Supplemental Appendix

Low presenting blood pressure and adverse outcomes in acute stroke: HeadPoST study explanations

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Supplemental Appendix. Multiple imputation methods

Multiple imputation was used to impute missing outcome data, using PROC MI and PROC MIANALYZE in SAS version 9.2 (or later) software. Multiple imputation is generally considered the least biased method since it incorporates uncertainty to the imputed value, and a non-monotone missing pattern is assumed modified Rankin scale (mRS) score at 90 days. A distribution for the outcome will be derived from a regression model that accounts for covariates (listed in the generalized linear mixed model) and a random sample from this distribution will be used to impute values for missing outcomes and covariates. Ten multiple sample data sets with complete outcome data will be generated through PROC MI using the fully conditional method (FCS) methods, the results (regression parameter and covariance matrix estimates) for each sample combined and analyzed with PROC MIANALYZE to derive a valid statistical inference about the association with outcomes.

Table e-1. Baseline characteristics by diastolic blood pressure

Variable	Diastolic blood pressure, mmHg			P value
	<70	70-89	≥90	
Number of patients	1301 (11.7)	5118 (46.2)	4664 (42.1)	
Age, yr	73 (±13.5)	69 (±13.5)	66 (±13.6)	<0.0001
Female	646 (49.7)	2048 (40.0)	1729 (37.1)	<0.0001
Region				<0.0001
Australia and UK	807 (62.0)	2209 (43.1)	1738 (37.3)	
China and Taiwan	330 (25.4)	2195 (42.9)	2127 (45.6)	
India and Sri Lanka	49 (3.8)	322 (6.3)	399 (8.6)	
South America	115 (8.8)	392 (7.7)	400 (8.6)	
Clinical features				
Final pathological type of stroke				<0.0001
AIS	1131 (87.2)	4436 (86.9)	3895 (83.7)	
ICH	71 (5.5)	320 (6.3)	539 (11.6)	
Uncertain	95 (7.3)	349 (6.8)	218 (4.7)	
Severity of neurological impairment, NIHSS score*	5.0 (2.0-10.0)	4.0 (2.0-8.0)	4.0 (2.0-8.0)	<0.0001
Score ≥15	201 (15.8)	524 (10.4)	482 (10.5)	<0.0001
SBP, mmHg	132 (116-149)	144 (130-160)	167 (150-186)	<0.0001
DBP, mmHg	63 (60-66)	80 (75-84)	100 (92-106)	<0.0001
Time from stroke onset, hr	5.6 (1.9-21.4)	8.1 (2.4-30.0)	7.4 (2.3-25.3)	<0.0001
Medical history				
Hypertension	814 (62.8)	3116 (61.0)	3218 (69.1)	<0.0001
Current treatment	690 (53.0)	2495 (48.7)	2431 (52.1)	<0.0001
Number of antihypertensive drugs	1.0 (1.0-2.0)	1.0 (1.0-2.0)	1.0 (1.0-2.0)	<0.0001
Diabetes mellitus	316 (24.4)	1282 (25.1)	1052 (22.6)	0.013
Atrial fibrillation	207 (16.0)	547 (10.8)	435 (9.4)	<0.0001
Coronary artery disease	268 (20.8)	733 (14.4)	539 (11.6)	<0.0001
Heart failure	88 (6.9)	204 (4.0)	121 (2.6)	<0.0001
Previous stroke	307 (23.7)	1191 (23.3)	1107 (23.8)	0.8596
Smoking	211 (16.4)	950 (18.8)	963 (20.8)	0.0010
High level of pre-morbid function (mRS 0-1)†	928 (71.4)	4050 (79.3)	3755 (80.6)	<0.0001
Hypercholesterolemia	435 (33.6)	1317 (25.9)	979 (21.1)	<0.0001
COPD/emphysema	74 (5.4)	180 (3.6)	152 (3.3)	0.0001
Medications				
Aspirin/other antiplatelet	641 (49.4)	2546 (49.8)	2211 (47.4)	0.0599
Anticoagulation	155 (11.9)	429 (8.4)	367 (7.9)	<0.0001
Statin/other lipid lowering	388 (29.8)	1119 (21.9)	788 (16.9)	<0.0001

Data are mean (SD), median (IQR), and n (%)

Analyses were ANOVA test for normally distributed variables, Kruskal-Wallis test for skewed continuous variables, and Chi-squared test for categorical variables.

AIS denotes acute ischemic stroke, DBP diastolic blood pressure, COPD chronic obstructive pulmonary disease, ICH intracerebral hemorrhage, mRS modified Rankin scale, NIHSS National Institutes of Health Stroke Scale, SBP systolic blood pressure, UK United Kingdom

*NIHSS is measure of neurological impairment caused by a stroke, composed of 11 items, each of which scores a specific ability between a 0 and 4. For each item, a score of 0 typically indicates normal function in that specific ability, while a higher score is indicative of some level of impairment. The individual scores from each item are summed in order to calculate a patient's total NIHSS score, ranging from 0 to 42.

†The mRS represents a global, 7-level assessment of disability, in which scores of 0 or 1 indicate good function without or with symptoms but no disability, scores of 2 indicates slight disability, 3 to 5 indicate increasing levels of disability (and dependency), and a score of 6 indicates death (not used).

Table e-2. Associations between baseline characteristics with low baseline systolic blood pressure

Variable	aOR (95% CI)	P value
Age, every 10 yrs increases	0.83 (0.78-0.88)	<0.0001
Female	0.95 (0.80-1.11)	0.5100
Region		<0.0001
Australia and UK	0.76 (0.54-1.06)	
China and Taiwan	0.46 (0.32-0.65)	
India and Sri Lanka	0.90 (0.58-1.40)	
South America	Reference	
Final pathological type of stroke		<0.0001
AIS	Reference	
ICH	0.56 (0.40-0.80)	
Uncertain	1.47 (1.11-1.94)	
Severity of neurological impairment, NIHSS every 5 score increases*	1.07 (1.01-1.14)	0.0465
Hypertension	0.48 (0.41-0.56)	<0.0001
Diabetes mellitus	0.81 (0.67-0.99)	0.0360
Atrial fibrillation	1.41 (1.10-1.80)	0.0073
Coronary disease	1.60 (1.29-1.99)	<0.0001
Heart failure	1.68 (1.20-2.36)	0.0025
Smoking	1.13 (0.93-1.37)	0.2318
High level of pre-morbid function (mRS 0-1) †	0.73 (0.59-0.88)	0.0010
Time from stroke onset, every 5 hrs	1.01 (0.99-1.03)	0.1018
Aspirin/other antiplatelet	0.95 (0.79-1.14)	0.5608
Anticoagulation	0.90 (0.68-1.20)	0.4806

AIS denotes acute ischemic stroke, aOR adjusted odds ratio, CI confidence interval, ICH intracerebral hemorrhage, mRS modified Rankin scale, NIHSS National Institutes of Health Stroke Scale, UK United Kingdom

Generalized linear mixed model adjusted for the study design (fixed effects of head position lying-flat versus sitting-up and cross-over period, random effects of cluster, and random interaction effects between cluster and crossover period) and clinical risk factors with $p<0.1$ listed in the Table 1.

*NIHSS is measure of neurological impairment caused by a stroke, composed of 11 items, each of which scores a specific ability between a 0 and 4. For each item, a score of 0 typically indicates normal function in that specific ability, while a higher score is indicative of some level of impairment. The individual scores from each item are summed in order to calculate a patient's total NIHSS score, ranging from 0 to 42.

†The mRS represents a global, 7-level assessment of disability, in which scores of 0 or 1 indicate good function without or with symptoms but no disability, scores of 2 indicates slight disability, 3 to 5 indicate increasing levels of disability (and dependency), and a score of 6 indicates death (not used).

Table e-3. Outcomes by categorical diastolic blood pressure

	Diastolic blood pressure, mmHg			
Outcome	**<70**	**70-89**	**≥90**	**P value***
Death or dependency (mRS* 3-6)	575/1128† (51.0)	1740/4473† (38.9)	1505/4138† (36.4)	<0.0001
Disability (mRS* 3-5)	438/1128 (38.8)	1384/4473 (30.9)	1202/4138 (29.0)	<0.0001
Death	137/1128 (12.1)	356/4473 (8.0)	303/4138 (7.3)	<0.0001
SAE	233/1301‡ (17.9)	716/5118‡ (14.0)	590/4664‡ (12.7)	<0.0001
Recurrent stroke	81/1301 (6.2)	249/5118 (4.9)	197/4664 (4.2)	0.0098
Cardiac or other vascular events	30/1301 (2.3)	116/5118 (2.3)	89/4664 (1.9)	0.4161
Pneumonia	41/1301 (3.2)	136/5118 (2.7)	115/4664 (2.5)	0.3899
Other infection	22/1301 (1.7)	56/5118 (1.1)	43/4664 (0.9)	0.0617
Other SAE	54/1301 (4.2)	124/5118 (2.4)	107/4664 (2.3)	0.0006

Data are n/N (%) and P value from Chi-squared test

DBP donates diastolic blood pressure, mRS modified Rankin Scale, SAE serious adverse event.

* The mRS represents a global, 7-level assessment of disability, in which scores of 0 or 1 indicate good function without or with symptoms but no disability, scores of 2 indicates slight disability, 3 to 5 indicate increasing levels of disability (and dependency), and a score of 6 indicates death.

†N is according to total number of patients at 90-day follow up

‡N is according to total number of patients randomized

Table e-4. NIHSS at Day 7/before discharge by categorical blood pressure (BP)

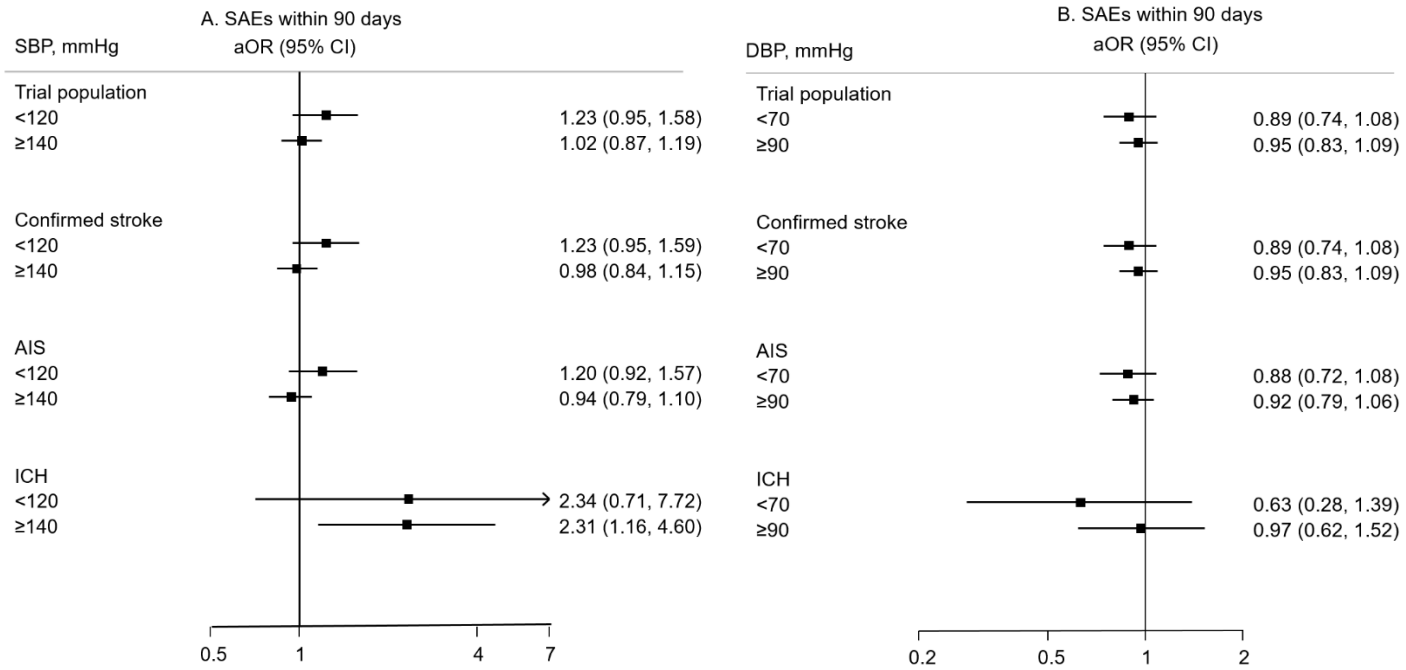
Categorical BP	NIHSS* at day 7/before discharge	P value†
SBP, mmHg		0.0013
<120	2.0 (1.0-6.0)	
120-139	2.0 (1.0-5.0)	
⩾140	2.0 (1.0-6.0)	
DBP, mmHg		0.0353
<70	2.0 (1.0-6.0)	
71-90	2.0 (1.0-6.0)	
⩾90	2.0 (1.0-6.0)	

BP donates blood pressure, DBP diastolic blood pressure, NIHSS National Institute Health Stroke Scale, SBP systolic blood pressure

*NIHSS is measure of neurological impairment caused by a stroke, composed of 11 items, each of which scores a specific ability between a 0 and 4. For each item, a score of 0 typically indicates normal function in that specific ability, while a higher score is indicative of some level of impairment. The individual scores from each item are summed in order to calculate a patient's total NIHSS score, ranging from 0 to 42.

†Kruskal-Wallis Test for P value;

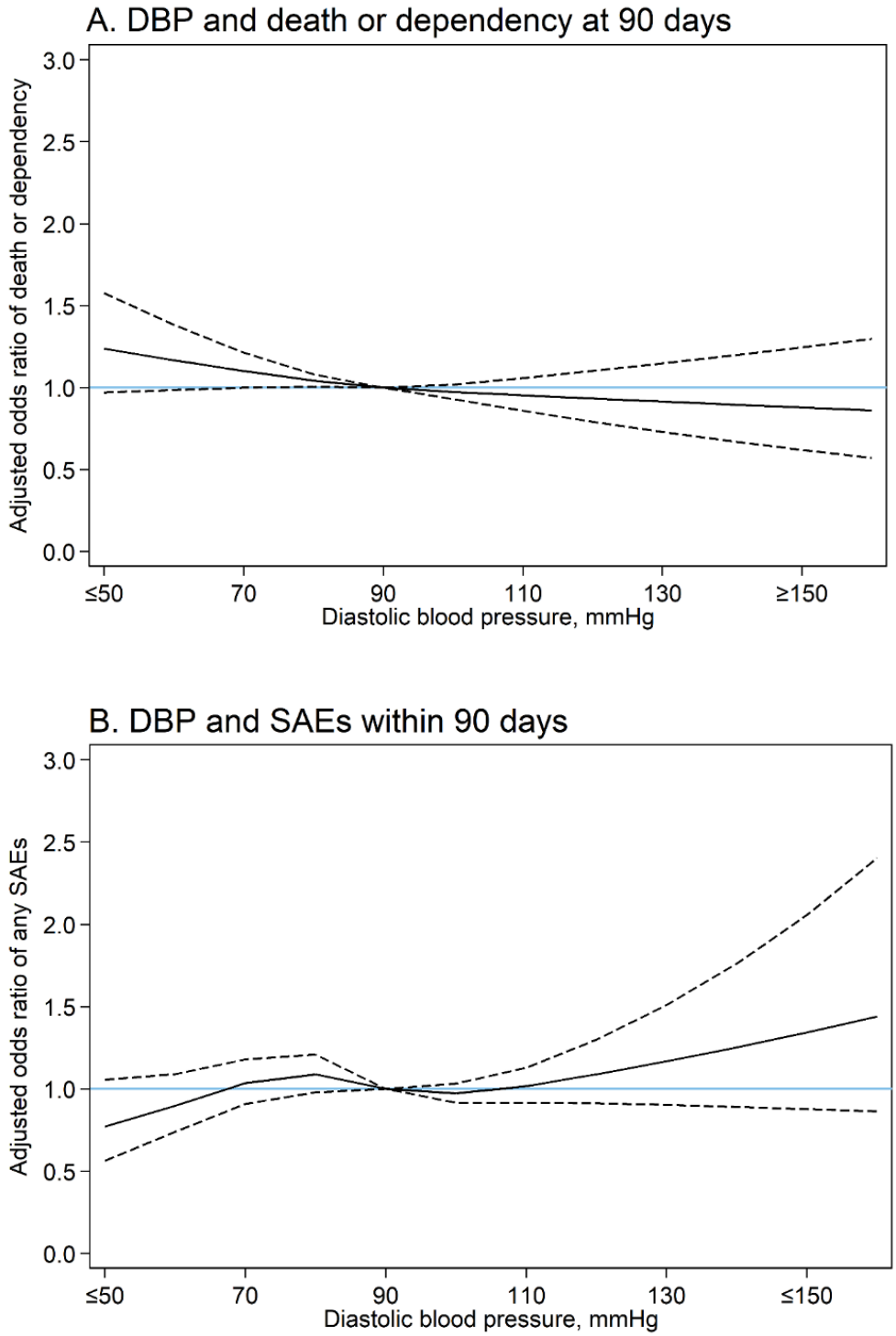
Figure e-1. Association of baseline blood pressure and any SAEs within 90 days



Footnote: AIS donates acute ischemic stroke, aOR donates adjusted odds ratio, CI confidence interval, DBP diastolic blood pressure, ICH intracerebral hemorrhage, SAE serious adverse events, SBP systolic blood pressure

Generalized linear mixed model adjusted for the fixed effects of head position (lying-flat versus sitting-up) and cross-over period, random effects of cluster, and random interaction effects between cluster and cross-over period, and prognostic variables including region, age, sex, National Institutes of Health Stroke Scale score, pre-morbid function according to the modified Rankin scale (0-1, independent; 2-5 disabled), stroke type, history of coronary artery disease, heart failure, hypertension, atrial fibrillation, and diabetes mellitus, aspirin/ other antiplatelet, anticoagulant treatment, time from stroke onset to hospital arrival and current smoking. A. SBP reference 120-139 mmHg; B. DBP reference 70-89 mmHg. Square boxes indicate odds ratios; line indicates 95% confidence intervals.

Figure e-2. Restricted cubic spline regression of baseline DBP and clinical outcomes at 90 days

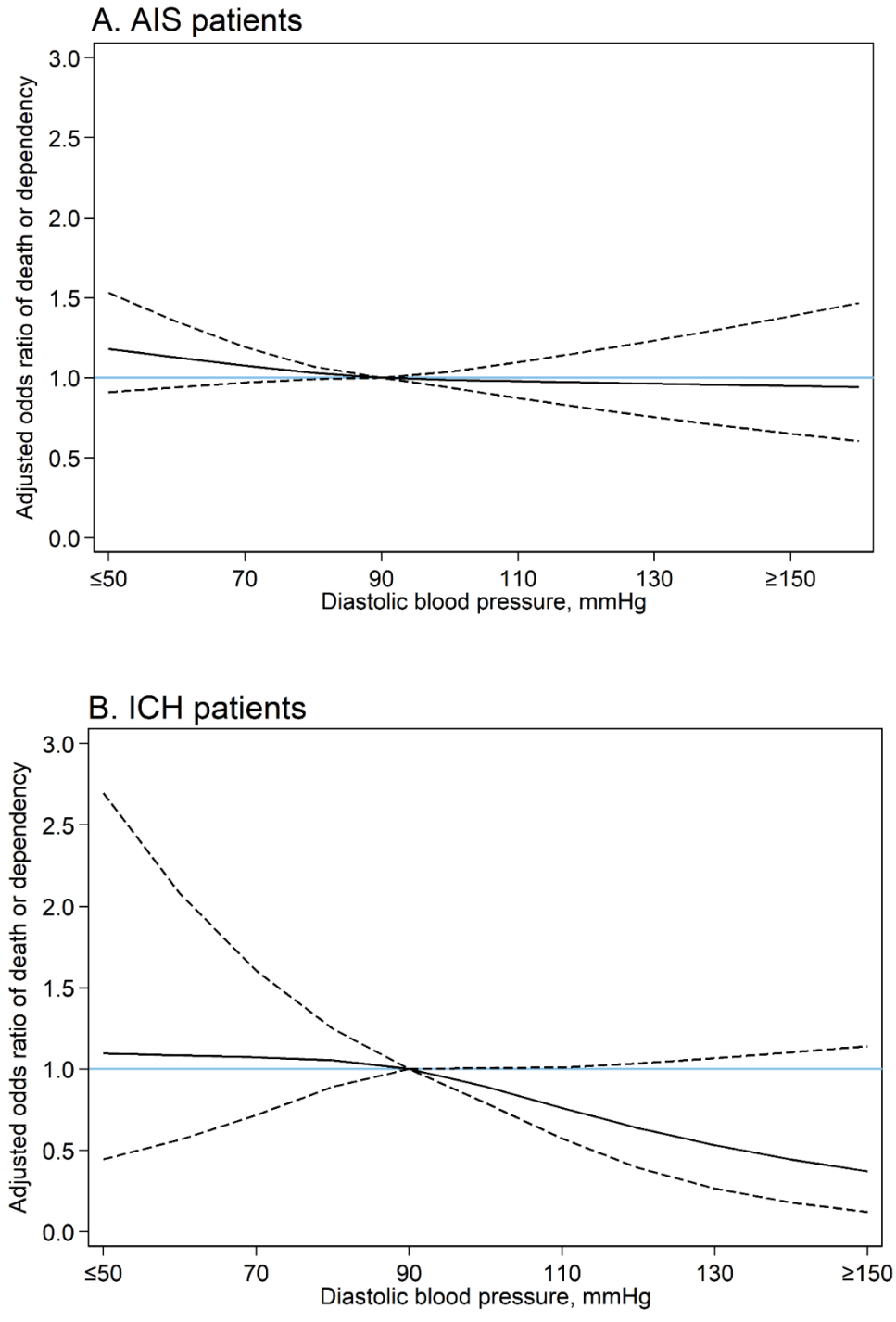


Footnote:

DBP donates diastolic blood pressure, SAE serious adverse events, SBP systolic blood pressure. Generalized linear mixed models with adjustment for study design (fixed effects of head position and cross-over period, random effects of cluster, and random interaction effects between cluster and crossover period) and potential confounders of age, sex, region, past

history of diabetes mellitus, hypertension, heart failure, atrial fibrillation, coronary heart disease, hyperlipidemia and chronic obstructive pulmonary disease, National Institutes of Health Stroke Scale, stroke type, pre-morbid score 0-1 on the modified Rankin Scale, aspirin/ other antiplatelet, anticoagulant treatment, time from stroke onset to hospital arrival and current smoking. A. Splines fitted with 3 knots (percentiles 10^{th}, 50^{th}, 95^{th}) for DBP; B. Splines fitted with 4 knots (percentiles 5^{th}, 35^{th}, 65^{th}, 95^{th}) for DBP. Reference diastolic blood pressure 90 mmHg. Solid line indicates odds ratios; dotted line indicates 95% confidence intervals.

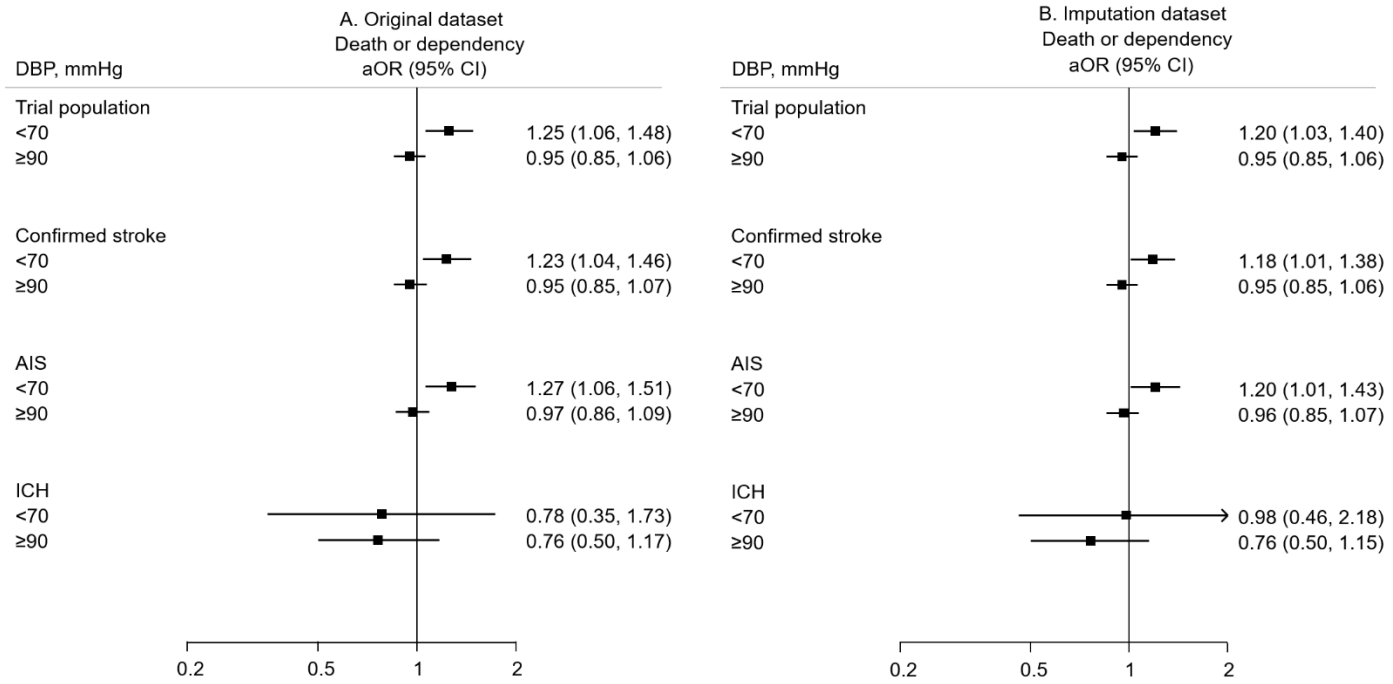
Figure e-3. Restricted cubic spline regression of baseline DBP and 90-day death or dependency (mRS 3-6), by stroke subtype



Footnote: AIS donates acute ischemic stroke, DBP diastolic blood pressure, ICH donates intracerebral hemorrhage. Generalized linear mixed model adjusted for the fixed effects of head position (lying-flat versus sitting-up) and cross-over period, random effects of cluster, and random interaction effects between cluster and crossover period and potential confounders: age, sex, region groups, history of diabetes mellitus, hypertension, heart failure, atrial fibrillation, coronary heart disease, hyperlipidemia and chronic obstructive pulmonary

disease, National Institutes of Health Stroke Scale, stroke type, pre-morbid score 0-1 on the modified Rankin Scale, aspirin/ other antiplatelet, anticoagulant treatment, time from stroke onset to hospital arrival and current smoking. Splines fitted with 3 knots (percentiles 10^{th}, 50^{th}, 95^{th}) for DBP. Reference diastolic blood pressure 90 mmHg. Solid line indicates odds ratios; dotted line indicates 95% confidence interval

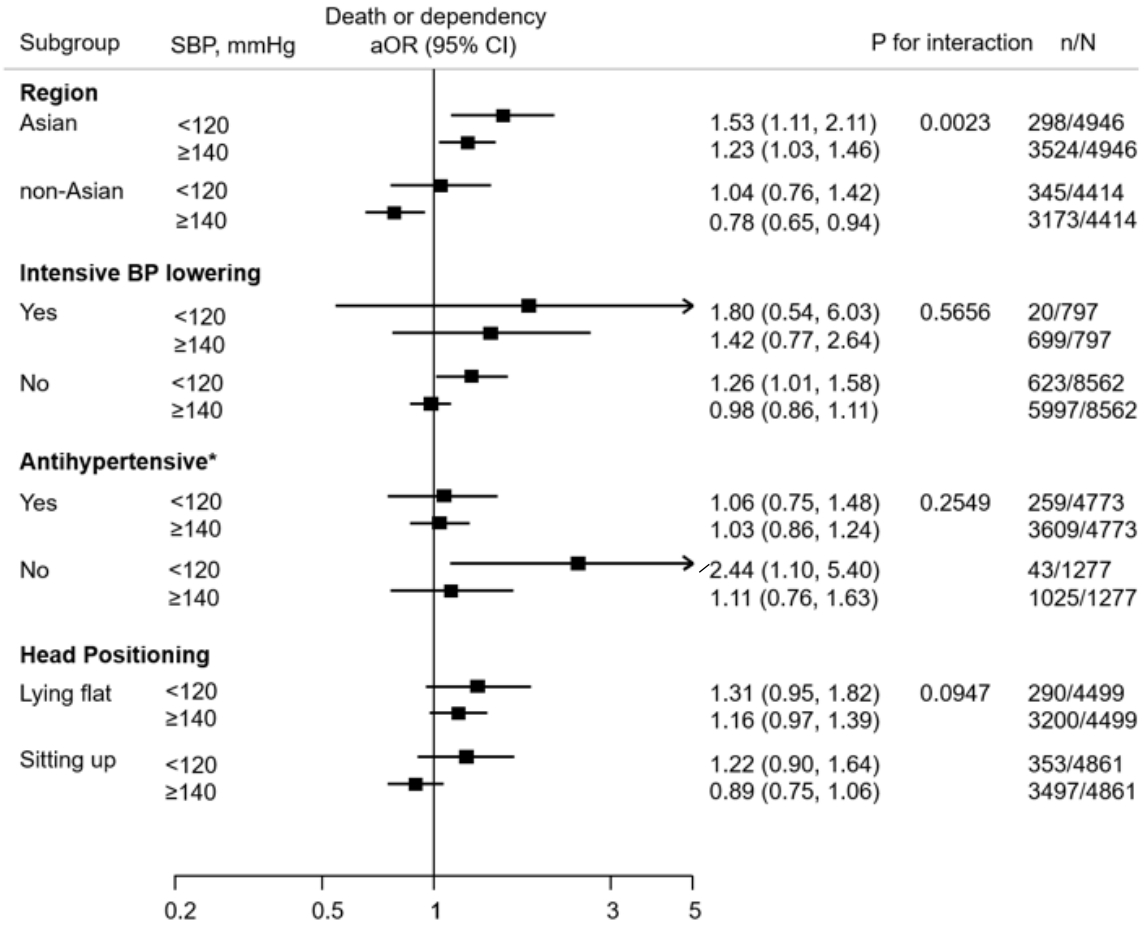
Figure e-4. Association of categorical baseline DBP and death or dependency (mRS 3-6) at 90 days, by type of dataset



Footnote: AIS denotes acute ischemic stroke, aOR adjusted odds ratio, CI confidence interval, DBP diastolic blood pressure, ICH intracerebral hemorrhage, mRS modified Rankin Scale

Generalized linear mixed model adjusted for study design (fixed effects of head position [lying-flat versus sitting-up] and cross-over period, random effects of cluster, and random interaction effects between cluster and cross-over period) and region, age, sex, National Institutes of Health Stroke Scale (NIHSS) score, pre-morbid function according to mRS, stroke type, history of diabetes mellitus, hypertension, heart failure, atrial fibrillation, coronary heart disease, hyperlipidemia and chronic obstructive pulmonary disease, National Institutes of Health Stroke Scale, stroke type, pre-morbid score 0-1 on the modified Rankin Scale, aspirin/ other antiplatelet, anticoagulant treatment, time from stroke onset to hospital arrival and current smoking. Reference diastolic blood pressure 70-89 mmHg; Square boxes indicate point estimate of odds ratios, solid line indicates 95% confidence intervals.

Figure e-5. Baseline systolic blood pressure and death or dependency (mRS 3-6) at 90 days, by pre-specified subgroups



Footnote:

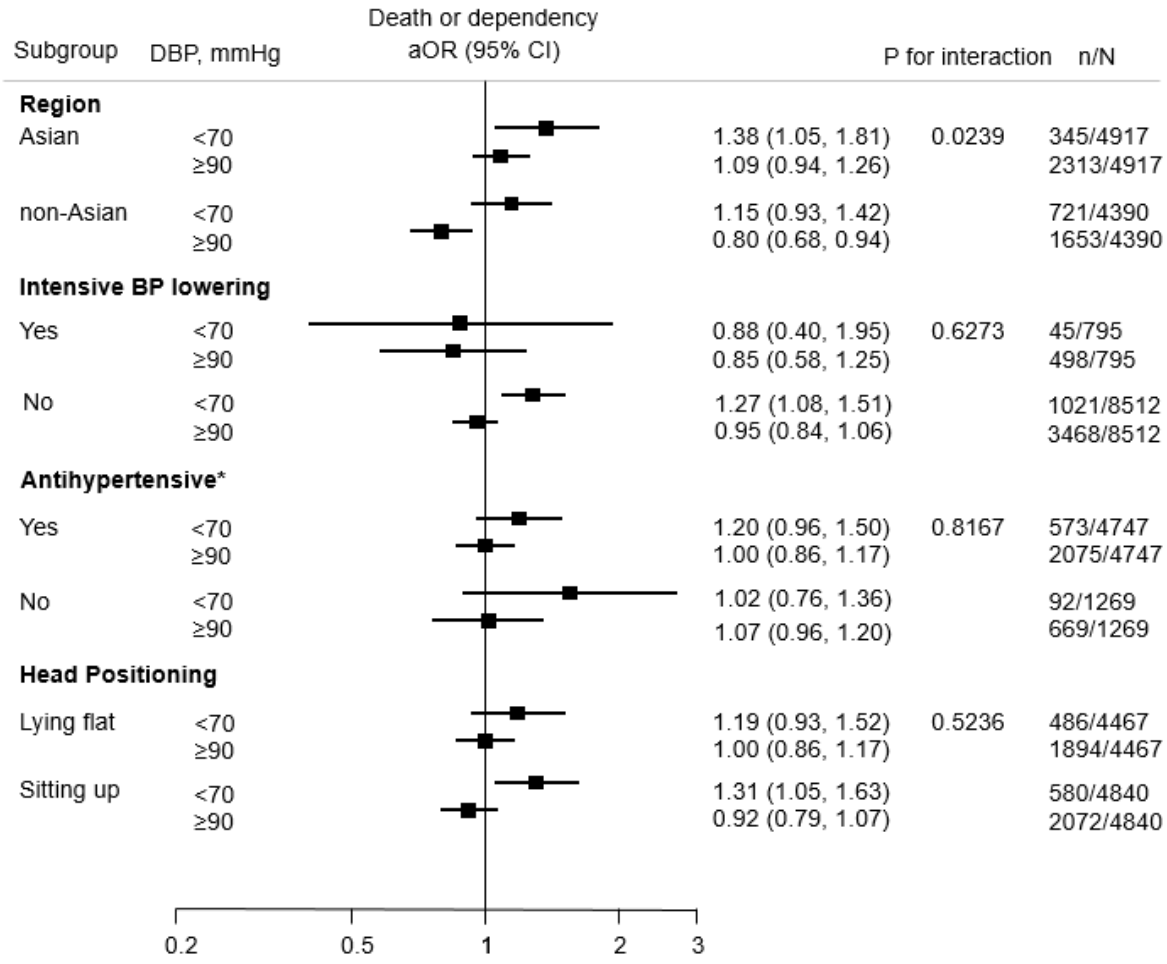
*Only includes patients with history of hypertension

aOR donates to adjusted odds ratio, BP blood pressure, mRS modified Rankin Scale, SBP systolic blood pressure

Generalized linear mixed models adjusted for the fixed effects of head position (lying-flat versus sitting-up) and cross-over period, random effects of cluster, and random interaction effects between cluster and cross-over period together with prognostic variables including age, sex, region, history of diabetes mellitus, hypertension, heart failure, atrial fibrillation, coronary artery disease, National Institutes of Health Stroke Scale, stroke type, pre-morbid function according to modified Rankin scale, aspirin/ other antiplatelet, anticoagulant treatment, time from stroke onset to hospital arrival and current smoking.

Reference systolic blood pressure120-139 mmHg. Square boxes indicate odds ratios; line indicates 95% confidence intervals.

Figure e-6. Baseline diastolic blood pressure and death or dependency (mRS 3-6) at 90 days, by pre-specified subgroups



Footnote:

*Only includes patients with history of hypertension

aOR donates to adjusted odds ratio, BP blood pressure, DBP diastolic blood pressure, mRS modified Rankin Scale

Generalized linear mixed models adjusted for the fixed effects of head position (lying-flat versus sitting-up) and cross-over period, random effects of cluster, and random interaction effects between cluster and crossover period together with prognostic variables including age, sex, region, history of diabetes mellitus, hypertension, heart failure, atrial fibrillation, coronary artery disease, hyperlipidemia and chronic obstructive pulmonary disease, National Institutes of Health Stroke Scale, stroke type, pre-morbid function according to modified Rankin scale, aspirin/ other antiplatelet, anticoagulant treatment, time from stroke onset to hospital arrival and current smoking.

Reference diastolic blood pressure 70-89 mmHg. Square boxes indicate odds ratios; line indicates 95% confidence intervals.