

Supplemental material

eTable 1: Baseline characteristics stratified by WMH

	White Matter Hyperintensities								
	None/mild			Moderate			Severe		
	Higher BP target	Lower BP target	p	Higher BP target	Lower BP target	p	Higher BP target	Lower BP target	p
	n=213	n=244		n=208	n=198		n=208	n=189	
Demographics									
Age (years, mean±SD)	71.91 (5.20)	72.58 (5.38)	0.19	73.86 (5.33)	74.13 (6.41)	0.64	75.32 (6.52)	75.86 (5.87)	0.59
Female (n, %)	146 (68.5)	144 (59.0)	0.04		111 (56.6)	0.27	116 (56.3)	89 (52.7)	0.55
Race/ethnicity (n, %)			0.75			0.83			0.18
White	124 (58.2)	133 (54.5)		118 (56.7)	113 (57.7)		106 (51.5)	99 (58.6)	
Hispanic	73 (34.3)	88 (36.1)		65 (31.2)	63 (32.1)		67 (32.5)	52 (30.8)	
Black	12 (5.6)	19 (7.8)		21 (10.1)	15 (7.7)		26 (12.6)	17 (10.1)	
Other	4 (1.9)	4 (1.6)		4 (1.9)	5 (2.6)		7 (3.4)	1 (0.6)	
Education (n, %)			0.14			0.18			0.97
0-8 years	65 (30.5)	93 (38.1)		72 (34.6)	71 (36.2)		74 (35.9)	59 (34.9)	
9-12 years	80 (37.6)	73 (29.9)		64 (30.8)	73 (37.2)		67 (32.5)	57 (33.7)	
>12 years	68 (31.9)	78 (32.0)		72 (34.6)	52 (26.5)		65 (31.6)	53 (31.4)	
Cardiovascular risk factors									
Blood pressure (mmHg, mean±SD)									
Systolic	140.54 (17.99)	142.09 (17.45)	0.35	144.86 (19.19)	145.55 (19.38)	0.65	146.24 (17.82)	146.92 (21.86)	0.74
Diastolic	75.73 (9.88)	74.59 (9.36)	0.21	78.24 (10.22)	76.09 (10.55)	0.27	78.44 (10.37)	76.34 (10.09)	0.92
Body-mass index (kg/m ² , mean±SD)	28.08 (4.16)	27.73 (4.61)	0.41	28.03 (5.81)	27.91 (7.37)	0.85	27.25 (4.95)	27.02 (4.52)	0.64
History of hypertension (n, %)	155 (72.8)	178 (72.1)	0.96	154 (74.0)	158 (80.6)	0.15	175 (85.0)	134 (79.3)	0.20
Diabetes mellitus (n, %)	70 (32.9)	80 (32.8)	1.00	63 (30.3)	77 (39.3)	0.07	59 (28.6)	57 (33.7)	0.34
Previous stroke or TIA (n, %)	18 (8.5)	28 (11.5)	0.36	34 (16.3)	33 (16.8)	1.00	40 (19.4)	28 (16.6)	0.56
History of ischemic heart disease	28 (13.1)	19 (7.8)	0.08	31 (14.9)	18 (9.2)	0.11	21 (10.2)	20 (11.8)	0.73
Current smoking (n, %)	24 (11.3)	30 (12.3)	0.85	17 (8.2)	28 (14.3)	0.07	18 (8.7)	14 (8.3)	1.00
CKD (eGFR < 60ml/min; n, %)	42 (19.7)	42 (17.2)	0.57	44 (21.2)	56 (28.6)	0.11	57 (27.7)	55 (32.5)	0.36
Medication									
ACE inhibitors / AT2 antagonists	130 (61.0)	158 (64.8)	0.47	128 (61.5)	135 (68.9)	0.15	150 (72.8)	118 (69.8)	0.60
Calcium-channel blockers	43 (20.2)	54 (22.1)	0.70	48 (23.1)	48 (24.5)	0.83	58 (28.2)	39 (23.1)	0.32
Beta blockers	49 (23.0)	50 (20.5)	0.59	43 (20.7)	44 (22.4)	0.75	55 (26.7)	49 (29.0)	0.71
Diuretics	70 (32.9)	71 (29.1)	0.44	77 (37.0)	68 (34.7)	0.70	77 (37.4)	57 (33.7)	0.53
Other antihypertensive medications	7 (3.3)	17 (7.0)	0.12	25 (12.0)	15 (7.7)	0.19	17 (8.3)	17 (10.1)	0.67
Statin (n, %)	144 (67.6)	180 (85.6)	0.72	148 (71.2)	140 (71.4)	1.00	137 (66.5)	105 (62.1)	0.44
Modified Rankin stroke disability score (n, %)									
			0.78			0.19			0.15
Score = 0	40 (18.8)	48 (19.7)		36 (17.3)	25 (12.8)		22 (10.7)	29 (17.2)	
Score = 1	115 (54.0)	121 (49.6)		115 (55.3)	104 (53.1)		108 (52.4)	83 (49.1)	
Score = 2	38 (18.9)	49 (20.1)		39 (18.8)	38 (19.4)		47 (22.8)	42 (24.9)	
Score = 3	22 (10.3)	26 (10.7)		18 (8.7)	29 (14.8)		29 (14.1)	15 (8.9)	

Abbreviations: BP, blood pressure; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; n, number; SD, standard deviation

eTable 2: Baseline characteristics stratified by ADL limitations

	No limitations		p	1+ limitations		p
	Higher BP target	Lower BP target		Higher BP target	Lower BP target	
	n=432	n=390		n=213	n=228	
Barthel Activities of Daily Living limitations						
<i>Demographics</i>						
Age (years, mean±SD)	72.98 (5.32)	73.80 (5.93)	0.04	75.06 (6.59)	74.12 (6.08)	0.12
Female (n, %)	298 (68.5)	240 (61.5)	0.04	110 (51.6)	112 (49.1)	0.67
Race/ethnicity (n, %)			0.31			0.30
White	261 (60.4)	260 (66.7)		100 (46.9)	92 (40.4)	
Hispanic	122 (28.2)	95 (24.4)		88 (41.3)	110 (48.2)	
Black	40 (9.3)	28 (7.2)		19 (8.9)	23 (10.1)	
Other	9 (2.1)	7 (1.8)		6 (2.8)	3 (1.3)	
Education (n, %)			0.89			0.35
0-8 years	118 (27.3)	106 (27.2)		96 (45.1)	118 (51.8)	
9-12 years	154 (35.6)	145 (37.2)		65 (30.5)	64 (28.1)	
>12 years	160 (37.0)	139 (35.6)		52 (24.4)	46 (20.2)	
<i>Cardiovascular risk factors</i>						
Blood pressure (mmHg, mean±SD)						
Systolic	142.98 (17.80)	144.48 (18.96)	0.24	145.03 (19.29)	144.30 (19.89)	0.70
Diastolic	76.23 (10.02)	75.69 (9.68)	0.44	76.26 (10.28)	74.48 (10.31)	0.07
Body-mass index (kg/m ² , mean±SD)	28.08 (5.07)	27.30 (4.47)	0.02	27.26 (4.81)	28.02 (7.11)	0.21
History of hypertension (n, %)	330 (76.4)	300 (76.9)	0.92	169 (79.3)	175 (76.8)	0.59
Diabetes mellitus (n, %)	119 (27.5)	117 (30.0)	0.48	75 (35.2)	100 (43.9)	0.08
Previous stroke or TIA (n, %)	65 (15.1)	53 (13.6)	0.62	30 (14.1)	38 (16.7)	0.54
History of ischemic heart disease	63 (14.6)	33 (8.5)	0.01	18 (8.5)	26 (11.4)	0.38
Current smoking (n, %)	42 (9.7)	45 (11.5)	0.46	17 (8.0)	28 (12.3)	0.18
CKD (eGFR < 60ml/min; n, %)	94 (21.8)	104 (26.7)	0.12	56 (26.3)	51 (22.4)	0.40
<i>Medication</i>						
ACE inhibitors / AT2 antagonists	273 (63.2)	261 (66.9)	0.30	147 (69.0)	156 (68.4)	0.98
Calcium-channel blockers	105 (24.3)	86 (22.1)	0.50	47 (22.1)	59 (25.9)	0.41
Beta blockers	106 (24.5)	102 (26.2)	0.65	43 (20.2)	43 (18.9)	0.82
Diuretics	153 (35.4)	145 (37.2)	0.65	77 (36.2)	54 (23.7)	0.01
Other antihypertensive medications	35 (8.1)	28 (7.2)	0.72	16 (7.5)	21 (9.2)	0.64
Statin (n, %)	309 (71.5)	271 (69.5)	0.57	131 (61.5)	142 (62.3)	0.94
<i>Modified Rankin stroke disability score (n, %)</i>						
			0.21			0.37
Score = 0	91 (21.1)	102 (26.2)		10 (4.7)	4 (1.8)	
Score = 1	277 (64.1)	233 (59.7)		69 (32.4)	78 (34.2)	
Score = 2	58 (13.4)	53 (13.6)		71 (33.3)	77 (33.8)	
Score = 3	6 (1.4)	2 (0.5)		63 (29.6)	69 (30.3)	

Abbreviations: BP, blood pressure; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; n, number; SD, standard deviation

eTable 3: Medication use during follow-up by blood pressure treatment target

	Lower (<130 mmHg)	Higher (130-149 mmHg)	P-value
At 1 year after baseline (n, %)			
ACE inhibitors / AT2 antagonists	353 (65)	349 (61)	< 0.001
Calcium-channel blockers	235 (43)	167 (29)	< 0.001
Beta blockers	151 (28)	128 (22)	0.02
Diuretics	360 (67)	263 (46)	< 0.001
Other antihypertensive medications	74 (14)	52 (9)	0.03
Statins	353 (65)	383 (67)	0.60
Mean number of antihypertensive medications at 1 year after baseline (SD)	2.0 (1.4)	1.5 (1.3)	< 0.001
At last visit			
ACE inhibitors / AT2 antagonists	484 (78)	377 (58)	< 0.001
Calcium-channel blockers	271 (44)	179 (28)	< 0.001
Beta blockers	184 (30)	159 (25)	0.04
Diuretics	382 (62)	268 (42)	< 0.001
Other antihypertensive medications	81 (13)	73 (11)	0.33
Statins	407 (66)	430 (67)	0.76
Mean number of antihypertensive medications at last visit (SD)	2.3 (1.2)	1.6 (1.4)	< 0.001

Abbreviations: ACE, angiotensin converting enzyme; AT2, angiotensin 2; SD, standard deviation

eTable 4: Effect modification of WMH and disability on mean CASI Z-scores over time

	N	Predicted baseline CASI Z-score and change per year*				Between-group difference	P for interaction**	
		Higher BP target		Lower BP target			Group x time	Group x time x effect modifier
		Baseline	Change/y	Baseline	Change/y			
Overall	1227	-0.66±0.05	-0.01±0.01	-0.72±0.05	0.00±0.01	0.01 (-0.03 to 0.04)	0.71	-
WMH ***								
No/mild WMH	443	-0.39±0.09	0.03±0.02	-0.55±0.09	0.01±0.02	-0.02 (-0.08 to 0.04)	0.58	
Moderate WMH	391	-0.62±0.09	-0.03±0.02	-0.75±0.10	0.02±0.02	0.04 (-0.02 to 0.11)	0.21	0.42
Severe WMH	366	-1.04±0.09	-0.02±0.03	-0.92±0.10	-0.02±0.03	0.00 (-0.07 to 0.07)	0.80	
Disability								
No ADL limitations	794	-0.42±0.06	0.00±0.02	-0.44±0.07	0.00±0.02	0.00 (-0.04 to 0.05)	0.99	
1+ ADL limitation	433	-1.15±0.09	-0.01±0.02	-1.18±0.09	0.01±0.02	0.02 (-0.05 to 0.08)	0.40	0.66

Abbreviations: ADL, activities of daily living; BP, blood pressure; CASI, Cognitive Abilities Screening Instrument; N, number; SE, standard error; WMH, white matter hyperintensities; y, year

* Mean±SE from linear mixed models adjusted for age, sex and race. Between-group difference is mean (95% confidence interval) difference in change/year for lower vs. higher BP treatment target.

** Calculated from a two-way interaction (treatment group x time) and a three-way interaction (treatment group x effect modifier x time), using linear mixed model adjusted for age, sex and race.

*** WMH was missing for 27 participants (9 in lower BP target group, 18 in higher BP target group).

eTable 5: Sensitivity analyses for mean CASI Z-scores over time

	N	Predicted baseline CASI Z-score and change per year*				Between-group difference	P for interaction **		
		Higher BP target		Lower BP target			Group x time	Group x time x effect modifier	
		Baseline	Change/y	Baseline	Change/y				
Hypertensive participants at baseline ***	1,172	-0.66±0.05	0.00±0.01	-0.72±0.06	0.00±0.01	0.01 (-0.03 to 0.04)	0.73	-	
WMH									
None/mild	419	-0.37±0.09	0.03±0.02	-0.56±0.09	0.01±0.02	-0.02 (-0.08 to 0.05)	0.56		
Moderate	369	-0.66±0.10	-0.02±0.02	-0.76±0.10	0.02±0.02	0.05 (-0.02 to 0.11)	0.18	0.37	
Severe	358	-1.03±0.10	-0.02±0.03	-0.93±0.10	-0.02±0.03	0.00 (-0.07 to 0.07)	0.75		
Disability									
No ADL limitations	749	-0.43±0.07	0.00±0.02	-0.45±0.07	0.00±0.02	0.00 (-0.05 to 0.05)	0.97		
1+ ADL limitation	423	-1.13±0.09	0.00±0.02	-1.16±0.09	0.01±0.02	0.02 (-0.05 to 0.08)	0.41	0.70	
Adjustment for baseline imbalances ****	1,227	-0.66±0.05	-0.01±0.01	-0.72±0.05	0.00±0.01	0.01 (-0.03 to 0.04)	0.71	-	
WMH									
None/mild	443	-0.39±0.09	0.03±0.02	-0.55±0.09	0.01±0.02	-0.02 (-0.08 to 0.04)	0.58		
Moderate	391	-0.61±0.09	-0.03±0.02	-0.75±0.10	0.02±0.02	0.04 (-0.02 to 0.10)	0.21	0.42	
Severe	366	-1.04±0.09	-0.02±0.03	-0.91±0.10	-0.02±0.03	0.00 (-0.07 to 0.07)	0.80		
Disability									
No ADL limitations	794	-0.42±0.06	0.00±0.02	-0.44±0.07	0.00±0.02	0.00 (-0.04 to 0.05)	0.99		
1+ ADL limitation	433	-1.15±0.09	-0.01±0.02	-1.18±0.09	0.01±0.02	0.02 (-0.05 to 0.08)	0.40	0.66	

Abbreviations: ADL, activities of daily living; BP, blood pressure; CASI, Cognitive Abilities Screening Instrument; N, number; SE, standard error; WMH, white matter hyperintensities; y, year

* Mean±SE from linear mixed models adjusted for age, sex and race (and for history of diabetes, history of ischemic disease, and baseline diastolic blood pressure in the analysis adjusting for baseline imbalances). Between-group difference is mean (95% confidence interval) difference in change/year for lower vs. higher BP treatment target.

** Calculated from a two-way interaction (treatment group x time) and a three-way interaction (treatment group x effect modifier x time), using a linear mixed model.

*** Non-hypertensive participants without antihypertensive medication at baseline excluded.

**** Analysis was adjusted for age, sex, race, history of diabetes, history of ischemic disease, and baseline diastolic blood pressure.

eTable 6: Sensitivity analyses for incident MCI

	Lower BP target		Higher BP target		HR (95% CI) *	P-Value	P for interaction
	N	Events	N	Events			
Hypertensive participants at baseline **	272	84	277	96	0.87 (0.65 - 1.18)	0.37	-
WMH							
None/mild	117	33	113	40	0.83 (0.52 - 1.32)	0.42	
Moderate	81	23	83	30	0.84 (0.48 - 1.46)	0.54	0.93
Severe	70	26	67	21	1.03 (0.57 - 1.86)	0.92	
Disability							
No ADL limitations	194	56	203	66	0.95 (0.66 - 1.37)	0.78	
1+ ADL limitation	78	28	74	30	0.85 (0.49 - 1.44)	0.54	0.52
Adjustment for baseline imbalances ***	288	91	293	99	0.94 (0.70 - 1.25)	0.65	-
WMH							
None/mild	124	35	118	41	0.93 (0.58 - 1.49)	0.77	
Moderate	87	28	92	32	0.88 (0.52 - 1.49)	0.64	0.89
Severe	72	26	69	21	1.00 (0.55 - 1.84)	0.99	
Disability							
No ADL limitations	209	62	217	68	1.08 (0.75 - 1.54)	0.68	
1+ ADL limitation	79	29	76	31	0.95 (0.55 - 1.61)	0.85	0.44

* Lower vs. higher target. Analysis was adjusted for age, sex and race.

** Non-hypertensive participants without antihypertensive medication at baseline excluded.

*** Analysis was adjusted for age, sex, race, history of diabetes, history of ischemic disease, and baseline diastolic blood pressure.

Abbreviations: ADL, activities of daily living; BP, blood pressure; CI, confidence interval; HR, hazard ratio; MCI, mild cognitive impairment; N, number; WMH, white matter hyperintensities

eTable 7: Sensitivity analyses for all stroke

	Lower BP target		Higher BP target		HR (95% CI) *	P-Value	P for interaction
	N	Events	N	Events			
Hypertensive participants at baseline **	593	55	613	66	0.89 (0.62 - 1.27)	0.52	-
WMH							
None/mild	232	22	200	9	2.33 (1.07 - 5.08)	0.03	
Moderate	187	15	194	22	0.74 (0.38 - 1.44)	0.38	0.02
Severe	166	17	201	34	0.57 (0.32 - 1.03)	0.06	
Disability							
No ADL limitations	369	30	407	39	0.91 (0.56 - 1.47)	0.71	0.84
1+ ADL limitation	224	25	206	27	0.87 (0.50 - 1.51)	0.63	
Adjustment for baseline imbalances ***	618	57	645	67	0.90 (0.63 - 1.28)	0.56	-
WMH							
None/mild	244	23	213	9	2.48 (1.14 - 5.41)	0.02	
Moderate	196	15	208	23	0.67 (0.35 - 1.30)	0.23	0.01
Severe	169	18	206	34	0.61 (0.34 - 1.09)	0.10	
Disability							
No ADL limitations	390	31	432	40	0.93 (0.58 - 1.50)	0.78	0.85
1+ ADL limitation	228	26	213	27	0.92 (0.53 - 1.59)	0.76	

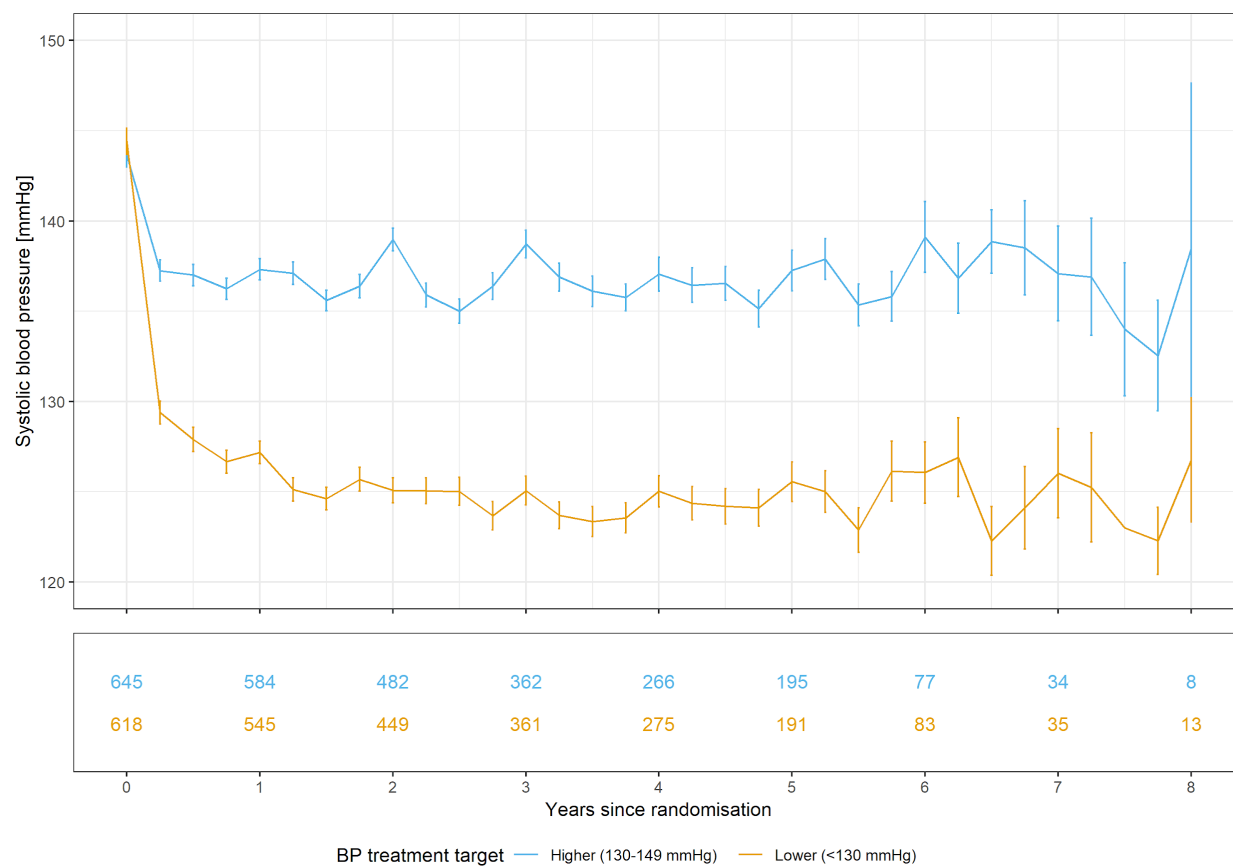
* Lower vs. higher target. Analysis was adjusted for age, sex and race.

** Non-hypertensive participants without antihypertensive medication at baseline excluded.

*** Analysis was adjusted for age, sex, race, history of diabetes, history of ischemic disease, and baseline diastolic blood pressure.

Abbreviations: ADL, activities of daily living; BP, blood pressure; CI, confidence interval; HR, hazard ratio; N, number; WMH, white matter hyperintensities

eFigure 1: Systolic blood pressure by treatment group over time



Data shown are mean systolic blood pressure; error bars indicate standard error.
Abbreviations: BP, blood pressure