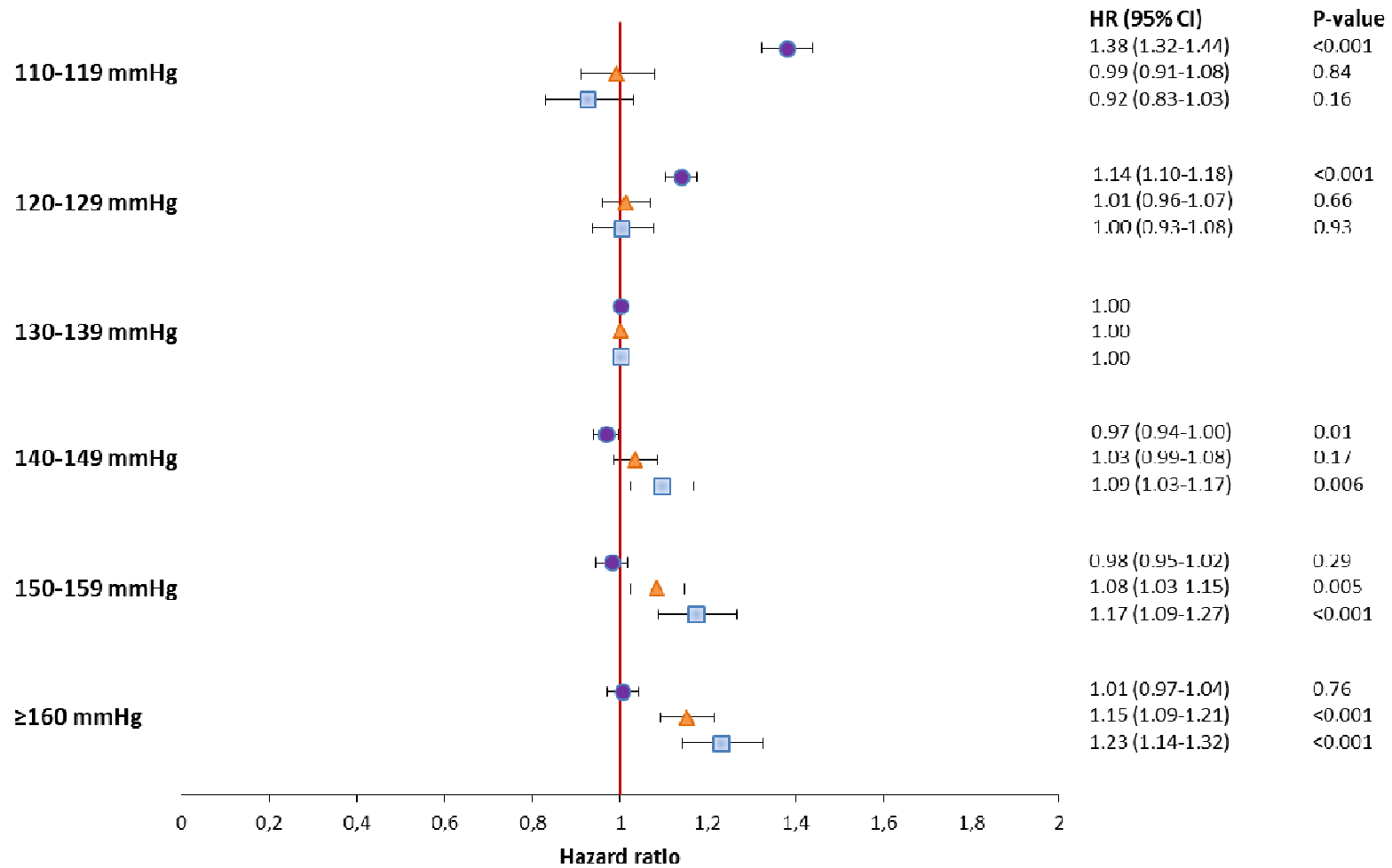

Light blue boxes represent the fully adjusted model including drug treatment covariates. Orange triangles represents the same analysis without drug treatment as covariates. Dark blue circles represent the model including individuals with previous diseases.

Figure H. Hazard ratios for different levels of baseline systolic blood pressure in relation to total coronary heart disease

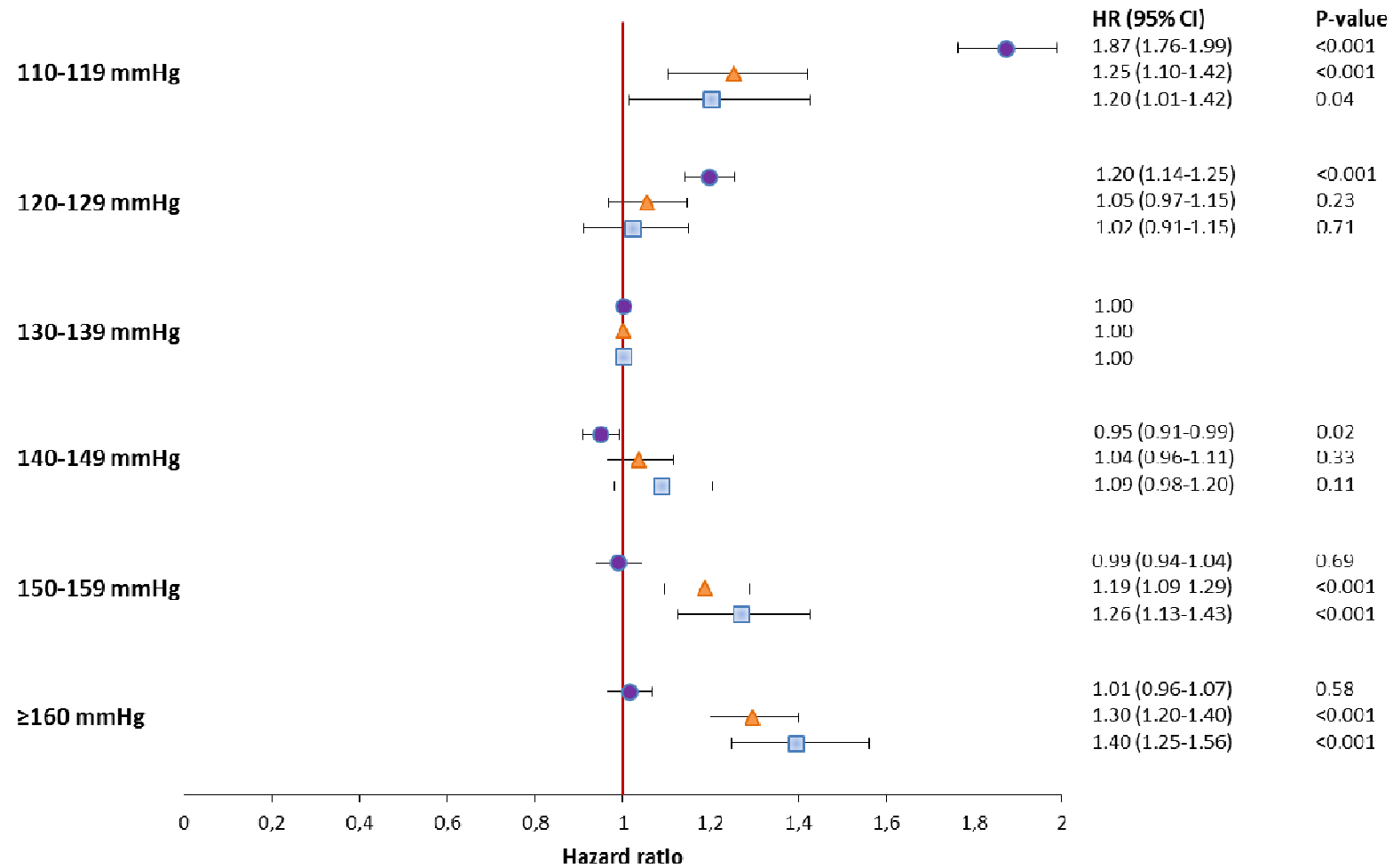|	HR (95% CI)	P-value
	1.38 (1.32-1.44)	<0.001
110-119 mmHg	0.99 (0.91-1.08)	0.84
	0.92 (0.83-1.03)	0.16
	1.14 (1.10-1.18)	<0.001
120-129 mmHg	1.01 (0.96-1.07)	0.66
	1.00 (0.93-1.08)	0.93
	1.00	
130-139 mmHg	1.00	
	1.00	
	0.97 (0.94-1.00)	0.01
140-149 mmHg	1.03 (0.99-1.08)	0.17
	1.09 (1.03-1.17)	0.006
	0.98 (0.95-1.02)	0.29
150-159 mmHg	1.08 (1.03-1.15)	0.005
	1.17 (1.09-1.27)	<0.001
	1.01 (0.97-1.04)	0.76
≥160 mmHg	1.15 (1.09-1.21)	<0.001
	1.23 (1.14-1.32)	<0.001

Light blue boxes represent the fully adjusted model including drug treatment covariates. Orange triangles represents the same analysis without drug treatment as covariates. Dark blue circles represent the model including individuals with previous diseases.

Figure I. Hazard ratios for different levels of baseline systolic blood pressure in relation to heart failure

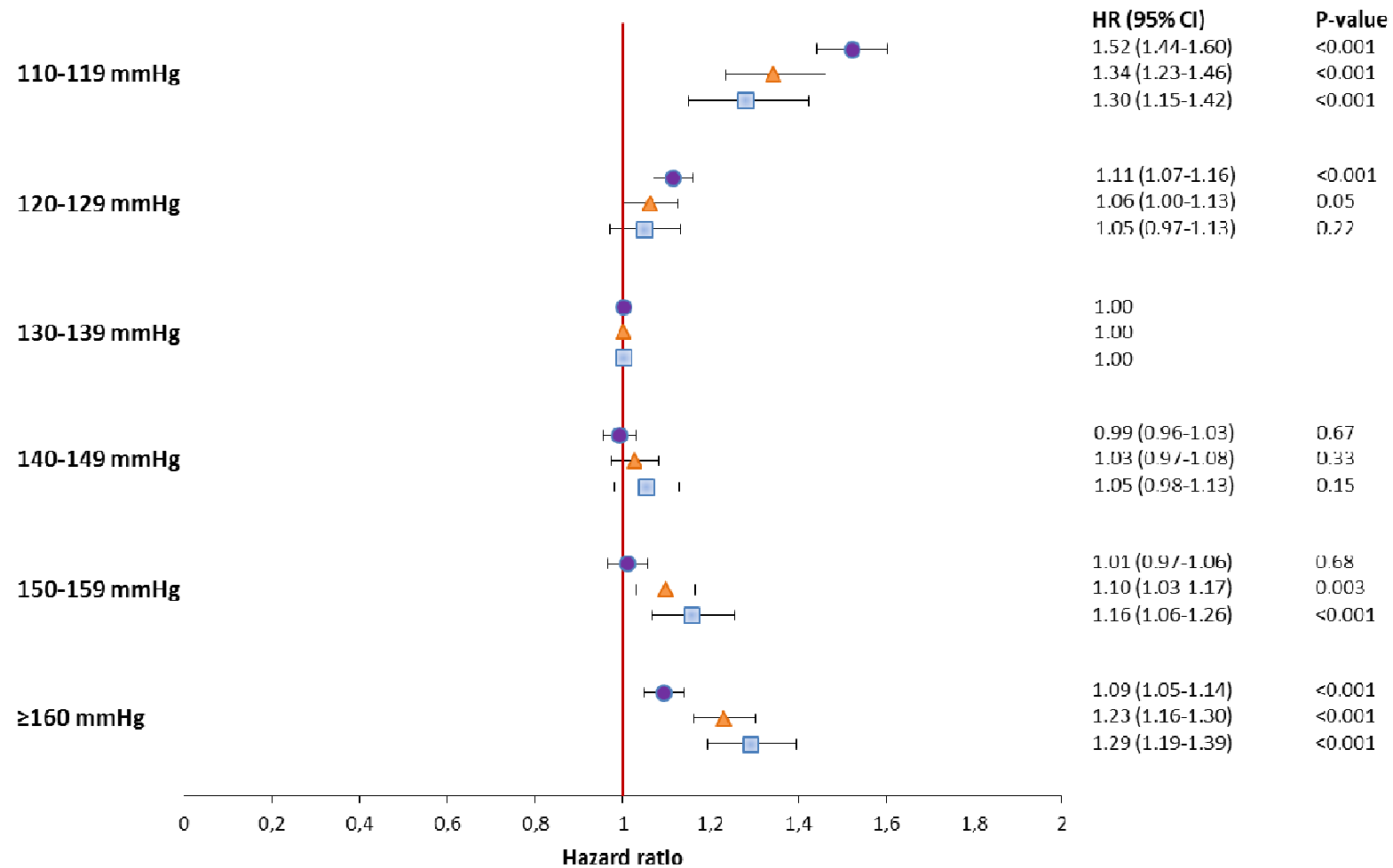|	HR (95% CI)	P-value
110-119 mmHg	1.87 (1.76-1.99)	<0.001
	1.25 (1.10-1.42)	<0.001
	1.20 (1.01-1.42)	0.04
120-129 mmHg	1.20 (1.14-1.25)	<0.001
	1.05 (0.97-1.15)	0.23
	1.02 (0.91-1.15)	0.71
130-139 mmHg	1.00	
	1.00	
	1.00	
140-149 mmHg	0.95 (0.91-0.99)	0.02
	1.04 (0.96-1.11)	0.33
	1.09 (0.98-1.20)	0.11
150-159 mmHg	0.99 (0.94-1.04)	0.69
	1.19 (1.09-1.29)	<0.001
	1.26 (1.13-1.43)	<0.001
≥160 mmHg	1.01 (0.96-1.07)	0.58
	1.30 (1.20-1.40)	<0.001
	1.40 (1.25-1.56)	<0.001

Hazard ratio

Light blue boxes represent the fully adjusted model including drug treatment covariates. Orange triangles represents the same analysis without drug treatment as covariates. Dark blue circles represent the model including individuals with previous diseases.

Figure J. Hazard ratios for different levels of baseline systolic blood pressure in relation to total mortality

	HR (95% CI)	P-value
110-119 mmHg	1.52 (1.44-1.60)	<0.001
	1.34 (1.23-1.46)	<0.001
	1.30 (1.15-1.42)	<0.001
120-129 mmHg	1.11 (1.07-1.16)	<0.001
	1.06 (1.00-1.13)	0.05
	1.05 (0.97-1.13)	0.22
130-139 mmHg	1.00	
	1.00	
	1.00	
140-149 mmHg	0.99 (0.96-1.03)	0.67
	1.03 (0.97-1.08)	0.33
	1.05 (0.98-1.13)	0.15
150-159 mmHg	1.01 (0.97-1.06)	0.68
	1.10 (1.03-1.17)	0.003
	1.16 (1.06-1.26)	<0.001
≥160 mmHg	1.09 (1.05-1.14)	<0.001
	1.23 (1.16-1.30)	<0.001
	1.29 (1.19-1.39)	<0.001

Light blue boxes represent the fully adjusted model including drug treatment covariates. Orange triangles represents the same analysis without drug treatment as covariates. Dark blue circles represent the model including individuals with previous diseases.

Table C. Frequencies of primary causes of death in different systolic blood pressure groups

Primary cause of death	110-119 mmHg (n=684)	120-129 mmHg (n=1841)	130-139 mmHg (n=2749)	140-149 mmHg (n=2916)	150-159 mmHg (n=1692)	≥160 mmHg (n=2270)
Certain infectious and parasitic diseases	22 (3·2%)	28 (1·5%)	67 (2·4%)	70 (2·4%)	37 (2·2%)	52 (2·3%)
Neoplasms	221 (32·3%)	670 (36·4%)	1091 (39·7%)	1056 (36·2%)	574 (33·9%)	690 (30·4%)
Diseases of the blood and blood-forming organs	3 (0·4%)	4 (0·2%)	9 (0·3%)	7 (0·2%)	5 (0·3%)	2 (0·1%)
Endocrine, nutritional and metabolic diseases	55 (8·0%)	154 (8·4%)	211 (7·7%)	246 (8·4%)	156 (9·2%)	267 (11·8%)
Mental, behavioural and neurodevelopmental disorders	6 (0·9%)	34 (1·8%)	57 (2·1%)	63 (2·2%)	29 (1·7%)	48 (2·1%)
Diseases of the nervous system	22 (3·2%)	55 (3·0%)	65 (2·4%)	60 (2·1%)	27 (1·6%)	41 (1·8%)
Diseases of the circulatory system	191 (27·9%)	500 (27·2%)	744 (27·1%)	870 (29·8%)	579 (34·2%)	779 (34·3%)
Diseases of the respiratory system	43 (6·3%)	91 (4·9%)	123 (4·5%)	150 (5·1%)	80 (4·7%)	100 (4·4%)
Diseases of the digestive system	46 (6·7%)	121 (6·6%)	133 (4·8%)	143 (4·9%)	72 (4·3%)	97 (4·3%)
Diseases of the skin and subcutaneous tissue	0 (0·0%)	1 (0·1%)	6 (0·2%)	5 (0·2%)	2 (0·1%)	1 (0·0%)

Primary cause of death	110-119 mmHg (n=684)	120-129 mmHg (n=1841)	130-139 mmHg (n=2749)	140-149 mmHg (n=2916)	150-159 mmHg (n=1692)	≥160 mmHg (n=2270)
Diseases of the musculoskeletal system and connective tissue	2 (0·3%)	8 (0·4%)	10 (0·4%)	11 (0·4%)	8 (0·5%)	12 (0·5%)
Diseases of the genitourinary system	6 (0·9%)	18 (1·0%)	22 (0·8%)	24 (0·8%)	20 (1·2%)	23 (1·0%)
Congenital malformations, deformations and chromosomal abnormalities	0 (0·0%)	3 (0·2%)	3 (0·1%)	1 (0·0%)	0 (0·0%)	3 (0·1%)
Symptoms, signs and abnormal clinical and laboratory finding	19 (2·8%)	47 (2·6%)	61 (2·2%)	64 (2·2%)	40 (2·4%)	65 (2·9%)
External causes of morbidity	42 (6·1%)	77 (4·2%)	110 (4·0%)	107 (3·7%)	47 (2·8%)	75 (3·3%)

Drugs as covariates and interaction terms.

Drugs were used as covariates in regression model 3 if they were associated with risk for CVD, interpreted as markers for comorbidity. The drugs were included with an interaction term with systolic blood pressure if the relationship with the endpoint nonfatal CVD was nonlinear.

The following drugs were tested: calcium antagonists, β-blockers, loop diuretics, thiazide diuretics, renin-angiotensin system inhibitors or angiotensin II blockers (RAAS blocking agents), and spironolactone. The drugs were tested one-by-one in separate cox regression models with nonfatal CVD as endpoint. The models were adjusted for age, sex, diabetes duration, smoking status, HbA1c, LDL-cholesterol, HDL-cholesterol, triglycerides, microalbuminuria, macroalbuminuria, diabetes treatment, BMI, and eGFR. The results are presented in figures S11-S16.

Conclusion/interpretation

The following drugs showed an increased risk with CVD and were thus included as covariates in regression model 3: thiazide diuretics, loop diuretics, calcium antagonists, spironolactone, and β-blockers. Of those, the following drugs were included with an interaction term with systolic blood pressure: thiazide diuretics, calcium antagonists, spironolactone, and β-blockers.

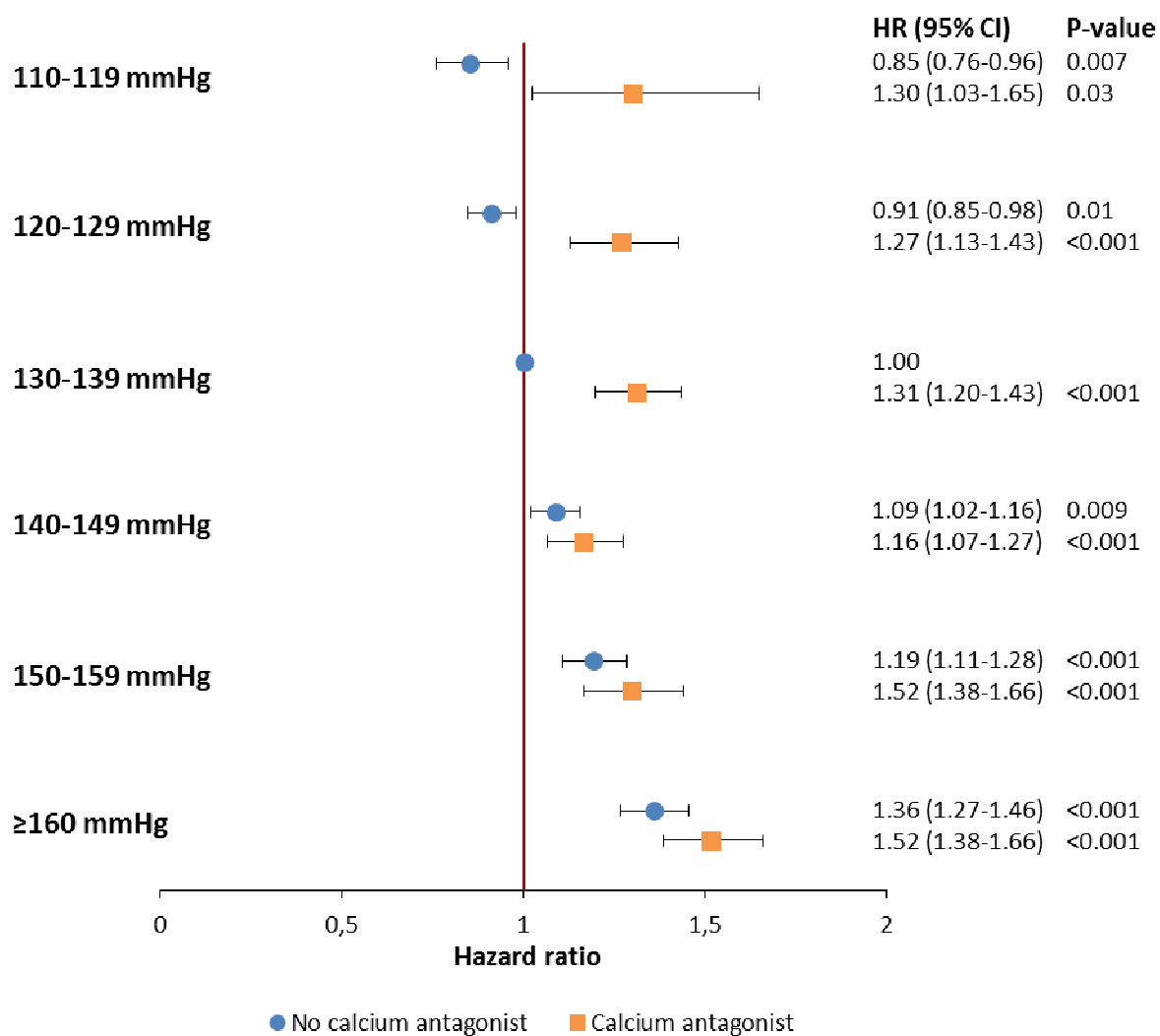Figure K. Hazard ratio for CVD for patients with, or without calcium antagonists

		HR (95% CI)	P-value
110-119 mmHg		0.85 (0.76-0.96)	0.007
		1.30 (1.03-1.65)	0.03
120-129 mmHg		0.91 (0.85-0.98)	0.01
		1.27 (1.13-1.43)	<0.001
130-139 mmHg		1.00	
		1.31 (1.20-1.43)	<0.001
140-149 mmHg		1.09 (1.02-1.16)	0.009
		1.16 (1.07-1.27)	<0.001
150-159 mmHg		1.19 (1.11-1.28)	<0.001
		1.52 (1.38-1.66)	<0.001
≥160 mmHg		1.36 (1.27-1.46)	<0.001
		1.52 (1.38-1.66)	<0.001

Hazard ratio

● No calcium antagonist   ■ Calcium antagonist

Figure L. Hazard ratio for CVD for patients with, or without β-blockers

	HR (95% CI)	P-value
110-119 mmHg	0.85 (0.76-0.96)	0.01
	1.09 (0.89-1.33)	0.40
120-129 mmHg	0.92 (0.85-0.99)	0.02
	1.12 (1.01-1.25)	0.04
130-139 mmHg	1.00	
	1.22 (1.12-1.33)	<0.001
140-149 mmHg	1.04 (0.98-1.11)	0.21
	1.23 (1.14-1.34)	<0.001
150-159 mmHg	1.18 (1.24-1.44)	<0.001
	1.27 (1.15-1.40)	<0.001
≥160 mmHg	1.34 (1.20-1.37)	<0.001
	1.48 (1.37-1.61)	<0.001

Hazard ratio

● No β-blockers   ■ β-blockers
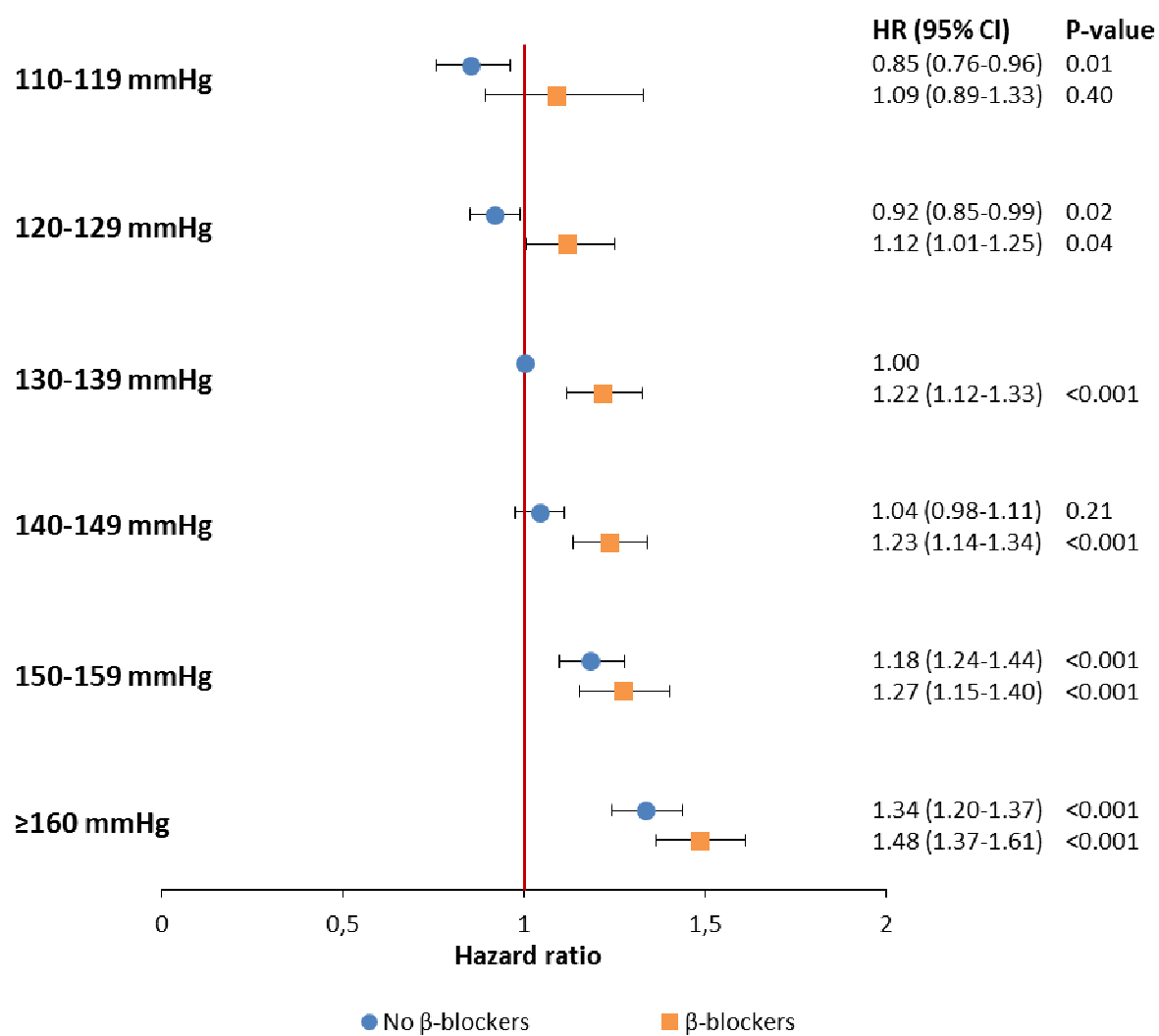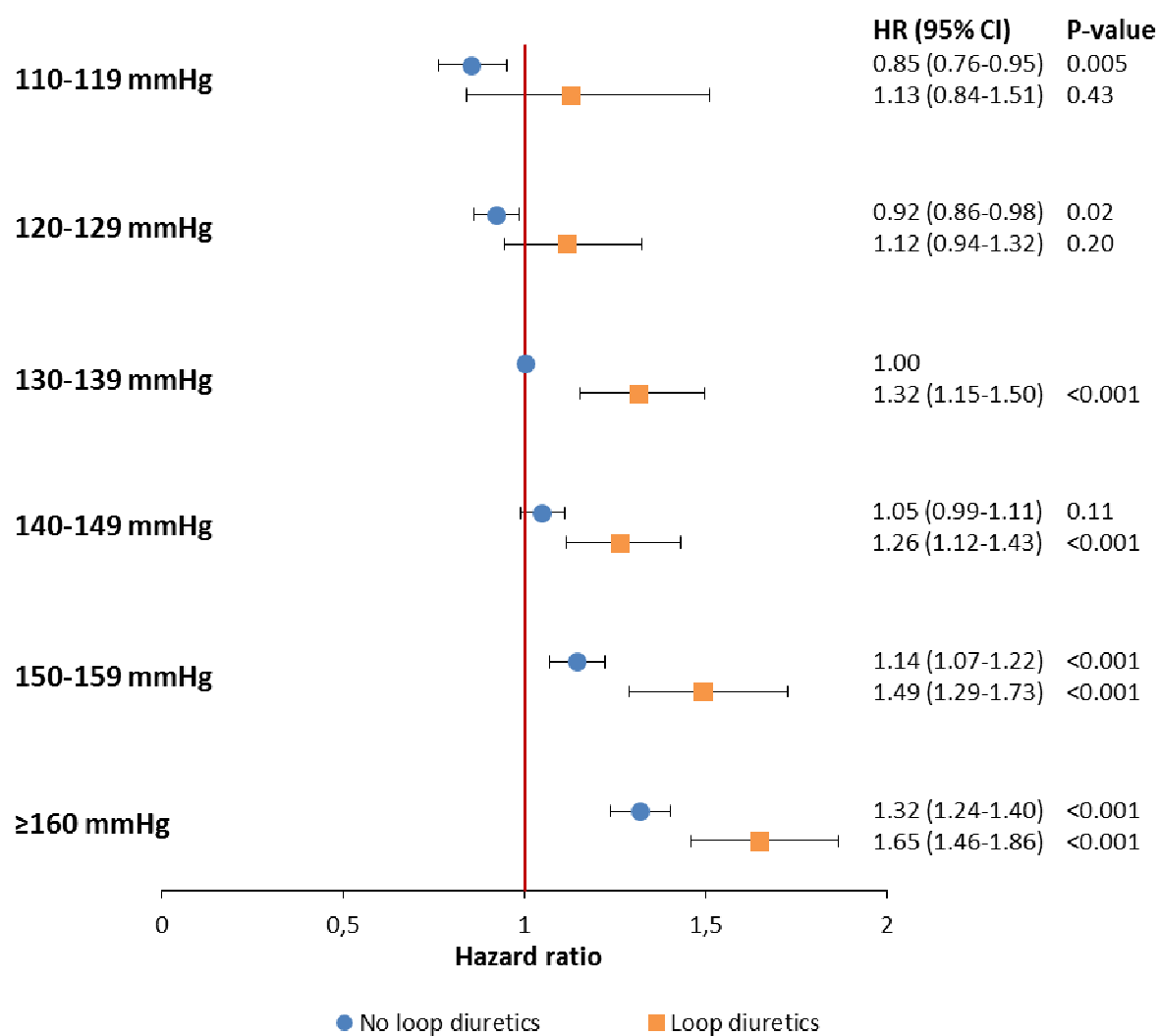
Figure M. Hazard ratio for CVD for patients with, or without loop diuretics

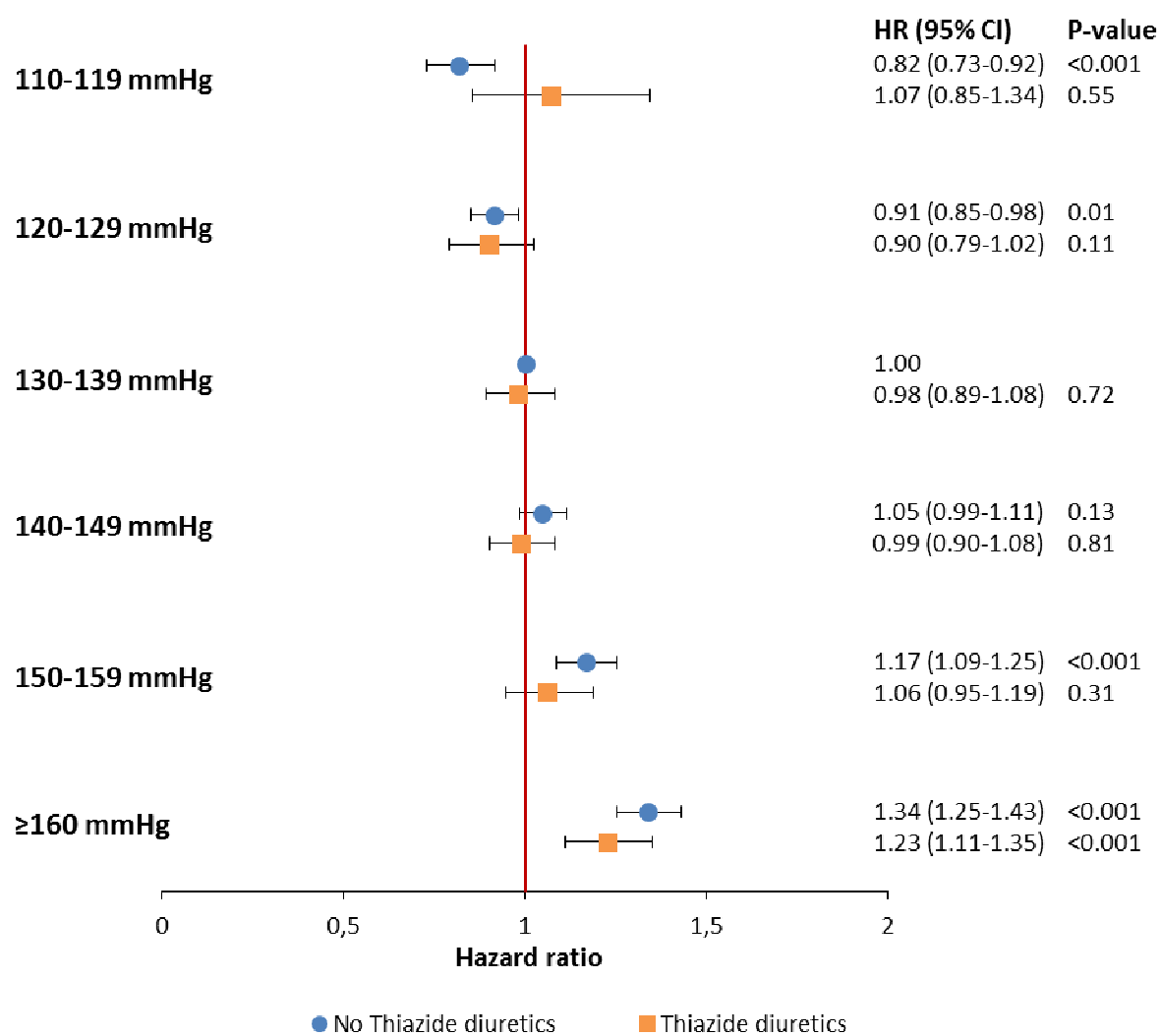Figure N. Hazard ratio for CVD for patients with, or without thiazide diuretics

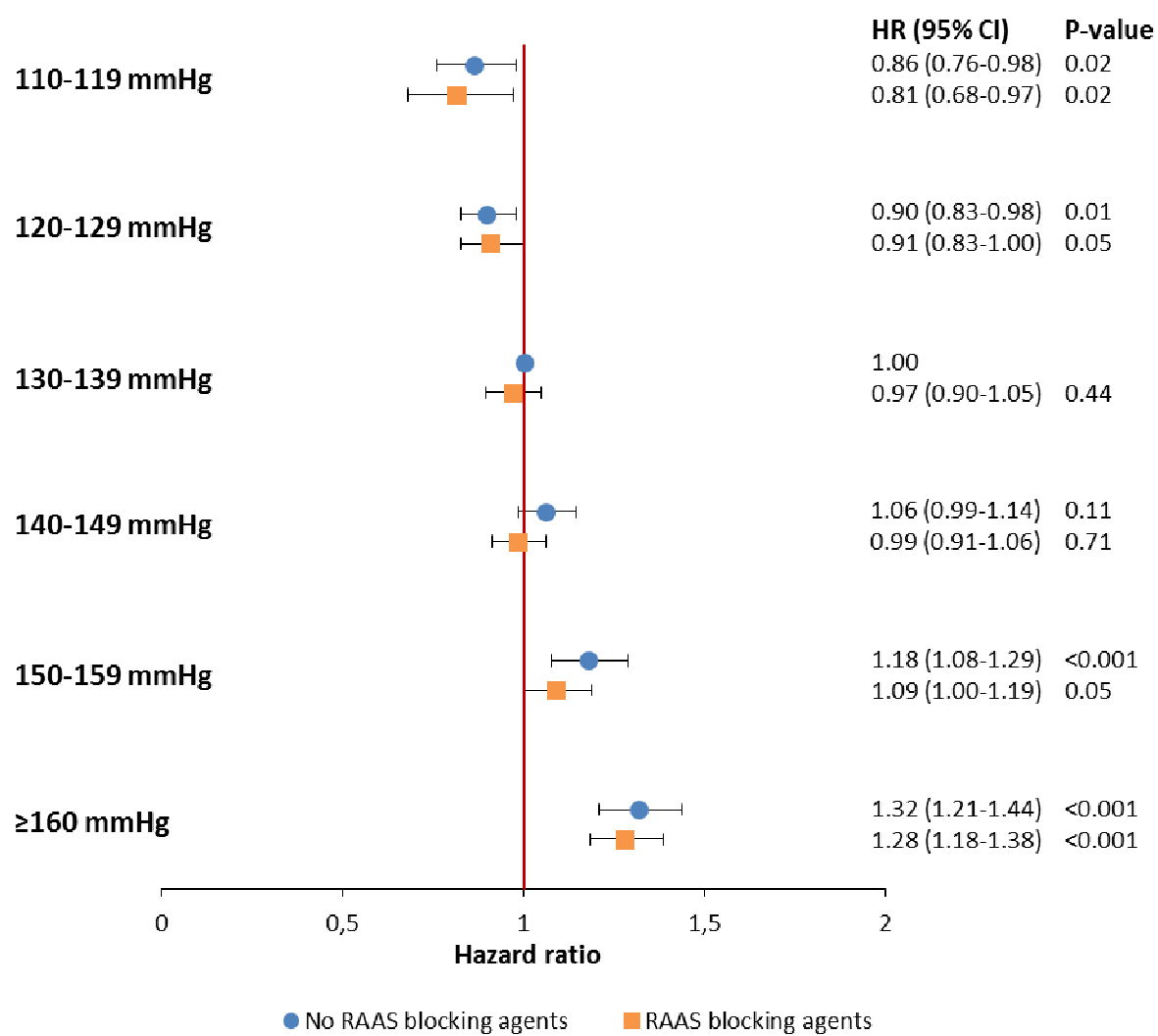|	HR (95% CI)	P-value
110-119 mmHg	0.82 (0.73-0.92)	<0.001
	1.07 (0.85-1.34)	0.55
120-129 mmHg	0.91 (0.85-0.98)	0.01
	0.90 (0.79-1.02)	0.11
130-139 mmHg	1.00	
	0.98 (0.89-1.08)	0.72
140-149 mmHg	1.05 (0.99-1.11)	0.13
	0.99 (0.90-1.08)	0.81
150-159 mmHg	1.17 (1.09-1.25)	<0.001
	1.06 (0.95-1.19)	0.31
≥160 mmHg	1.34 (1.25-1.43)	<0.001
	1.23 (1.11-1.35)	<0.001

Hazard ratio

● No Thiazide diuretics   ■ Thiazide diuretics

Figure O. Hazard ratio for CVD for patients with, or without RAAS blocking agents

	HR (95% CI)	P-value
110-119 mmHg	0.86 (0.76-0.98)	0.02
	0.81 (0.68-0.97)	0.02
120-129 mmHg	0.90 (0.83-0.98)	0.01
	0.91 (0.83-1.00)	0.05
130-139 mmHg	1.00	
	0.97 (0.90-1.05)	0.44
140-149 mmHg	1.06 (0.99-1.14)	0.11
	0.99 (0.91-1.06)	0.71
150-159 mmHg	1.18 (1.08-1.29)	<0.001
	1.09 (1.00-1.19)	0.05
≥160 mmHg	1.32 (1.21-1.44)	<0.001
	1.28 (1.18-1.38)	<0.001

Hazard ratio

● No RAAS blocking agents   ■ RAAS blocking agents

Figure P. Hazard ratio for CVD for patients with, or without spironolactone

	HR (95% CI)	P-value
110-119 mmHg	0.85 (0.76-0.94)	0.02
	1.54 (0.99-2.39)	0.02
120-129 mmHg	0.92 (0.86-0.98)	0.01
	0.93 (0.68-1.27)	0.05
130-139 mmHg	1.00	
	1.40 (1.11-1.76)	0.44
140-149 mmHg	1.04 (0.99-1.10)	0.11
	1.34 (1.06-1.70)	0.71
150-159 mmHg	1.16 (1.08-1.23)	<0.001
	1.18 (0.85-1.63)	0.05
≥160 mmHg	1.32 (1.25-1.41)	<0.001
	1.45 (1.09-1.94)	<0.001

Hazard ratio

● No spironolactone   ■ Spironolactone
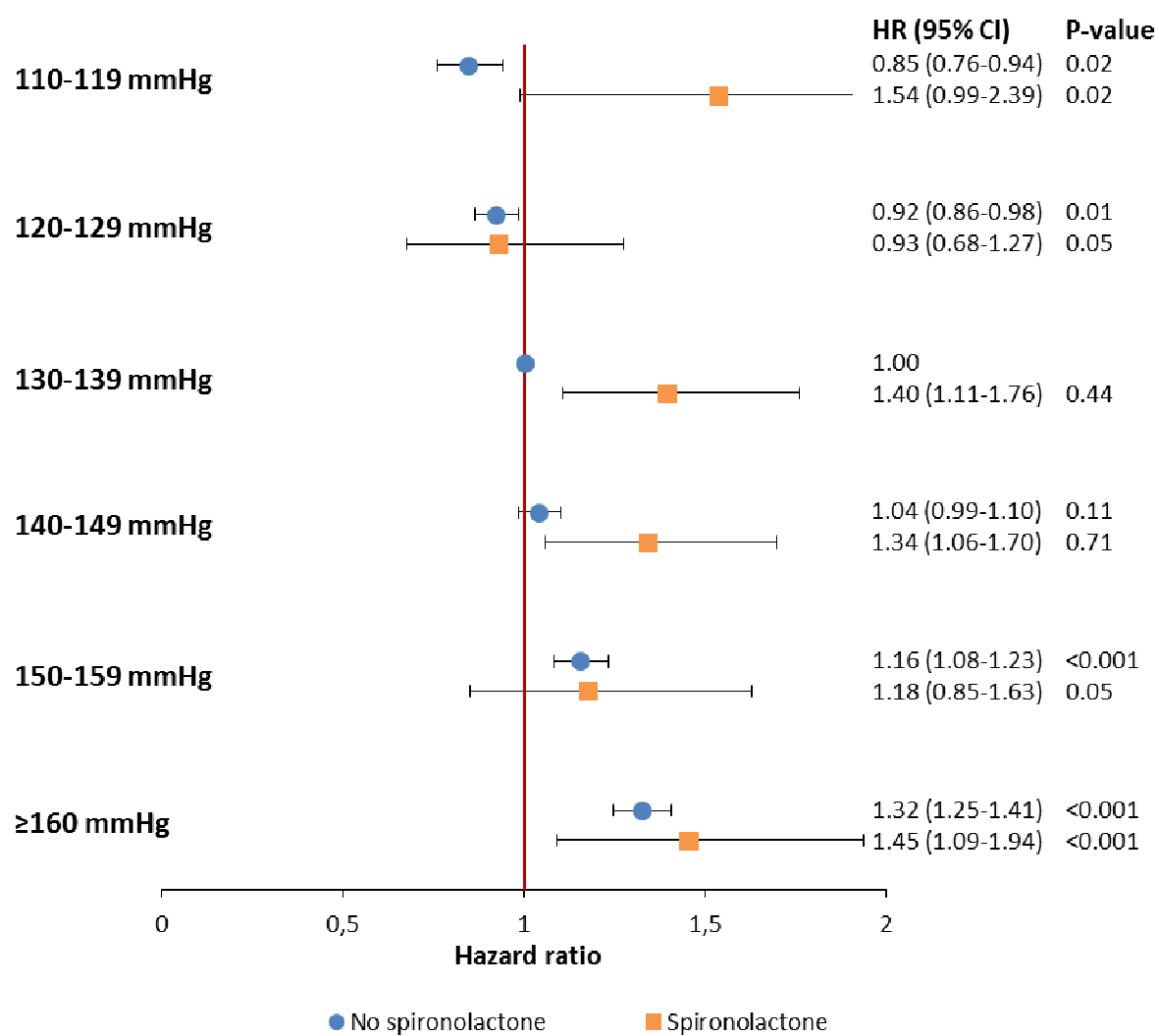
Table D. Drugs included in Cox regression model as a covariate for medication for heart disease (1/0)

ATC code	International Nonproprietory Name
B01AC04	Clopidogrel
B01AC05	Ticlopidine
B01AC07	Dipyridamole
B01AC22	Prasugrel
B01AC24	Ticagrelor
B01AC30	Combinations
C01AA04	Digitoxin
C01AA05	Digoxin
C01BA01	Kinidine
C01BA03	Disopyramide
C01BB02	Mexiletine
C01BC03	Propafenone
C01BC04	Flecainide
C01BD01	Amiodarone
C01BD07	Dronedarone

Treatment intensity at the care unit level

As a measure of antihypertensive treatment at the care unit level, the percentage of patients receiving a combination of a thiazide diuretic, calcium antagonist and either a renin-angiotensin system inhibitor or angiotensin II blocker (triple therapy) was used. The hypothesis was that the approach offers an indicator for a step-up strategy and thus a measure of low blood pressure due to antihypertensive treatment rather than spontaneous low blood pressure.

In order to avoid outlier bias, the frequency with which the triple drug regimen is used was determined by examining individuals in the 125-140 mmHg range at clinics with ≥150 patients. A total of 21,902 individuals were excluded because their clinics had too few patients.

Values were standardized by transforming the 10th percentile to 0 and the 90th percentile to 1.

Results

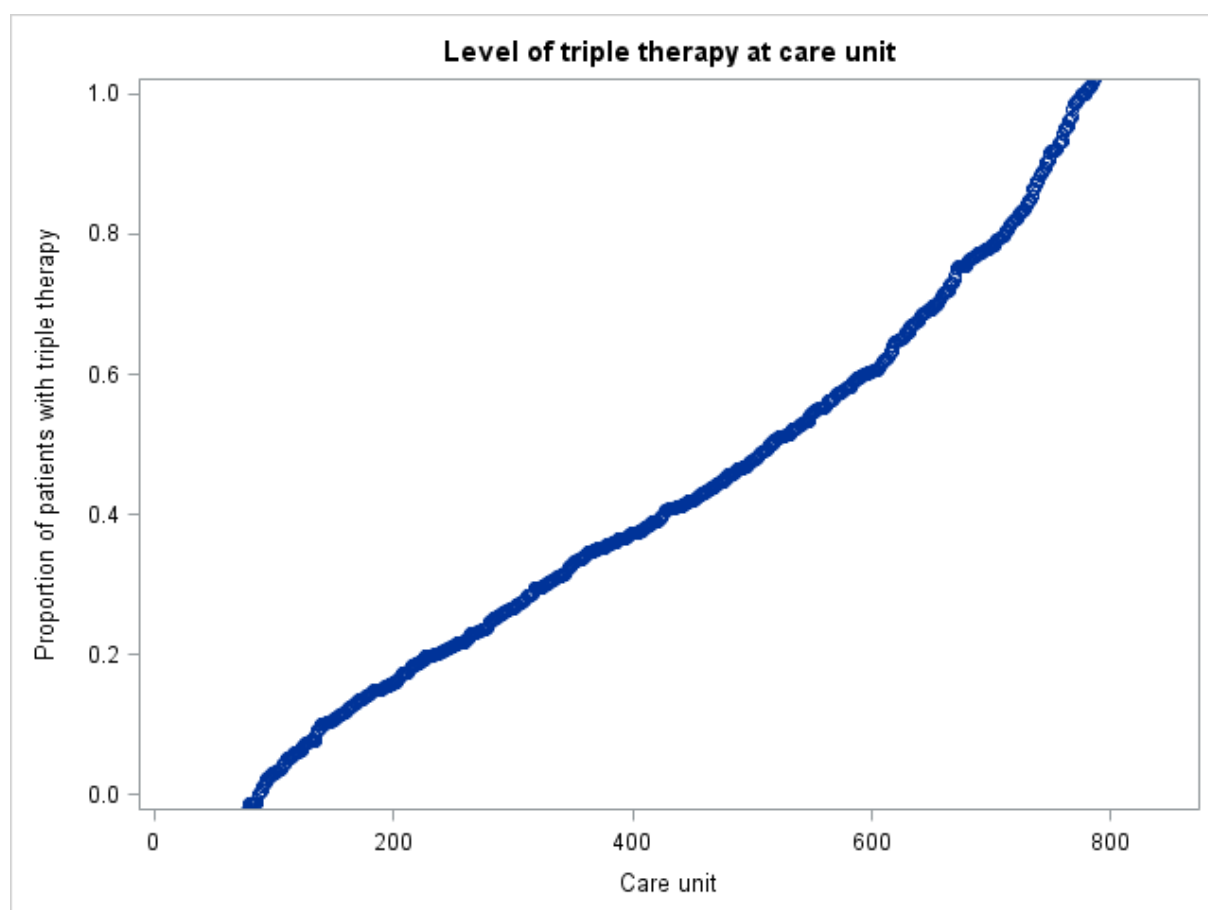Figure Q. Distribution of covariate for triple therapy for individual care units.

Table E. Logistic regression showing individual patient's probability to reach systolic blood pressure lower than 130 mmHg in relation to care unit treatment activity

Variable	Odds ratio (95% CI)	p-value
Age, per year	0·947 (0·946 to 0·948)	<0·001
Diabetes duration, per year	0·987 (0·985 to 0·989)	<0·001
Female (vs. male)	1·190 (1·164 to 1·217)	<0·001
HbA1c, per mmol/mol	0·993 (0·993 to 0·994)	<0·001
BMI, kg/m^2	0·961 (0·959 to 0·963)	<0·001
HDL-cholesterol, per mmol/l	0·877 (0·853 to 0·902)	<0·001
LDL-cholesterol, per mmol/l	0·904 (0·894 to 0·915)	<0·001
eGFR, ml/min/1·73 m^2	0·998 (0·998 to 0·999)	<0·001
Albuminuria	0·810 (0·793 to 0·827)	<0·001
Smoking (yes vs. no)	1·024 (0·996 to 1·052)	0·09
Tablet diabetes treatment only (vs. diet treatment only)	1·036 (1·010 to 1·063)	0·006
Insulin diabetes treatment only (vs. diet treatment only)	1·219 (1·169 to 1·272)	<0·001
Tablet & insulin treatment (vs. diet treatment only)	0·995 (0·956 to 1·036)	0·81
Triple therapy	**1·129 (1·100 to 1·160)**	**<0·001**

The likelihood to reach target blood pressure increased by 13 % in the most active care units.

The following alternative covariates were tested as measure of care unit antihypertensive activity: Triple therapy, calcium antagonists, β-blockers, loop-diuretics, thiazide diuretics, renin-angiotensin system inhibitor, angiotensin II blocker, fixed pill combination of renin-angiotensin system inhibitor or angiotensin II blocker (RAAS blocking agent), proportion high-dose felodipine users, proportion high-dose amlodipine users, other antihypertensive drugs, and spironolactone.

Conclusion/interpretation

As a covariate of treatment intensity at the care unit, the percentage of patients receiving a combination of a thiazide diuretic, calcium antagonist and either a renin-angiotensin system inhibitor or angiotensin II blocker (triple therapy) was used.