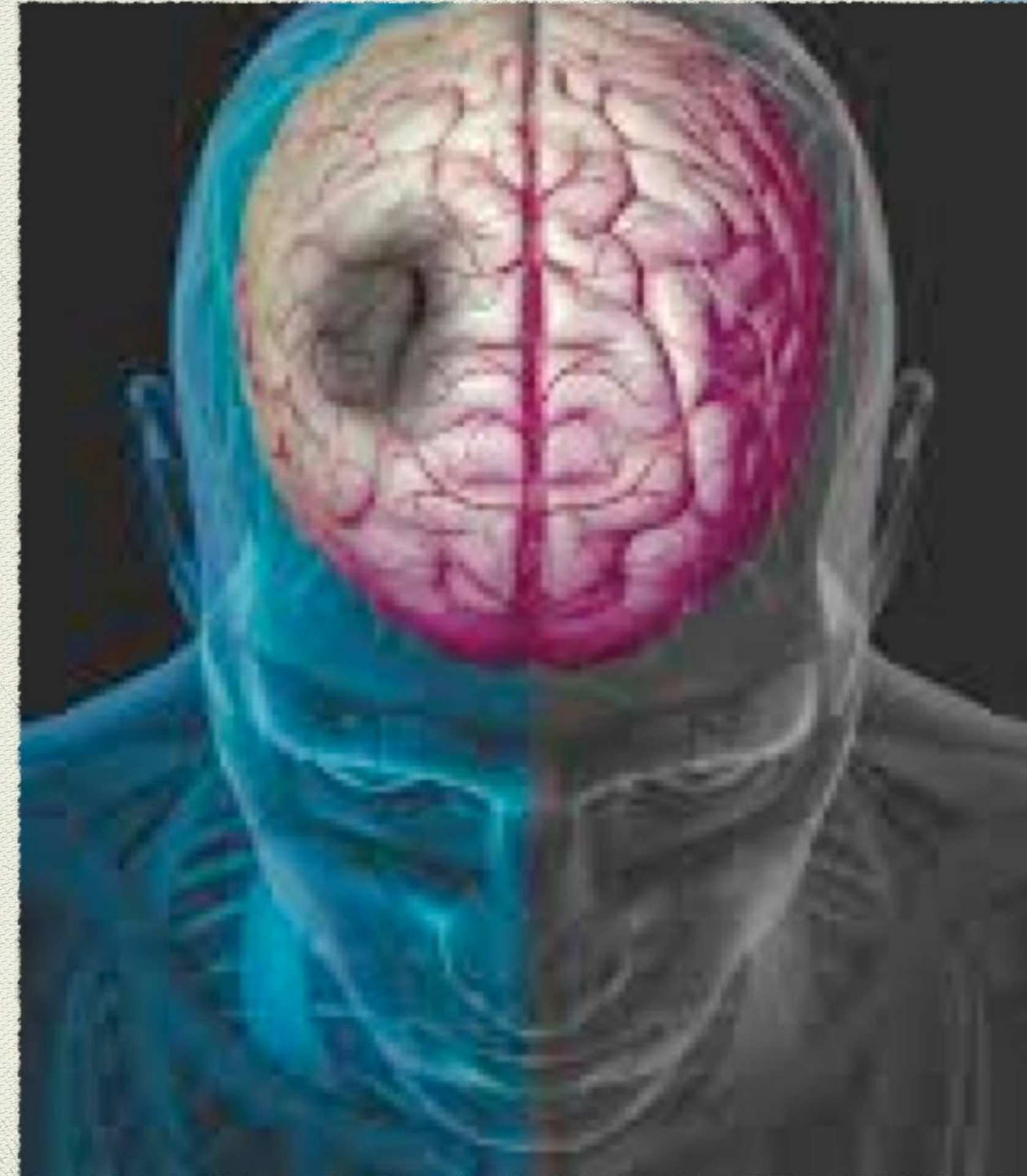# Cerebral Blood Pressure Targets

Cenker EKEN

Akdeniz University Medical Faculty

Department of Emergency Medicine

Soma Mine Disaster

Ischemic Stroke

Limited to

What can ED physicians do for stroke patients alternatively?

Thrombolytic Therapy
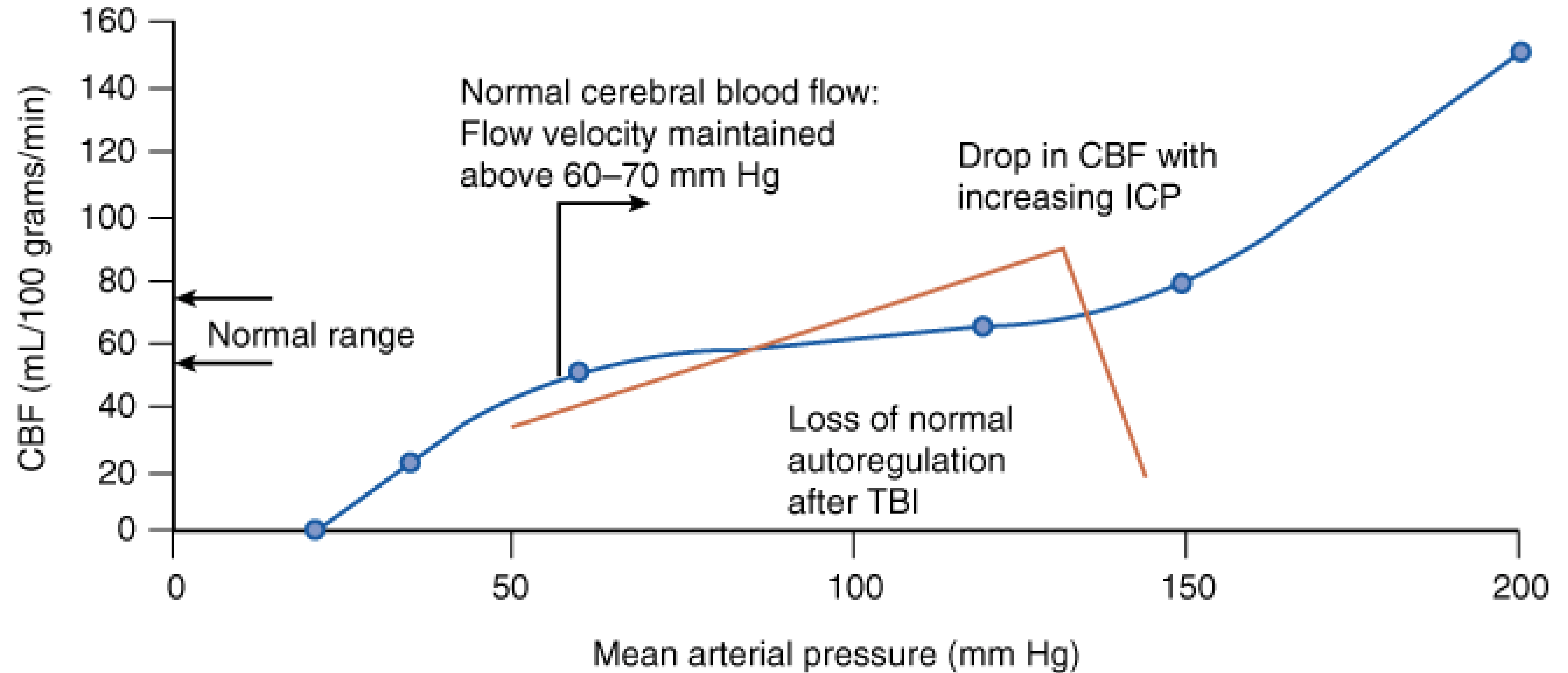
Blood Pressure in Acute Setting of Stroke

- Over 60% of patients with either ischemic or hemorrhagic stroke have elevated blood pressure in the ED.

- 15% of them over 184 mmHg.

- Acute hypertensive response

- A physiologic response

- Disruption of autonomic control

  - Increased sympathetic control

  - Impaired parasympathetic activity

Cerebral Autoregulation

- If the blood pressure exceeds the upper limit of auto-regulation may result with cerebral edema or blood-brain barrier dysfunction.

- However, if the blood pressure decreased the lower limit of auto-regulation may result with decreased perfusion, worsening ischemia or stroke progression.

Normotensive   Chronic Hypertensi

Mean Arterial Pressure

Right shift of cerebral autoregulation in normot hypertensive patients.
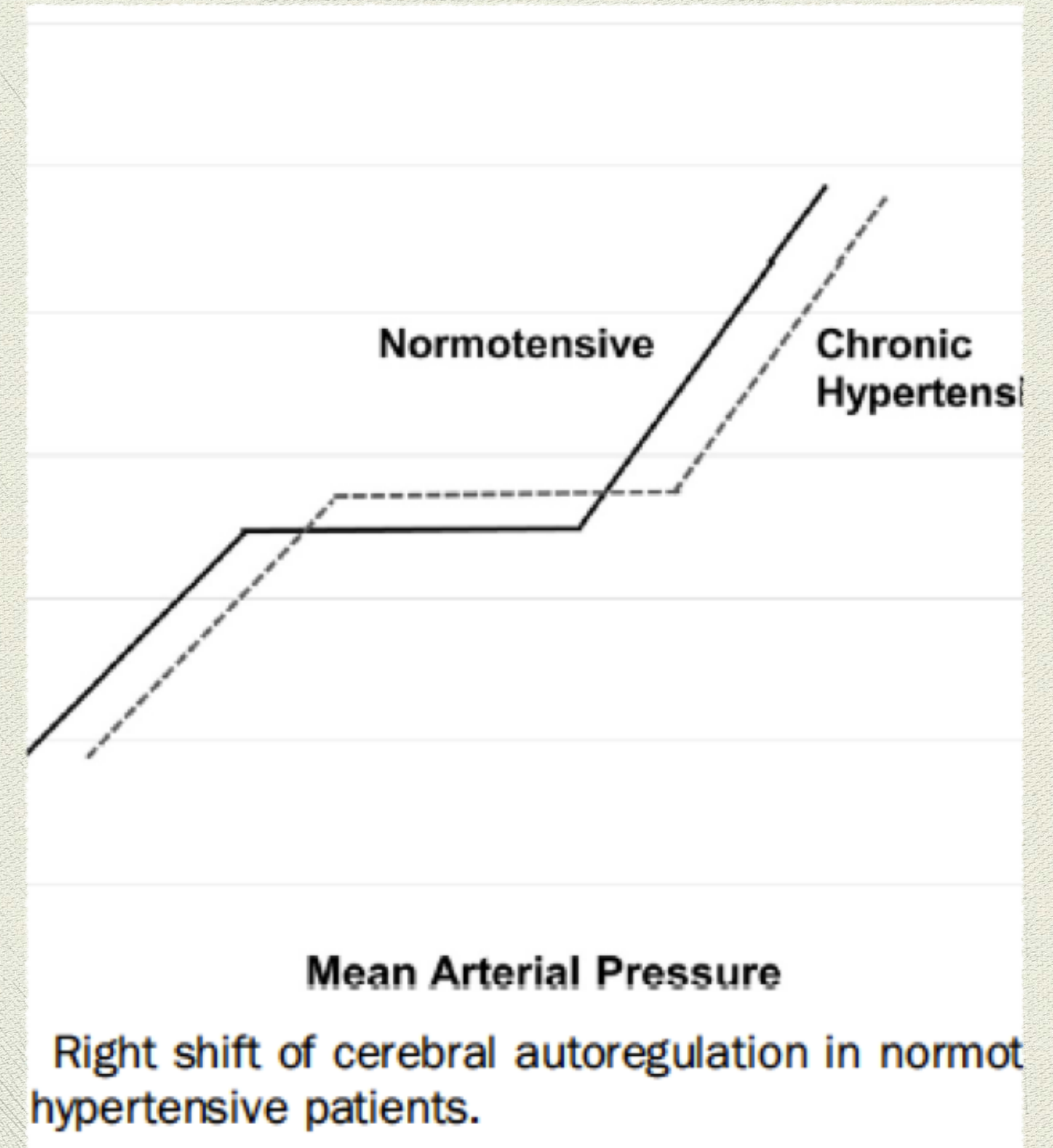
Why is Elevated Blood Pressure Important?

- Have prognostic significance

- Related with cardiovascular events, renal injury and encephalopathy

- May promote hemorrhage propagation

- May increase the likelihood of hemorrhagic transformation in ischemic stroke

Blood Pressure and Clinical Outcomes in the International Stroke Trial

Jo Leonardi-Bee, Philip M.W. Bath, Stephen J. Phillips and Peter A.G. Sandercock.
Stroke. 2002;33:1315-1320
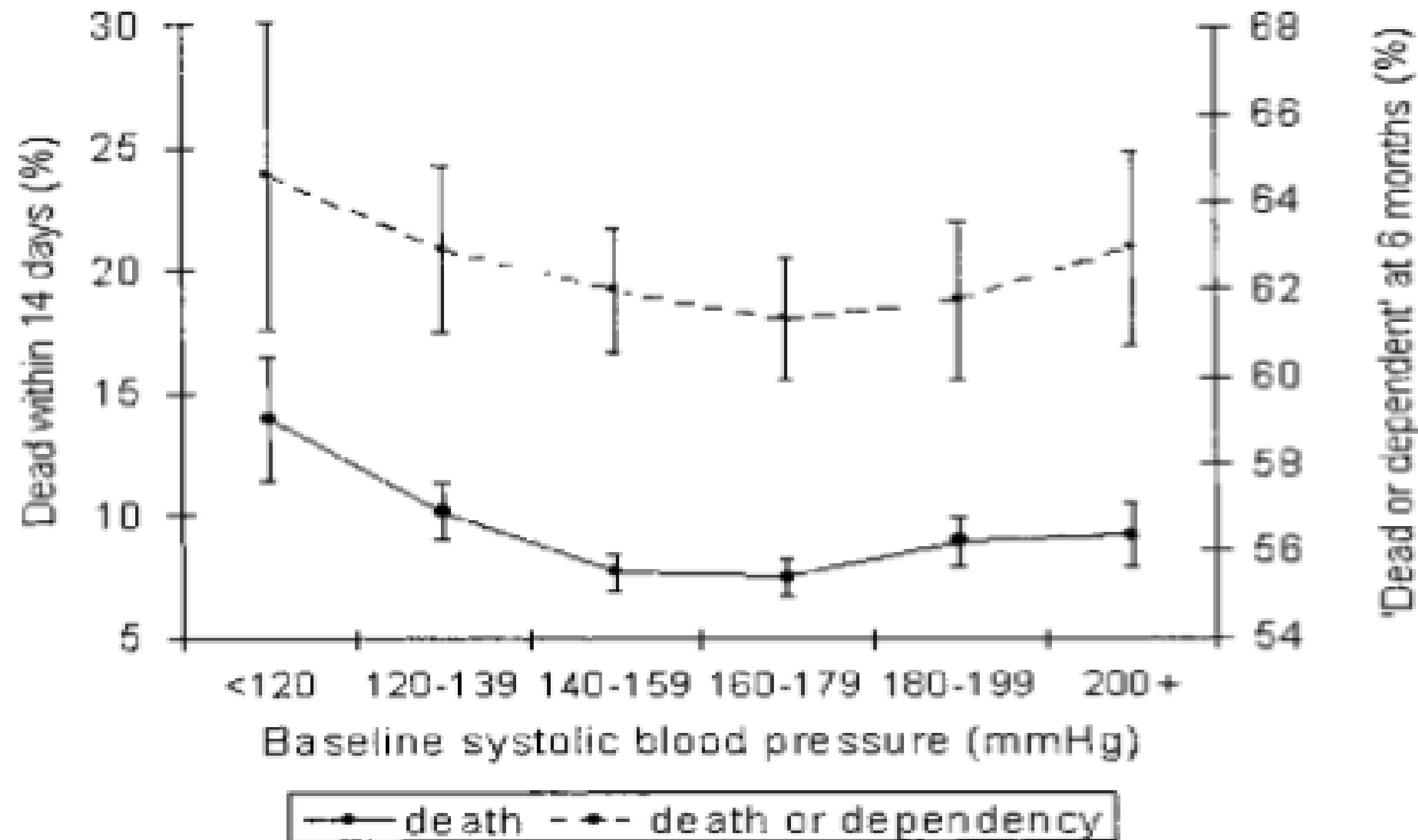
Figure 2. Proportion of patients who died within 14 days (solid lines) or were dead or dependent at 6 months (dashed lines) by baseline SBP. Circles and squares indicate the mean percent-

Jo Leonardi-Bee, MSc; Philip M.W. Bath, FRCP; Stephen J. Phillips, FRCPC; Peter A.G. Sandercock, FRCP; for the IST Collaborative Group. **Blood Pressure and Clinical Outcomes in the International Stroke Trial**. S*troke*. 2002;33:1315-1320.
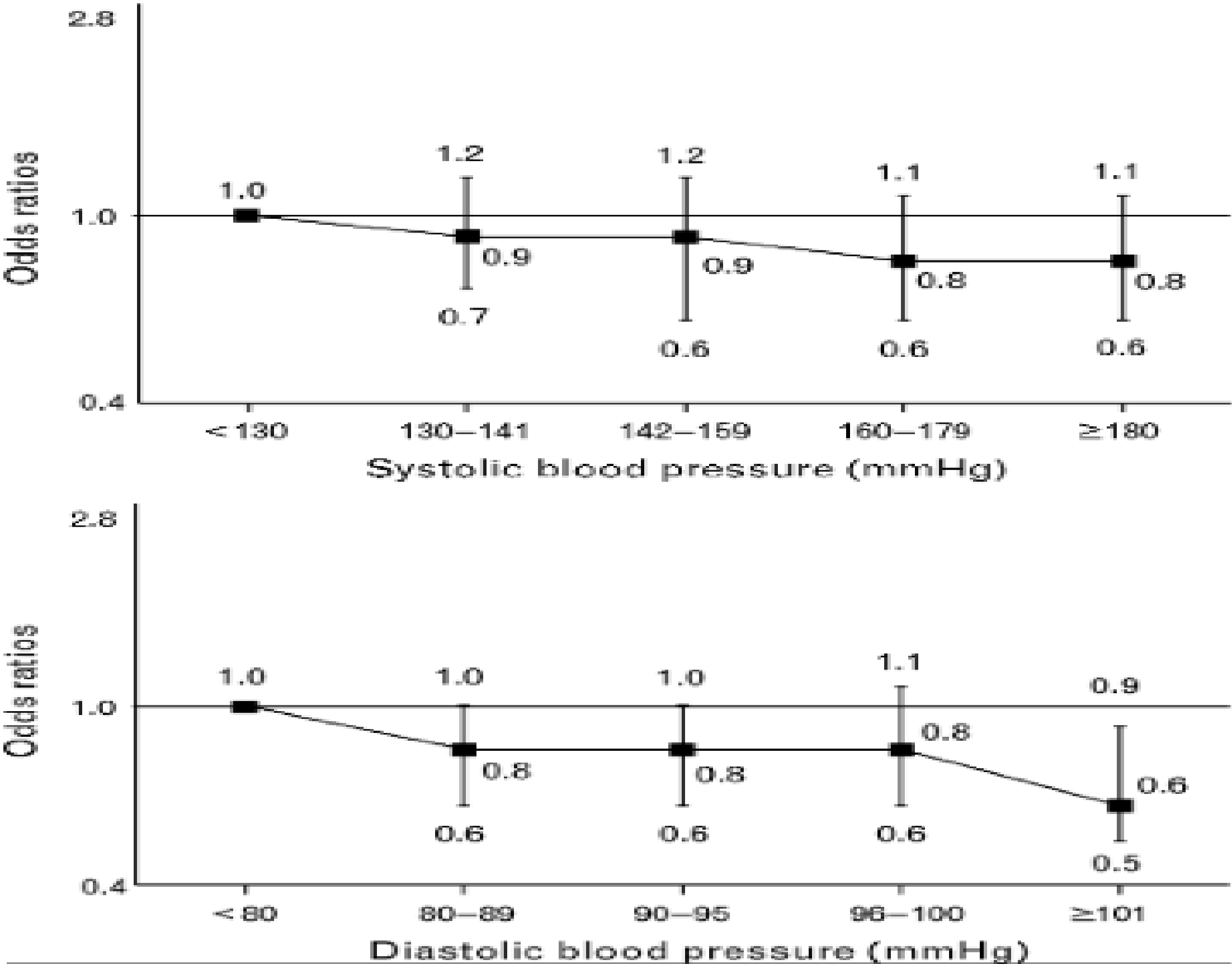
Multiple-adjusted odds ratios and 95% confidence interval of death/ disability by the quintiles of systolic blood pressure (top panel) and diastolic blood pressure (lower panel) among ischemic stroke patients.
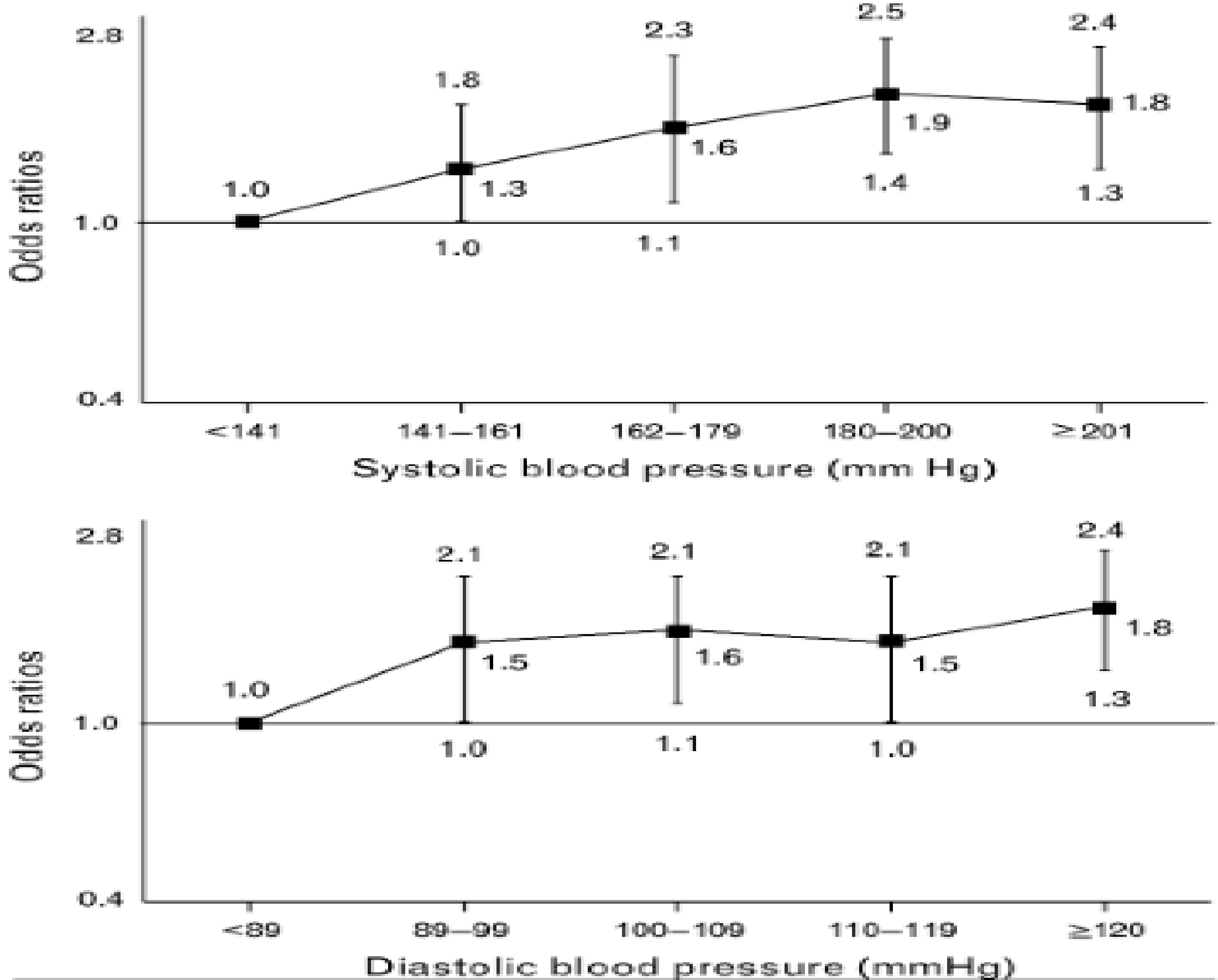
Multiple-adjusted odds ratios and 95% confidence interval of death/ disability by the quintiles of systolic blood pressure (top panel) and diastolic blood pressure (lower panel) among hemorrhagic stroke patients.

Stroke patients with elevated blood pressure in acute setting

Drop the Blood Pressure

VS

Do not Drop the Blood Pressure

Outcome?

Outcome?

Ischemic Stroke

- Concerns with lowering the blood pressure are the potential to reduce blood flow of penumbra.

  - Enlarge the area of infarction

- Concerns with keeping patients with high blood pressure are cerebral edema, hemorrhagic transformation, vascular injury and cardiovascular complications

Stroke

American Heart Association | American Stroke Association

Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

Edward C. Jauch, Jeffrey L. Saver, Harold P. Adams, Jr, Askiel Bruno, J.J. (Buddy) Connors, Bart M. Demaerschalk, Pooja Khatri, Paul W. McMullan, Jr, Adnan I. Qureshi, Kenneth Rosenfield, Phillip A. Scott, Debbie R. Summers, David Z. Wang, Max Wintermark and Howard Yonas
on behalf of the American Heart Association Stroke Council, Council on Cardiovascular Nursing, Council on Peripheral Vascular Disease, and Council on Clinical Cardiology

Table 9. Potential Approaches to Arterial Hypertension in Acute Ischemic Stroke Patients Who Are Candidates for Acute Reperfusion Therapy

Patient otherwise eligible for acute reperfusion therapy except that BP is >185/110 mm Hg:

Labetalol 10–20 mg IV over 1–2 minutes, may repeat 1 time; or

Nicardipine 5 mg/h IV, titrate up by 2.5 mg/h every 5–15 minutes, maximum 15 mg/h; when desired BP reached, adjust to maintain proper BP limits; or

Other agents (hydralazine, enalaprilat, etc) may be considered when appropriate

If BP is not maintained at or below 185/110 mm Hg, do not administer rtPA

Management of BP during and after rtPA or other acute reperfusion therapy to maintain BP at or below 180/105 mm Hg:

Monitor BP every 15 minutes for 2 hours from the start of rtPA therapy, then every 30 minutes for 6 hours, and then every hour for 16 hours

If systolic BP >180–230 mm Hg or diastolic BP >105–120 mm Hg:

Labetalol 10 mg IV followed by continuous IV infusion 2–8 mg/min; or

Nicardipine 5 mg/h IV, titrate up to desired effect by 2.5 mg/h every 5–15 minutes, maximum 15 mg/h

If BP not controlled or diastolic BP >140 mm Hg, consider IV sodium nitroprusside

BP indicates blood pressure; IV, intravenously; and rtPA, recombinant tissue-type plasminogen activator.

7. In patients with markedly elevated blood pressure who do not receive fibrinolysis, a reasonable goal is to lower blood pressure by 15% during the first 24 hours after onset of stroke. The level of blood pressure that would mandate such treatment is not known, but consensus exists that medications should be withheld unless the systolic blood pressure is >220 mm Hg or the diastolic blood pressure is >120 mm Hg (*Class I; Level of Evidence C*). (Revised from the previous guideline[13])

Hypertension

American Heart Association®

Relationship Between Therapeutic Changes in Blood Pressure and Outcomes in Acute Stroke: A Metaregression

Chamila M. Geeganage and Philip M.W. Bath

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/54/4/775

Data Supplement (unedited) at:
http://hyper.ahajournals.org/content/suppl/2009/08/03/HYPERTENSIONAHA.109.133538.DC1.html

Type of Studies

- Included studies were composed of published and unpublished randomized, controlled trials in acute ischemic stroke or acute primary intracerebral hemorrhage of drugs that had the potential for altering BP.

- Therapy had to be initiated within 1 week of stroke onset.

- Uncontrolled studies, confounded trials (where interventions were compared with each other rather than control/placebo), studies of patients with subarachnoid hemorrhage, and studies where BP or clinical outcome data were unobtainable were excluded.

Study Search

- The Cochrane Library (issue 2, 2008), Medline (1966 to January 2009), EMBASE (1980 to January 2009), and Science Citation Index(ISI Web of Science, 1981 to January 2009) were searched.

- No language restrictions were applied.

Type of Participants

- Adults (age 18 years) of either sex with acute ischemic or hemorrhagic stroke who were eligible for randomization to either active treatment or placebo/open control were included.

Figure 1. Search process for relevant studies.

Death Within One Month

Left Column

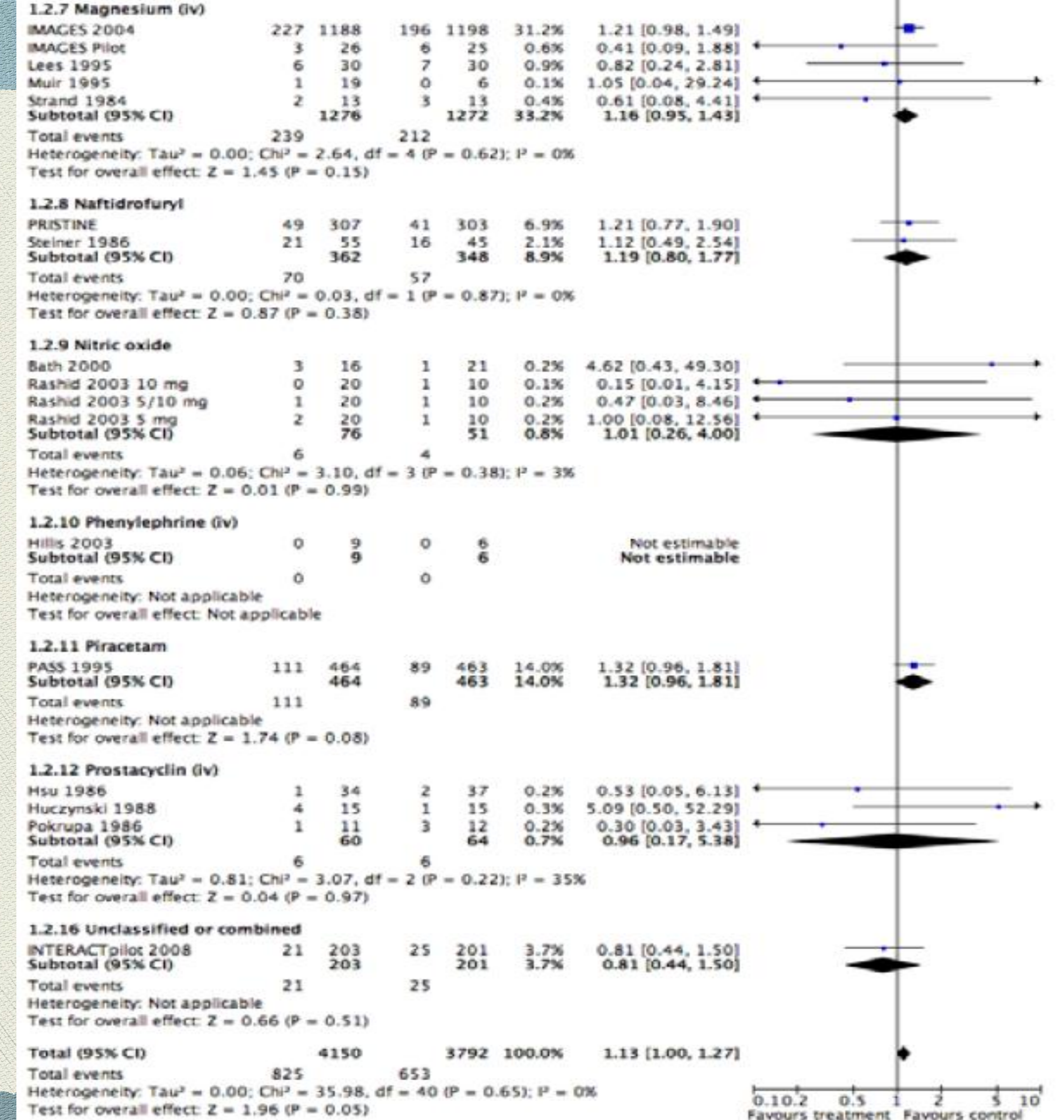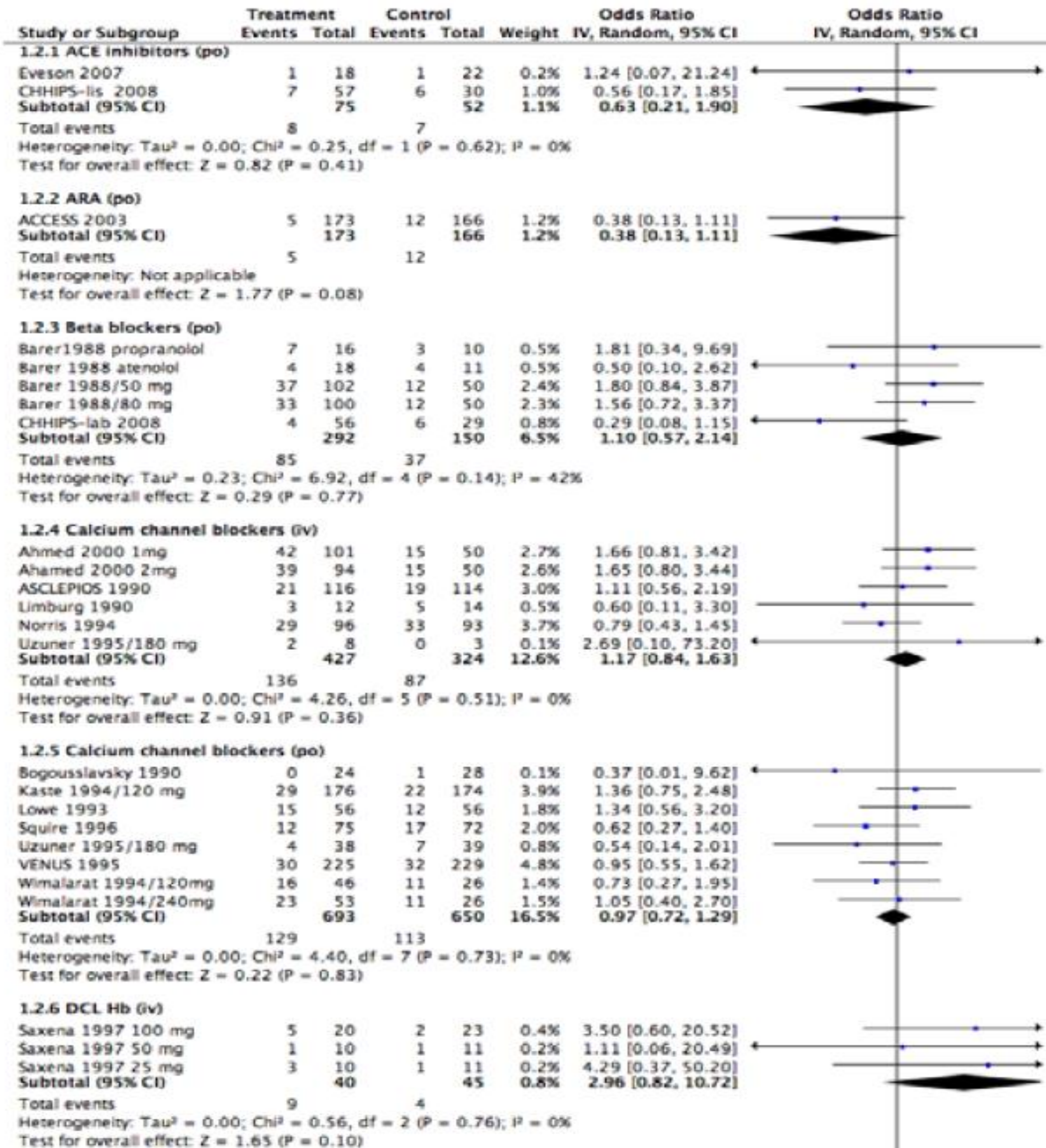| Study or Subgroup	Treatment Events	Total	Control Events	Total	Weight	Odds Ratio IV, Random, 95% CI
1.2.1 ACE inhibitors (po)						
Eveson 2007	1	18	1	22	0.2%	1.24 [0.07, 21.24]
CHHIPS-lis 2008	7	57	6	30	1.0%	0.56 [0.17, 1.85]
Subtotal (95% CI)		75		52	1.1%	0.63 [0.21, 1.90]
Total events	8		7			
Heterogeneity: Tau² = 0.00; Chi² = 0.25, df = 1 (P = 0.62); I² = 0%						
Test for overall effect: Z = 0.82 (P = 0.41)						
1.2.2 ARA (po)						
ACCESS 2003	5	173	12	166	1.2%	0.38 [0.13, 1.11]
Subtotal (95% CI)		173		166	1.2%	0.38 [0.13, 1.11]
Total events	5		12			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.77 (P = 0.08)						
1.2.3 Beta blockers (po)						
Barer1988 propranolol	7	16	3	10	0.5%	1.81 [0.34, 9.69]
Barer 1988 atenolol	4	18	4	11	0.5%	0.50 [0.10, 2.62]
Barer 1988/50 mg	37	102	12	50	2.4%	1.80 [0.84, 3.87]
Barer 1988/80 mg	33	100	12	50	2.3%	1.56 [0.72, 3.37]
CHHIPS-lab 2008	4	56	6	29	0.8%	0.29 [0.08, 1.15]
Subtotal (95% CI)		292		150	6.5%	1.10 [0.57, 2.14]
Total events	85		37			
Heterogeneity: Tau² = 0.23; Chi² = 6.92, df = 4 (P = 0.14); I² = 42%						
Test for overall effect: Z = 0.29 (P = 0.77)						
1.2.4 Calcium channel blockers (iv)						
Ahmed 2000 1mg	42	101	15	50	2.7%	1.66 [0.81, 3.42]
Ahamed 2000 2mg	39	94	15	50	2.6%	1.65 [0.80, 3.44]
ASCLEPIOS 1990	21	116	19	114	3.0%	1.11 [0.56, 2.19]
Limburg 1990	3	12	5	14	0.5%	0.60 [0.11, 3.30]
Norris 1994	29	96	33	93	3.7%	0.79 [0.43, 1.45]
Uzuner 1995/180 mg	2	8	0	3	0.1%	2.69 [0.10, 73.20]
Subtotal (95% CI)		427		324	12.6%	1.17 [0.84, 1.63]
Total events	136		87			
Heterogeneity: Tau² = 0.00; Chi² = 4.26, df = 5 (P = 0.51); I² = 0%						
Test for overall effect: Z = 0.91 (P = 0.36)						
1.2.5 Calcium channel blockers (po)						
Bogousslavsky 1990	0	24	1	28	0.1%	0.37 [0.01, 9.62]
Kaste 1994/120 mg	29	176	22	174	3.9%	1.36 [0.75, 2.48]
Lowe 1993	15	56	12	56	1.8%	1.34 [0.56, 3.20]
Squire 1996	12	75	17	72	2.0%	0.62 [0.27, 1.40]
Uzuner 1995/180 mg	4	38	7	39	0.8%	0.54 [0.14, 2.01]
VENUS 1995	30	225	32	229	4.8%	0.95 [0.55, 1.62]
Wimalarat 1994/120mg	16	46	11	26	1.4%	0.73 [0.27, 1.95]
Wimalarat 1994/240mg	23	53	11	26	1.5%	1.05 [0.40, 2.70]
Subtotal (95% CI)		693		650	16.5%	0.97 [0.72, 1.29]
Total events	129		113			
Heterogeneity: Tau² = 0.00; Chi² = 4.40, df = 7 (P = 0.73); I² = 0%						
Test for overall effect: Z = 0.22 (P = 0.83)						
1.2.6 DCL Hb (iv)						
Saxena 1997 100 mg	5	20	2	23	0.4%	3.50 [0.60, 20.52]
Saxena 1997 50 mg	1	10	1	11	0.2%	1.11 [0.06, 20.49]
Saxena 1997 25 mg	3	10	1	11	0.2%	4.29 [0.37, 50.20]
Subtotal (95% CI)		40		45	0.8%	2.96 [0.82, 10.72]
Total events	9		4			
Heterogeneity: Tau² = 0.00; Chi² = 0.56, df = 2 (P = 0.76); I² = 0%						
Test for overall effect: Z = 1.65 (P = 0.10)						

Right Column

Study or Subgroup	Treatment Events	Total	Control Events	Total	Weight	Odds Ratio IV, Random, 95% CI
1.2.7 Magnesium (iv)						
IMAGES 2004	227	1188	196	1198	31.2%	1.21 [0.98, 1.49]
IMAGES Pilot	3	26	6	25	0.6%	0.41 [0.09, 1.88]
Lees 1995	6	30	7	30	0.9%	0.82 [0.24, 2.81]
Muir 1995	1	19	0	6	0.1%	1.05 [0.04, 29.24]
Strand 1984	2	13	3	13	0.4%	0.61 [0.08, 4.41]
Subtotal (95% CI)		1276		1272	33.2%	1.16 [0.95, 1.43]
Total events	239		212			
Heterogeneity: Tau² = 0.00; Chi² = 2.64, df = 4 (P = 0.62); I² = 0%						
Test for overall effect: Z = 1.45 (P = 0.15)						
1.2.8 Naftidrofuryl						
PRISTINE	49	307	41	303	6.9%	1.21 [0.77, 1.90]
Steiner 1986	21	55	16	45	2.1%	1.12 [0.49, 2.54]
Subtotal (95% CI)		362		348	8.9%	1.19 [0.80, 1.77]
Total events	70		57			
Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.87); I² = 0%						
Test for overall effect: Z = 0.87 (P = 0.38)						
1.2.9 Nitric oxide						
Bath 2000	3	16	1	21	0.2%	4.62 [0.43, 49.30]
Rashid 2003 10 mg	0	20	1	10	0.1%	0.15 [0.01, 4.15]
Rashid 2003 5/10 mg	1	20	1	10	0.2%	0.47 [0.03, 8.46]
Rashid 2003 5 mg	2	20	1	10	0.2%	1.00 [0.08, 12.56]
Subtotal (95% CI)		76		51	0.8%	1.01 [0.26, 4.00]
Total events	6		4			
Heterogeneity: Tau² = 0.06; Chi² = 3.10, df = 3 (P = 0.38); I² = 3%						
Test for overall effect: Z = 0.01 (P = 0.99)						
1.2.10 Phenylephrine (iv)						
Hillis 2003	0	9	0	6		Not estimable
Subtotal (95% CI)		9		6		Not estimable
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.2.11 Piracetam						
PASS 1995	111	464	89	463	14.0%	1.32 [0.96, 1.81]
Subtotal (95% CI)		464		463	14.0%	1.32 [0.96, 1.81]
Total events	111		89			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.74 (P = 0.08)						
1.2.12 Prostacyclin (iv)						
Hsu 1986	1	34	2	37	0.2%	0.53 [0.05, 6.13]
Huczynski 1988	4	15	1	15	0.3%	5.09 [0.50, 52.29]
Pokrupa 1986	1	11	3	12	0.2%	0.30 [0.03, 3.43]
Subtotal (95% CI)		60		64	0.7%	0.96 [0.17, 5.38]
Total events	6		6			
Heterogeneity: Tau² = 0.81; Chi² = 3.07, df = 2 (P = 0.22); I² = 35%						
Test for overall effect: Z = 0.04 (P = 0.97)						
1.2.16 Unclassified or combined						
INTERACTpilot 2008	21	203	25	201	3.7%	0.81 [0.44, 1.50]
Subtotal (95% CI)		203		201	3.7%	0.81 [0.44, 1.50]
Total events	21		25			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.66 (P = 0.51)						
Total (95% CI)		4150		3792	100.0%	1.13 [1.00, 1.27]
Total events	825		653			
Heterogeneity: Tau² = 0.00; Chi² = 35.98, df = 40 (P = 0.65); I² = 0%						
Test for overall effect: Z = 1.96 (P = 0.05)						

0.1 0.2 0.5 1 2 5 10
Favours treatment   Favours control

1.4.9 Piracetam

Study	Treatment events	Treatment total	Control events	Control total	Weight	Risk Ratio M-H, Random, 95% CI
Herrschaft 1988	8	23	10	17	1.2%	0.37 [0.10, 1.36]
Subtotal (95% CI)		23		17	1.2%	**0.37 [0.10, 1.36]**

Total events 8   10
Heterogeneity: Not applicable
Test for overall effect: Z = 1.49 (P = 0.13)

1.4.10 Prostacyclin (iv)

Study	Treatment events	Treatment total	Control events	Control total	Weight	Risk Ratio M-H, Random, 95% CI
Huczynski 1988	4	14	2	15	0.6%	2.60 [0.39, 17.16]
Subtotal (95% CI)		14		15	0.6%	**2.60 [0.39, 17.16]**

Total events 4   2
Heterogeneity: Not applicable
Test for overall effect: Z = 0.99 (P = 0.32)

1.4.11 Unclassified or combined

Study	Treatment events	Treatment total	Control events	Control total	Weight	Risk Ratio M-H, Random, 95% CI
INTERACTpilot 2008	95	203	95	201	8.5%	0.98 [0.66, 1.45]
Subtotal (95% CI)		203		201	8.5%	**0.98 [0.66, 1.45]**

Total events 95   95
Heterogeneity: Not applicable
Test for overall effect: Z = 0.09 (P = 0.93)

Total (95% CI)   3220   2957   100.0%   **1.10 [0.95, 1.27]**

Total events 1786   1618
Heterogeneity: Tau² = 0.03; Chi² = 39.89, df = 33 (P = 0.19); I² = 17%
Test for overall effect: Z = 1.27 (P = 0.21)

0.1 0.2   0.5   1   2   5 10
Favours treatment   Favours control
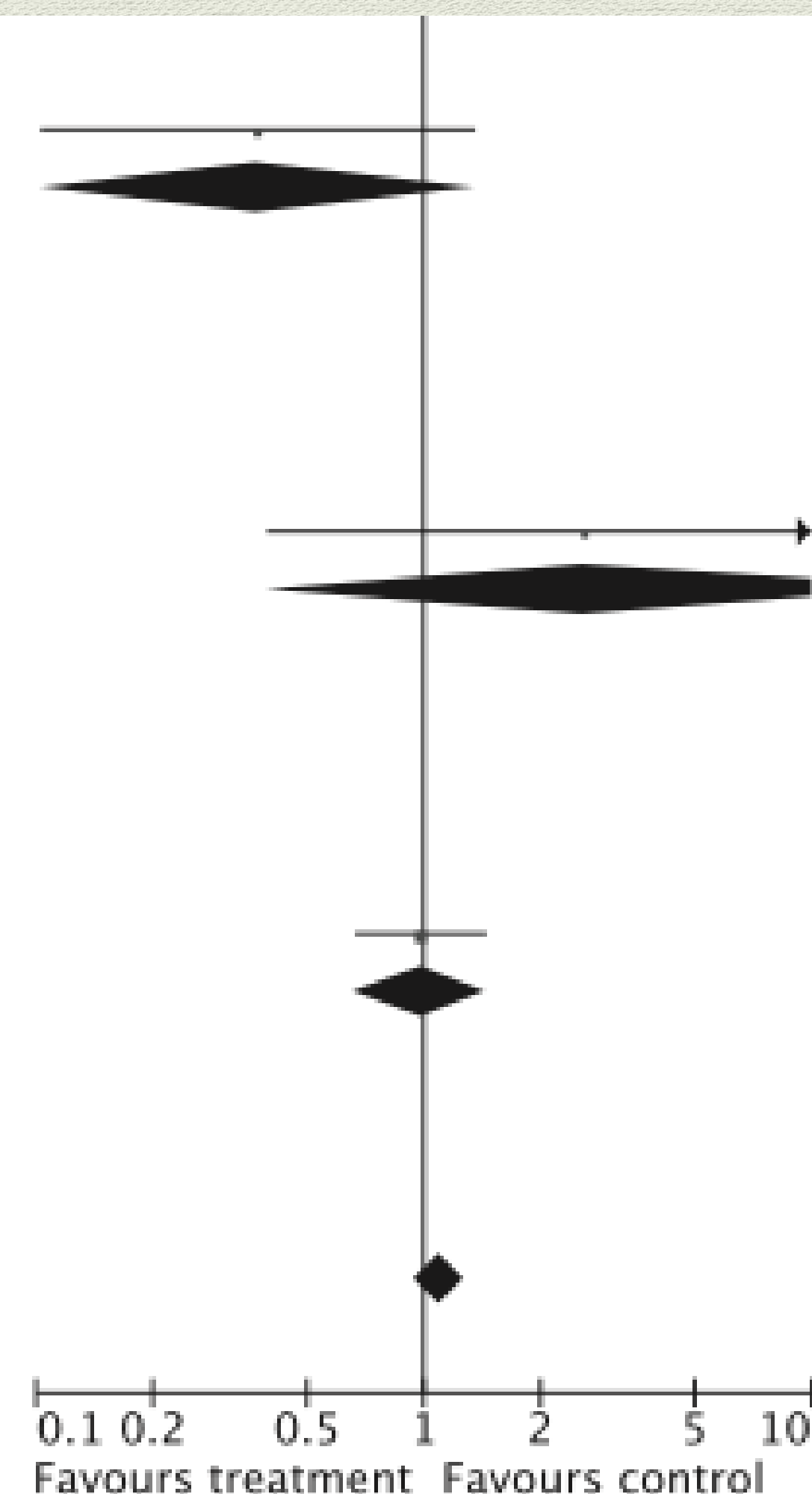
Limitations

- Methodologies of studies are heterogenous

  - Some of them studied patients with hemorrhagic stroke

  - Some of them studied patients with ischemic stroke

  - Some of them studied both

- Included patients with symptom onset of within one week.

Original Investigation

Effects of Immediate Blood Pressure Reduction on Death and Major Disability in Patients With Acute Ischemic Stroke
The CATIS Randomized Clinical Trial

Jiang He, MD, PhD; Yonghong Zhang, MD, PhD; Tan Xu, MD, PhD; Qi Zhao, MD, PhD; Dali Wang, MD; Chung-Shiuan Chen, MS; Weijun Tong, MD; Changjie Liu, MD; Tian Xu, MD; Zhong Ju, MD; Yanbo Peng, MD; Hao Peng, MD; Qunwei Li, MD; Deqin Geng, MD; Jintao Zhang, MD; Dong Li, MD; Fengshan Zhang, MD; Libing Guo, MD; Yingxian Sun, MD; Xuemei Wang, MD; Yong Cui, MD; Yongqiu Li, MD ; Dihui Ma, MD; Guang Yang, MD; Yanjun Gao, MD; Xiaodong Yuan, MD; Lydia A. Bazzano, MD, PhD; Jing Chen, MD, MS; for the CATIS Investigators

Supplemental content at jama.com

IMPORTANCE Although the benefit of reducing blood pressure for primary and secondary prevention of stroke has been established, the effect of antihypertensive treatment in patients with acute ischemic stroke is uncertain.

OBJECTIVE To evaluate whether immediate blood pressure reduction in patients with acute ischemic stroke would reduce death and major disability at 14 days or hospital discharge.

DESIGN, SETTING, AND PARTICIPANTS The China Antihypertensive Trial in Acute Ischemic Stroke, a single-blind, blinded end-points randomized clinical trial, conducted among 4071 patients with nonthrombolysed ischemic stroke within 48 hours of onset and elevated systolic blood pressure. Patients were recruited from 26 hospitals across China between August 2009 and May 2013.

JAMA. doi:10.1001/jama.2013.282543

- Inclusion Criteria:

  - Patients with ischemic stroke

  - 22 years old or older

  - Within 48 hours of symptom onset

  - Systolic blood pressure between 140 and 220

- Exclusion criteria

  - patients with severe heart failure, acute myocardial in- farction or unstable angina, atrial fibrillation, aortic dissection, cerebrovascular stenosis, or resistant hypertension, and those in a deep coma, were excluded.

- Intervention:

  - Lowering systolic blood pressure by 10% to 25% within the first 24 hours after randomization, achieving a systolic blood pressure less than 140 mm Hg and diastolic blood pressure less than 90 mm Hg within 7 days,

  - Discontinue of anti-hypertensive medication in control group.

- Outcome:

  - The primary outcome was a combination of death within 14 days after randomization and major disability at 14 days or at hospital discharge if earlier than 14 days.

CONSORT flow diagram:

22230 Patients assessed for eligibility

18159 Excluded
- 8861 Blood pressure outside inclusion criteria
- 3821 Onset >48 h
- 1937 Clinical contraindications[a]
- 978 Could not be followed up
- 828 No consent obtained
- 169 Refused to participate
- 142 Transferred to another hospital[b]
- 82 Resistant hypertension
- 1341 Other

4071 Randomized

2038 Randomized to receive antihypertensive treatment
- 2031 Received antihypertensive treatment
- 7 Did not receive antihypertensive treatment

2033 Randomized to control
- 1986 Discontinued antihypertensive medications
- 47 Did not discontinued antihypertensive medications

2038 Included in analysis at 14 d or hospital discharge (primary analysis)

2033 Included in analysis at 14 d or hospital discharge (primary analysis)

50 Lost to follow-up
- 24 Relocated
- 18 Lost contact
- 8 Withdrew

46 Lost to follow-up
- 29 Relocated
- 11 Lost contact
- 6 Withdrew

1988 Included in analysis at 3 mo
50 Excluded (lost to follow-up)

1987 Included in analysis at 3 mo
46 Excluded (lost to follow-up)

Table 1. Baseline Characteristics of the Trial Participants

Characteristics	Antihypertensive Treatment (n = 2038)	Control (n = 2033)
Age, mean (SD), y	62.1 (10.8)	61.8 (11.0)
Men, No. (%)	1317 (64.6)	1287 (63.3)
Time from onset to randomization, mean (SD), h	15.3 (12.9)	14.9 (13.0)
Blood pressure at entry, mean (SD), mm Hg		
Systolic	166.7 (17.3)	165.6 (16.5)
Diastolic	96.8 (10.8)	96.5 (11.4)
Body mass index, mean (SD)[a]	24.9 (3.2)	25.0 (3.1)
NIHSS score, median (IQR)[b]	4.0 (2.0-7.0)	4.0 (3.0-8.0)
History of hypertension, No. (%)	1610 (79.0)	1599 (78.7)
Current use of antihypertensive medications, No. (%)	1014 (49.8)	983 (48.4)
Hyperlipidemia, No. (%)	137 (6.7)	140 (6.9)
Diabetes mellitus, No. (%)	369 (18.1)	350 (17.2)
Coronary heart disease, No. (%)	216 (10.6)	228 (11.2)
Current cigarette smoking, No. (%)	725 (35.6)	760 (37.4)
Current alcohol drinking, No. (%)	614 (30.1)	639 (31.4)
Ischemic stroke subtype, No. (%)[c]		
Thrombotic	1575 (77.3)	1595 (78.5)
Embolic	99 (4.9)	103 (5.1)
Lacunar	417 (20.5)	385 (18.9)

Table 2. Blood Pressure Reduction and Primary and Secondary Outcomes at 14 Days or Hospital Discharge

Variable	Antihypertensive Treatment (n = 2038)	Control (n = 2033)	Blood Pressure Difference or OR (95% CI)	P Value
Blood pressure reduction				
Blood pressure at 24 h after randomization, mean (SD), mm Hg				
Systolic	144.7 (15.0)	152.9 (15.9)	−8.1 (−9.1 to −7.2)	<.001
Diastolic	85.9 (8.9)	89.6 (9.6)	−3.8 (−4.3 to −3.2)	<.001
Absolute blood pressure changes from baseline to 24 h after randomization, mean (SD), mm Hg				
Systolic	−21.8 (15.9)	−12.7 (17.3)	−9.1 (−10.2 to −8.1)	<.001
Diastolic	−11.0 (10.5)	−6.9 (11.0)	−4.1 (−4.7 to −3.4)	<.001
Proportional blood pressure changes from baseline to 24 h after randomization, mean (SD), %				
Systolic	−12.7 (8.7)	−7.2 (9.8)	−5.5 (−4.9 to −6.1)	<.001
Diastolic	−10.7 (10.1)	−6.4 (11.1)	−4.3 (−3.6 to −4.9)	<.001
Blood pressure at day 7 after randomization, mean (SD), mm Hg				
Systolic	137.3 (11.8)	146.5 (13.6)	−9.3 (−10.1 to −8.4)	<.001
Diastolic	82.4 (7.2)	86.4 (8.1)	−4.0 (−4.5 to −3.5)	<.001
Blood pressure at day 14 after randomization, mean (SD), mm Hg				
Systolic	135.2 (10.4)	143.7 (14.0)	−8.6 (−9.7 to −7.4)	<.001
Diastolic	81.4 (7.4)	85.3 (8.3)	−3.9 (−4.6 to −3.1)	<.001

Primary outcome				
Death or major disability, No. (%)[a]	683 (33.6)	681 (33.6)	1.00 (0.88 to 1.14)	.98
Secondary outcomes				
Score on modified Rankin scale[b], median (IQR)	2.0 (1.0 to 3.0)	2.0 (1.0 to 3.0)		.70
Participants, No. (%)				
0 (no symptoms)	204 (10.0)	154 (7.6)	0.98 (0.88 to 1.09)[c]	.70
1 (no significant disability despite symptoms)	653 (32.2)	701 (34.6)		
2 (slight disability)	491 (24.2)	491 (24.2)		
3 (moderate disability)	292 (14.4)	297 (14.7)		
4 (moderately severe disability)	258 (12.7)	285 (14.1)		
5 (severe disability)	108 (5.3)	77 (3.8)		
6 (dead)	25 (1.2)	25 (1.2)		
Death, No. (%)	25 (1.2)	25 (1.2)	1.00 (0.57 to 1.74)	.99
Duration of initial hospitalization, median (IQR), d	13.0 (9.0 to 14.0)	13.0 (9.0 to 14.0)		.28

Subgroup	Antihypertensive Treatment		Control		Odds Ratio (95% CI)	P Value for Homogeneity
	Total, No.	Events, No. (%)	Total, No.	Events, No. (%)		
Age, y						
<65	1198	352 (29.4)	1203	325 (27.0)	1.12 (0.94-1.34)	.05
≥65	833	331 (39.7)	824	356 (43.2)	0.87 (0.71-1.05)	
Sex						
Women	715	267 (37.3)	743	269 (36.2)	1.05 (0.85-1.30)	.61
Men	1316	416 (31.6)	1284	412 (32.1)	0.98 (0.83-1.15)	
Time to randomization, h						
<12	1015	376 (37.0)	1082	412 (38.1)	0.96 (0.80-1.14)	.59
12-23	401	132 (32.9)	331	99 (29.9)	1.15 (0.84-1.57)	
≥24	609	172 (28.2)	609	167 (27.4)	1.04 (0.81-1.34)	
Baseline SBP, mm Hg						
<160	715	225 (31.5)	765	228 (29.8)	1.08 (0.87-1.35)	.59
160-179	838	288 (34.4)	851	297 (34.9)	0.98 (0.80-1.19)	
≥180	478	170 (35.6)	411	156 (38.0)	0.90 (0.69-1.19)	
History of hypertension						
No	428	150 (35.0)	430	151 (35.1)	1.00 (0.75-1.32)	.97
Yes	1603	533 (33.3)	1597	530 (33.2)	1.00 (0.87-1.16)	
Use of antihypertension medications						
No	1022	354 (33.8)	1045	366 (35.0)	0.95 (0.79-1.13)	.36
Yes	1009	338 (33.5)	982	315 (32.1)	1.07 (0.88-1.29)	
Baseline NIHSS score						
0-4	1065	134 (12.6)	1009	113 (11.2)	1.14 (0.87-1.49)	.66
5-15	871	460 (52.8)	923	479 (51.9)	1.04 (0.86-1.25)	
≥16	95	89 (93.7)	93	89 (95.7)	0.67 (0.18-2.44)	
Baseline Rankin score						
<3	914	47 (5.1)	900	46 (5.1)	1.01 (0.66-1.53)	.95
≥3	1117	636 (56.9)	1125	635 (56.4)	1.02 (0.86-1.21)	
Stroke subtype						
Thrombolic	1513	539 (35.6)	1540	544 (35.3)	1.01 (0.87-1.18)	.06
Embolic	93	60 (64.5)	92	48 (52.2)	1.67 (0.92-3.01)	
Lacunar	366	66 (18.0)	338	78 (23.1)	0.73 (0.51-1.06)	
Overall	2031	683 (33.6)	2027	681 (33.6)	1.00 (0.88-1.14)	

Odds Ratio (95% CI)
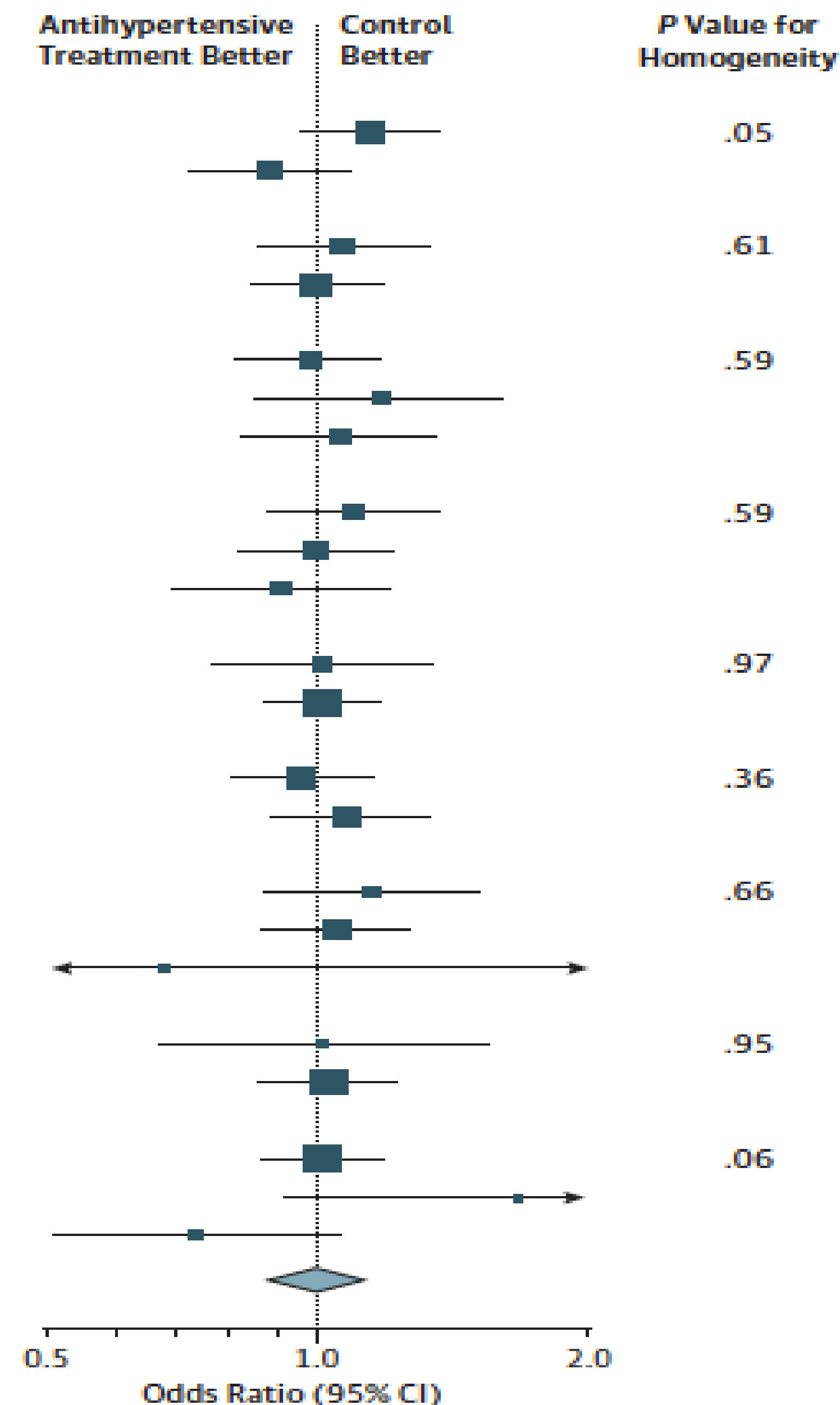
Limitations

- Did not enrolled patienst in the early period of stroke (within six hours)

- Heterogenity of hypertensive agents

- Lack of reporting adverse effects of anti-hypertensive agents

- The clinically insignificant blood pressure difference between two groups

- Lack of drawing a conclusion between patients with a blood pressure of 180 mmHg vs 140 mmHg

Conclusion

- Dropping the blood pressure in patients with ischemic stroke under 140 mmHg does not result with a decreased mortality or better neurological outcome.

- Blood pressure of ischemic stroke patients decreases slightly after a while without a medication.

The angiotensin-receptor blocker candesartan for treatment of acute stroke (SCAST): a randomised, placebo-controlled, double-blind trial

Else Charlotte Sandset, Philip M W Bath, Gudrun Boysen, Dalius Jatuzis, Janika Kõrv, Stephan Lüders, Gordon D Murray, Przemyslaw S Richter, Risto O Roine, Andreas Terént, Vincent Thijs, Eivind Berge, on behalf of the SCAST Study Group

Summary

Background Raised blood pressure is common in acute stroke, and is associated with an increased risk of poor outcomes. We aimed to examine whether careful blood-pressure lowering treatment with the angiotensin-receptor blocker candesartan is beneficial in patients with acute stroke and raised blood pressure.

Methods Participants in this randomised, placebo-controlled, double-blind trial were recruited from 146 centres in nine north European countries. Patients older than 18 years with acute stroke (ischaemic or haemorrhagic) and systolic blood pressure of 140 mm Hg or higher were included within 30 h of symptom onset. Patients were randomly allocated to candesartan or placebo (1:1) for 7 days, with doses increasing from 4 mg on day 1 to 16 mg on days 3 to 7. Randomisation was stratified by centre, with blocks of six packs of candesartan or placebo. Patients and investigators were masked to treatment allocation. There were two co-primary effect variables: the composite endpoint of vascular death, myocardial infarction, or stroke during the first 6 months; and functional outcome at 6 months, as measured by the modified Rankin Scale. Analyses were by intention to treat. The study is registered, number NCT00120003 (ClinicalTrials.gov), and ISRCTN13643354.

Findings 2029 patients were randomly allocated to treatment groups (1017 candesartan, 1012 placebo), and data for status at 6 months were available for 2004 patients (99%; 1000 candesartan, 1004 placebo). During the 7-day treatment period, blood pressures were significantly lower in patients allocated candesartan than in those on placebo (mean 147/82 mm Hg [SD 23/14] in the candesartan group on day 7 *vs* 152/84 mm Hg [22/14] in the placebo group; $p < 0.0001$). During 6 months' follow-up, the risk of the composite vascular endpoint did not differ between treatment groups (candesartan, 120 events, *vs* placebo, 111 events; adjusted hazard ratio 1.09, 95% CI $0.84-1.41$; $p = 0.52$). Analysis of functional outcome suggested a higher risk of poor outcome in the candesartan group (adjusted common odds ratio 1.17, 95% CI $1.00-1.38$; $p = 0.048$ [not significant at $p \leq 0.025$ level]). The observed effects were similar for all prespecified secondary endpoints (including death from any cause, vascular death, ischaemic stroke, haemorrhagic stroke, myocardial infarction, stroke progression, symptomatic hypotension, and renal failure) and outcomes (Scandinavian Stroke Scale score at 7 days and Barthel index at 6 months), and there was no evidence of a differential effect in any of the prespecified subgroups. During follow-up, nine (1%) patients on candesartan and five (<1%) on placebo had symptomatic hypotension, and renal failure was reported for 18 (2%) patients taking candesartan and 13 (1%) allocated placebo.

Inclusion Criteria

- Patients aged 18 years or older with a clinical diagnosis of stroke (ischemic or haemorrhagic),

- Presenting within 30 h of symptom onset

- Systolic blood pressure higher than 140 mm Hg

- Patients were allocated in a 1:1 ratio to treatment with candesartan or placebo.

- The randomisation sequence was computer-generated and stratifi ed by centre, with blocks of six packs of candesartan or placebo.

- Patients and investigators were masked to treatment allocation; the candesartan and placebo tablets were identical in appearance and came in prepacked, consecutively numbered drug packs.

- Intervention: 4 mg candesartan on day 1, 8 mg on day 2 and 16 mg on day 3-7.

- Outcome: death and mRS at 6th months.

- Stroke progression was defined as a neurological deterioration of 2 or more points on the SSS occurring within the first 72 h of stroke onset and believed to be caused by the index stroke, after exclusion of recurrent stroke or systemic reasons for deterioration.

	Candesartan (n=1017)	Placebo (n=1012)
Women	405 (40%)	448 (44%)
Age (years)	70·8 (11·2)	71·0 (11·0)
Systolic blood pressure (mm Hg)	171·2 (19·0)	171·6 (19·2)
Diastolic blood pressure (mm Hg)	90·3 (13·9)	90·6 (14·2)
Creatinine (µmol/L)	82·2 (21·9)	81·8 (21·5)
Qualifying event		
Ischaemic stroke	862 (85%)	871 (86%)
Haemorrhagic stroke	144 (14%)	130 (13%)
Other	9 (1%)	11 (1%)
Unknown	2 (<1%)	0
SSS score	40·6 (12·3)	40·5 (12·6)
OCSP syndrome		
Total anterior	79 (8%)	79 (8%)
Partial anterior	502 (49%)	486 (48%)
Posterior	153 (15%)	132 (13%)
Lacunar	279 (27%)	309 (31%)
Other	4 (<1%)	6 (1%)
Duration of symptoms (h)	17·6 (8·1)	17·9 (8·1)
Premorbid mRS score	0 (0–0)	0 (0–0)
Medical history		
Hypertension	676 (69%)	670 (70%)
Diabetes mellitus	163 (16%)	157 (16%)
Current or previous atrial fibrillation	190 (19%)	186 (19%)
Previous stroke or TIA	252 (25%)	204 (21%)
Current use of an ACE inhibitor	270 (27%)	264 (27%)
Thrombolytic treatment before randomisation	69 (8%)	82 (9%)

Data are n (%), mean (SD), or median (IQR). Percentages are proportion of valid data entries, which might be lower than the number of patients in each group. SSS=Scandinavian Stroke Scale. OCSP syndrome=Oxfordshire Community Stroke Project syndrome (both ischaemic and haemorrhagic strokes included). mRS=modified Rankin Scale. TIA=transient ischaemic attack. ACE=angiotensin-converting enzyme.

Table 1: Baseline characteristics
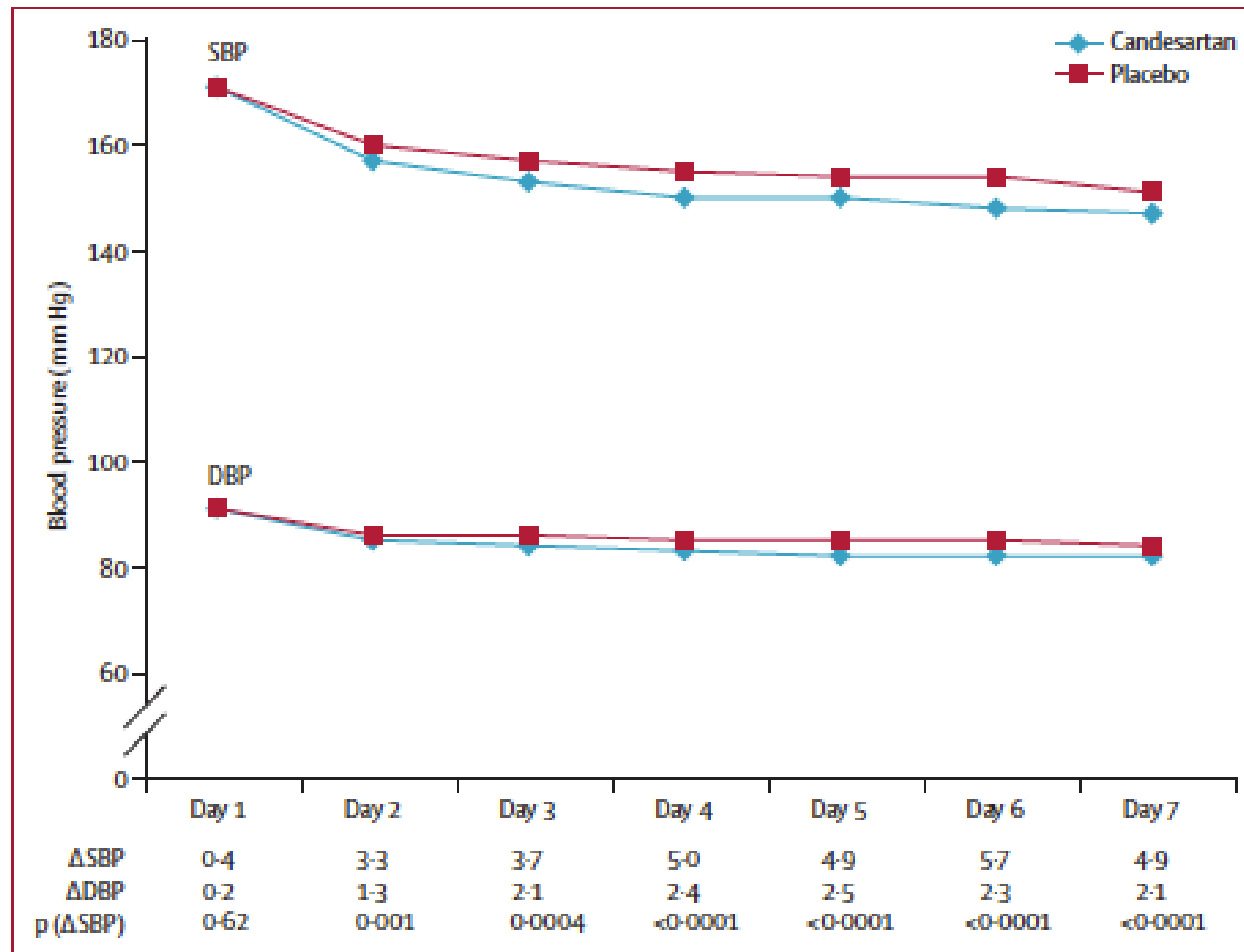
Figure 2: Blood pressure during 7 days' treatment

ΔSBP and ΔDBP signify mean difference in systolic and diastolic blood pressure between the two groups; p values were calculated with the independent sample t test, and are for difference in systolic blood pressure between groups.

	Candesartan (n=1017)	Placebo (n=1012)	Risk ratio (95% CI)	p value
Death from any cause	84 (8%)	78 (8%)	1·07 (0·80–1·44)	0·65
Vascular death	63 (6%)	60 (6%)	1·05 (0·74–1·47)	0·80
Ischaemic stroke	58 (6%)	50 (5%)	1·15 (0·80–1·67)	0·44
Haemorrhagic stroke	10 (1%)	8 (1%)	1·24 (0·49–3·14)	0·64
Recurrent stroke (ischaemic, haemorrhagic, or unspecified)	69 (7%)	59 (6%)	1·16 (0·83–1·63)	0·38
Myocardial infarction	16 (2%)	11 (1%)	1·45 (0·68–3·10)	0·34
Stroke progression	65 (6%)	44 (4%)	1·47 (1·01–2·13)	0·04
Symptomatic hypotension	9 (1%)	5 (<1%)	1·79 (0·60–5·33)	0·29
Renal failure	18 (2%)	13 (1%)	1·38 (0·68–2·80)	0·37
Symptomatic venous thromboembolism	11 (1%)	6 (1%)	1·82 (0·68–4·91)	0·33

Data are n (%).

Table 3: Secondary events during 6 months' follow-up
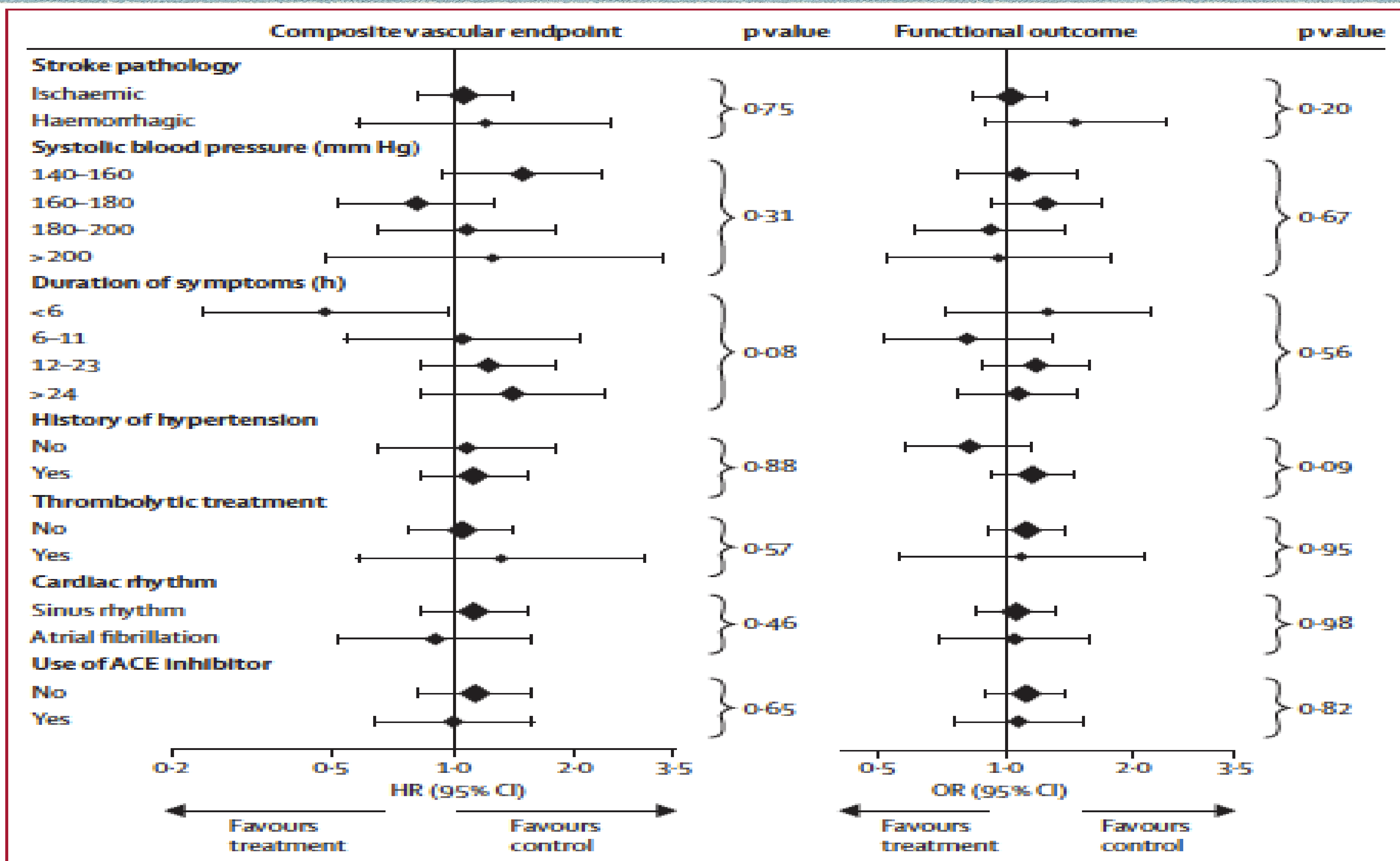
Figure 5: Subgroup analysis of effects on the composite vascular endpoint during 6 months' follow-up and functional outcome at 6 months

Functional outcome has been dichotomised into favourable (modified Rankin Scale score 0–2) or unfavourable outcome (modified Rankin Scale score 3–6). p values are for the interaction between subgroup and allocated treatment. ACE=angiotensin-converting enzyme. HR=hazard ratio. OR=odds ratio.

Limitations

- Included patients either with ischemic or hemorrhagic stroke

- Included patients within 30 h of symptom onset

- The progress of mean systolic blood pressure is so close between to draw a conclusion.

Conclusion

- Can not draw conclusion between high blood pressure and low blood pressures in stroke

- Starting candesartan in the first day of the treatment is not superior to placebo.

Interpretation of the Literature
About Ischemic Stroke

- There is no evidence to drop the blood pressure in patients

  with ischemic stroke either with oral or intravenous

  antihypertensive

Hemorrhagic Stroke
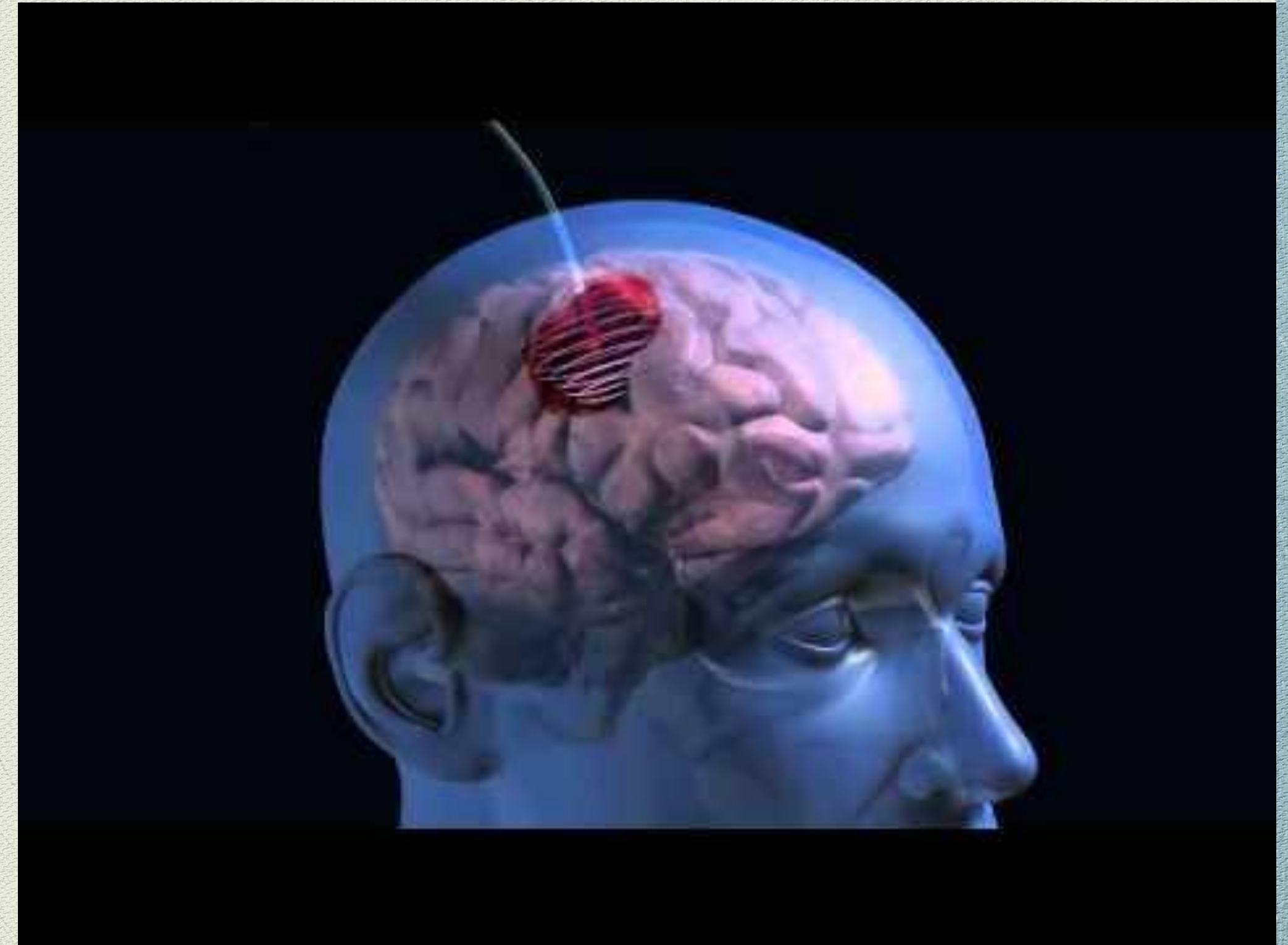
Stroke

JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Stroke Association℠

A Division of American Heart Association

Guidelines for the Management of Spontaneous Intracerebral Hemorrhage: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

Lewis B. Morgenstern, J. Claude Hemphill, III, Craig Anderson, Kyra Becker, Joseph P. Broderick, E. Sander Connolly, Jr, Steven M. Greenberg, James N. Huang, R. Loch Macdonald, Steven R. Messé, Pamela H. Mitchell, Magdy Selim, Rafael J. Tamargo and on behalf of the American Heart Association Stroke Council and Council on Cardiovascular Nursing

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/cgi/content/full/41/9/2108

Recommendations

In patients presenting with a systolic blood pressure of 150 to 220 mmHg, acute lowering of systolic blood pressure to 140 mmHg is probably safe (Class IIa; Level of Evidence B).

Until going clinical trials of BP intervention for ICH are completed physicians must manage BP on the basis of the present incomplete efficacy evidence.

Antihypertensive treatment of acute cerebral hemorrhage*

Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH) investigators

Objective: To determine the feasibility and acute (i.e., within 72 hrs) safety of three levels of systolic blood pressure reduction in subjects with supratentorial intracerebral hemorrhage treated within 6 hrs after symptom onset.

Design: A traditional phase I, dose-escalation, multicenter prospective study.

Settings: Emergency departments and intensive care units.

Patients: Patients with intracerebral hemorrhage with elevated systolic blood pressure ≥170 mm Hg who present to the emergency department within 6 hrs of symptom onset.

Intervention: Intravenous nicardipine to reduce systolic blood pressure to a target of: (1) 170 to 200 mm Hg in the first cohort of patients; (2) 140 to 170 mm Hg in the second cohort; and (3) 110 to 140 mm Hg in the third cohort.

Measurements and Main Results: Primary outcomes of interest were: (1) treatment feasibility (achieving and maintaining the systolic blood pressure goals for 18–24 hrs); (2) neurologic deterioration within 24 hrs; and (3) serious adverse events within 72 hrs. Safety stopping rules based on neurologic deterioration and serious adverse events were prespecified and approved by an NIH-appointed Data and Safety Monitoring Board, which provided oversight on subject safety. Each subject was followed-up for 3 months to preliminarily assess mortality and the clinical outcomes. A total of 18, 20, and 22 patients were enrolled in the respective three tiers of systolic blood pressure treatment goals. Overall, 9 of 60 patients had treatment failures (all in the last tier). A total of seven subjects with neurologic deterioration were observed: one (6%), two (10%), and four (18%) in tier one, two, and three, respectively. Serious adverse events were observed in one subject (5%) in tier two and in three subjects (14%) in tier three. However, the safety stopping rule was not activated in any of the tiers. Three (17%), two (10%), and five (23%) subjects in tiers one, two, and three, respectively, died within 3 months.

Conclusions: The observed proportions of neurologic deterioration and serious adverse events were below the prespecified safety thresholds, and the 3-month mortality rate was lower than expected in all systolic blood pressure tiers. The results form the basis of a larger randomized trial addressing the efficacy of systolic blood pressure reduction in patients with intracerebral hemorrhage. (Crit Care Med 2010; 38:637–648)

KEY WORDS: intracerebral hemorrhage; hypertension; nicardipine; systolic blood pressure; hematoma expansion

A cute hypertensive response (1) is observed in 46% to 75% of patients with intracerebral hemor-

associated with hematoma expansion (4, 5), increased mortality (6), and perihematoma brain edema formation (7) among patients

(15) recommend maintaining SBP <180 mm Hg in the acute period using short half-life IV antihypertensive medication.

- Patient: Hemorrhagic stroke within 6 hours over 18 years old, GCS≥8 and BP≥170

- Intervention: IV nicardipine

  - First group: 170-200 mmHg between 18 and 24 hours.

  - Second group: 140-170

  - Third group: 110-140

- Outcome: The two primary safety end points were:

  - (1) neurologic deterioration (defined by a decline in the GCS score ≥2 or increase in NIHSS score ≥4 points that is not explained by use of sedatives or hypnotics) within 24 hrs from treatment initiation; and

  - (2) SAE (defined per FDA guidelines) occurring within 72 hrs of treatment initiation.

Table 3. Demographic and clinical and treatment characteristics of subjects by SBP target tier

Characteristics	First Tier, SBP 170–200 mm Hg, n = 18	Second Tier, (SBP 140–170 mm Hg, n = 20	Third Tier, SBP 110–140 mm Hg, n = 22
Mean age ($\pm$SD)	62.0 (17.7)	58.5 (13.0)	65.1 (14.6)
Men	9 (50%)	12 (60%)	13 (59%)
Race/ethnicity			
White	5 (28%)	13 (65%)	13 (59%)
Black	11 (61%)	7 (35%)	7 (32%)
Others	2 (11%)	0	2 (9%)
Initial SBP in mm Hg, median	209	212	201
Initial NIHSS score, median	11	9	8
Initial GCS score, median	14	15	15
Mean time from symptom onset to emergency department arrival ($\pm$SD)	1.72 hrs (1.27)	1.70 hrs (1.13)	1.86 hrs (1.78)
Mean time from symptom onset to initiating treatment ($\pm$SD)	3.94 hrs (1.45)	4.13 hrs (1.50)	4.44 hrs (2.08)
N (%) treated within 3 hrs of symptom onset	7 (39%)	5 (25%)	6 (27.3%)
N (%) with previous use of oral antihypertensive medications	6 (33.3%)	11 (55%)	14 (63.6%)
N (%) compliant with oral antihypertensive medications	0	3 (15%)	8 (36.4%)
N (%) noncompliant or unknown compliance with oral antihypertensive medications	6 (33%)	8 (40%)	6 (27%)
N (%) with diabetes mellitus	2 (11.1%)	4 (20%)	4 (18.2%)
N (%) who currently smoke cigarettes	4 (22.2%)	6 (30%)	4 (18.2%)
N (%) with hyperlipidemia	2 (11.1%)	4 (20%)	5 (22.7%)
Initial hematoma volume ($\pm$SD)	15.45 mL (14.60)	14.84 mL (17.15)	10.94 mL (10.87)
Duration of nicardipine infusion ($\pm$SD)	12.93 hrs (13.5)	30.06 hrs (23.8)	45.82 hrs (37.3)
Maximum dose of nicardipine used ($\pm$SD)	8.47 (5.75)	8.90 (4.48)	12.52 (6.76)

NIHSS, National Institutes of Health Stroke Scale; GCS, Glasgow Coma Scale; SBP, systolic blood pressure.

A. Treatment tier one

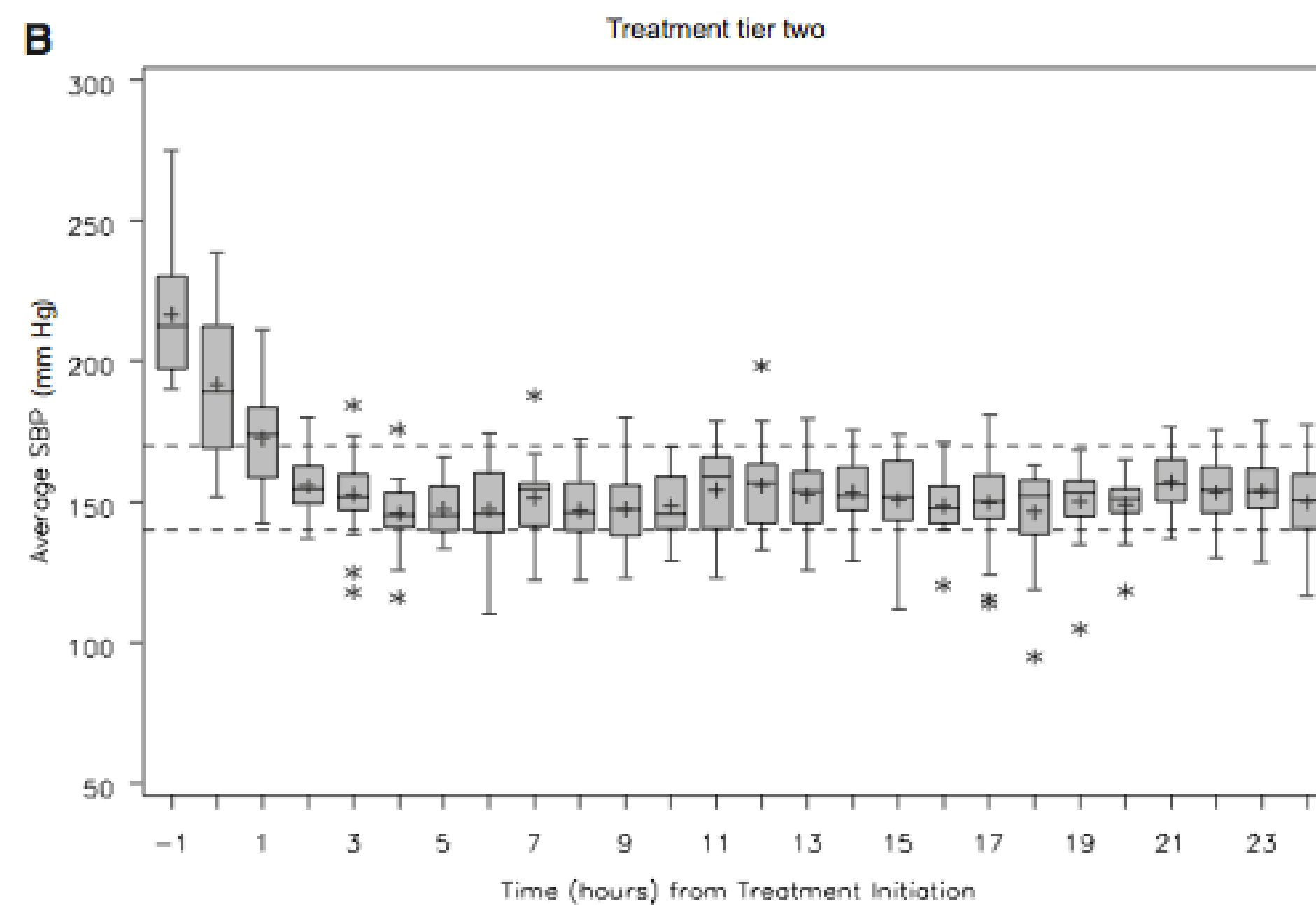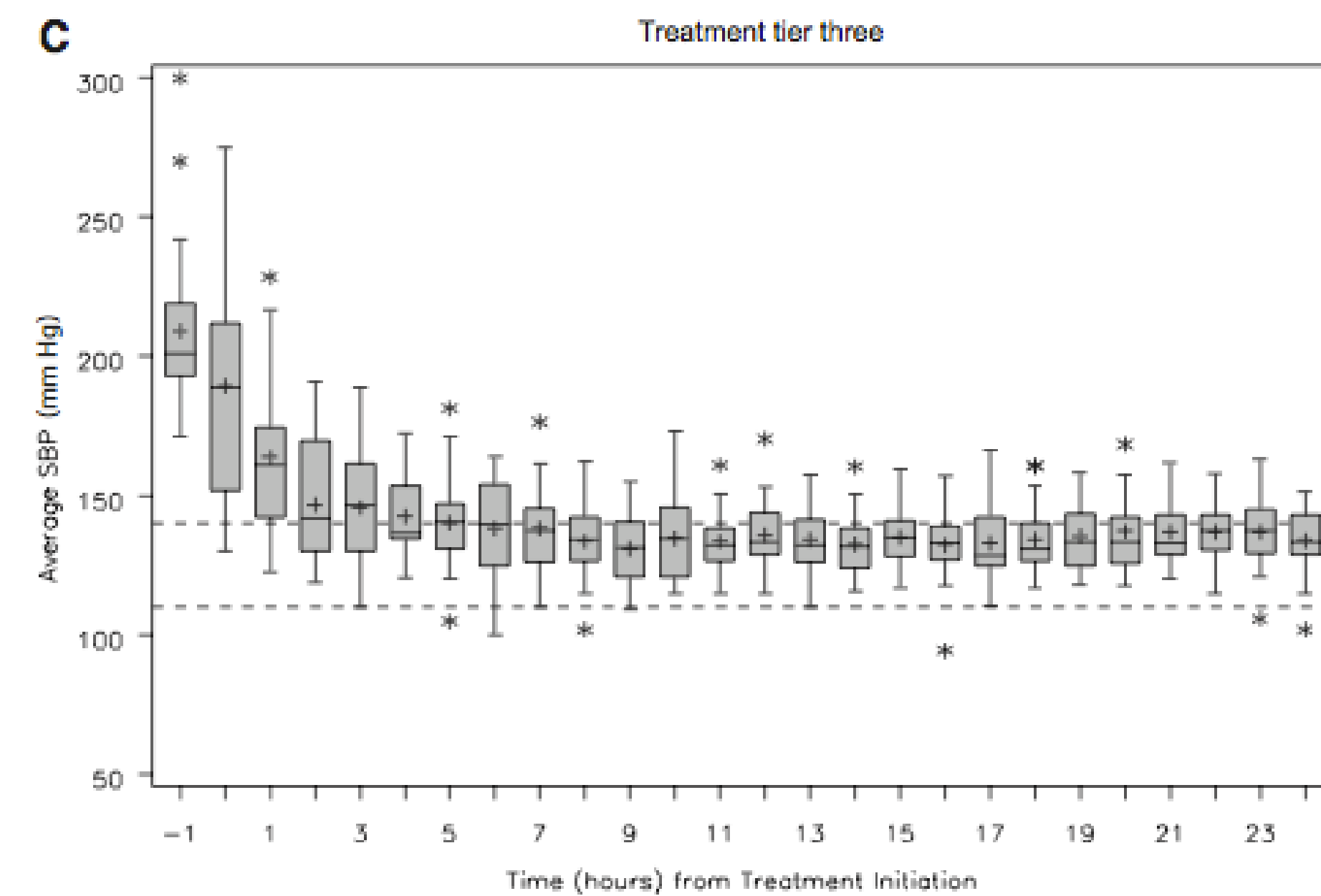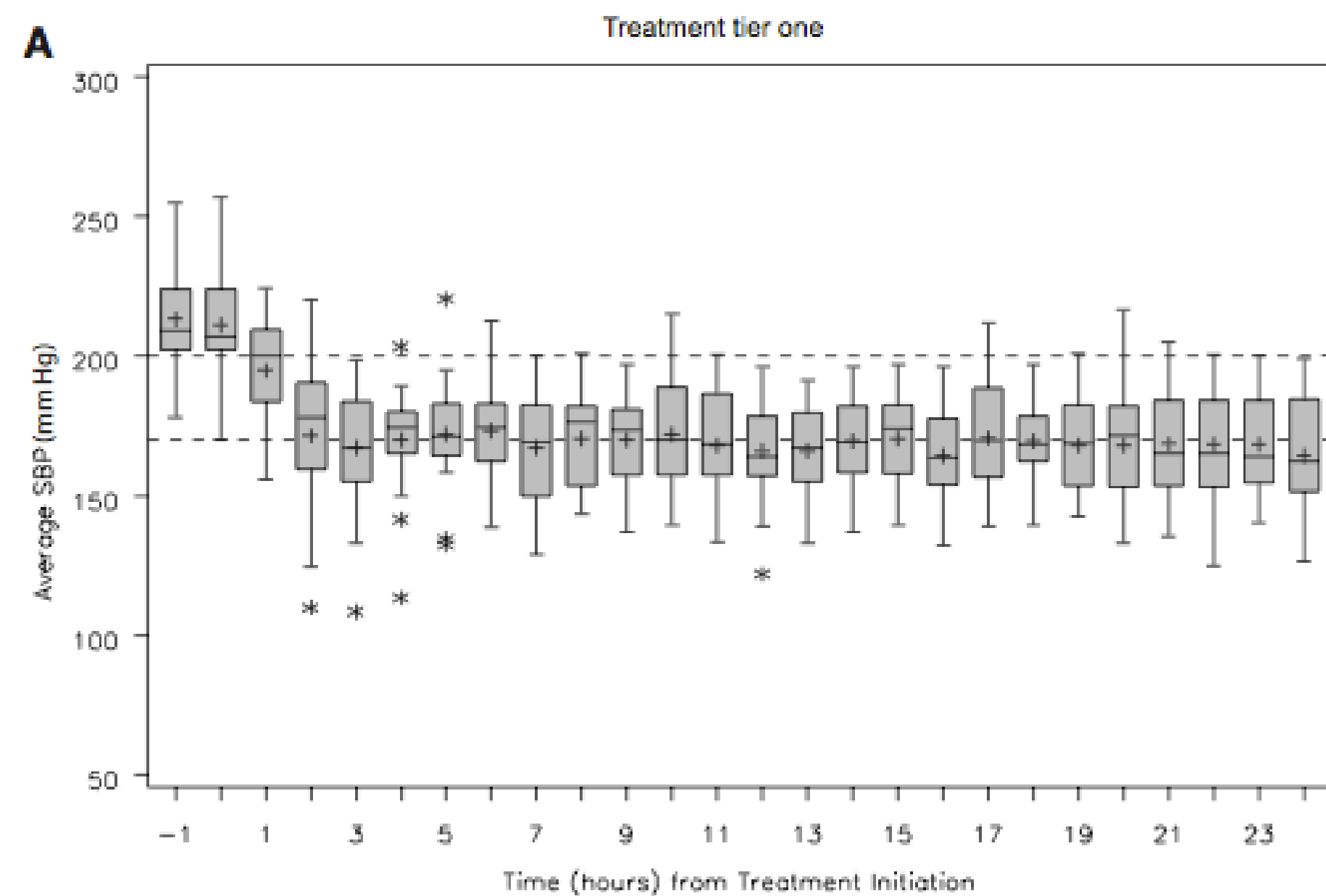B. Treatment tier two

C. Treatment tier three

49

Table 6. End points observed within subjects according to SBP target tier

Characteristics	First Tier, SBP 170–200 mm Hg, n = 18	Second Tier, SBP 140–170 mm Hg, n = 20	Third Tier, SBP 110–140 mm Hg, n = 22
Treatment failure	0	0	9 (41%)
N (%) with SAE within 72 hrs	0	1 (5%)	3 (14%)
N (%) with neurologic deterioration within 24 hrs	1 (6%)	2 (10%)	4 (18%)
N (%) with symptomatic hematoma expansion	0	1 (5%)	4 (18%)
N (%) with asymptomatic hematoma expansion	6 (33%)	2 (10%)	3 (14%)
N (%) with in-hospital mortality	2 (11%)	1 (5%)	1 (4 %)
N (%) with 3-mo mortality	3 (17%)	2 (10%)	5 (23%)
1-mo favorable outcome, mRS 0–2	4 (3 missing)	6 (3 missing)	4 (2 missing)
3-mo favorable outcome, mRS 0–2	8 (3 missing)	9 (4 missing)	7 (2 missing)

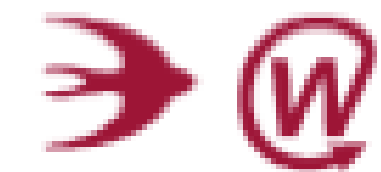SBP, systolic blood pressue; SAE, serious adverse event; mRS, modified Rankin score.

Limitations

- Very small sample size

- Predisposed to random bias

Intensive blood pressure reduction in acute cerebral haemorrhage trial (INTERACT): a randomised pilot trial

Craig S Anderson, Yining Huang, Ji Guang Wang, Hisatomi Arima, Bruce Neal, Bin Peng, Emma Heeley, Christian Skulina, Mark W Parsons, Jong Sung Kim, Qing Ling Tao, Yue Chun Li, Jian Dong Jiang, Li Wen Tai, Jin Li Zhang, En Xu, Yan Cheng, Stephane Heritier, Lewis B Morgenstern, John Chalmers, for the INTERACT Investigators*

Summary

Background There is much uncertainty about the effects of early lowering of elevated blood pressure (BP) after acute intracerebral haemorrhage (ICH). Our aim was to assess the safety and efficiency of this treatment, as a run-in phase to a larger trial.

Methods Patients who had acute spontaneous ICH diagnosed by CT within 6 h of onset, elevated systolic BP (150–220 mm Hg), and no definite indication or contraindication to treatment were randomly assigned to early intensive lowering of BP (target systolic BP 140 mm Hg; n=203) or standard guideline-based management of BP (target systolic BP 180 mm Hg; n=201). The primary efficacy endpoint was proportional change in haematoma volume at 24 h; secondary efficacy outcomes included other measurements of haematoma volume. Safety and clinical outcomes were assessed for up to 90 days. Analysis was by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00226096.

Findings Baseline characteristics of patients were similar between groups, but mean haematoma volumes were smaller in the guideline group (12·7 mL, SD 11·6) than in the intensive group (14·2 mL, SD 14·5). From randomisation to 1 h, mean systolic BP was 153 mm Hg in the intensive group and 167 mm Hg in the guideline group (difference 13·3 mm Hg, 95% CI 8·9–17·6 mm Hg; p<0·0001); from 1 h to 24 h, BP was 146 mm Hg in the intensive group and 157 mm Hg in the guideline group (10·8 mm Hg, 95% CI 7·7–13·9 mm Hg; p<0·0001). Mean proportional

- Patient: spontaneous ICH within 6 hours, ≥18 years old, BP between 150-220 mmHg, GCS ≥6

- Intervention: Lower blood pressure under 140 mmHg within 1st hour by IV anti-hypertensive

- Control: Keep blood pressure approximately 180mmHg.

- Outcome: the primary outcome was death from any cause and the secondary outcomes were early neurological deterioration (defined by a fall of ≥2 points on the GCS or a gain of ≥4 points in the NIHSS from baseline to 72 h)

	Guideline (n=201)	Intensive (n=203)
Median time from ICH onset to randomisation (h:min)	3:36 (2:54–4:54)	3:42 (2:54–4:48)
Age (years)	62 (13)	63 (12)
Male	139 (69%)	123 (61%)
Country of residence		
China	191 (95%)	193 (95%)
Australia	7 (3%)	6 (3%)
South Korea	3 (1%)	4 (2%)
Medical history*		
Hypertension	149 (74%)	151 (74%)
Previous ICH	19 (9%)	27 (13%)
Ischaemic stroke	24 (12%)	20 (10%)
Acute coronary event	7 (3%)	7 (3%)
Diabetes mellitus	13 (6%)	21 (10%)
Drug use*		
Antihypertensive therapy	90 (45%)	85 (42%)
Antiplatelet therapy	13 (6%)	19 (9%)
Warfarin anticoagulation	1 (0%)	3 (1%)
Clinical features		
Systolic blood pressure (mm Hg)	182 (19)	180 (18)
Diastolic blood pressure (mm Hg)	105 (15)	101 (14)
Heart rate (beats per min)	79 (15)	79 (14)
Median NIHSS score†	9 (5–16)	9 (5–14)
NIHSS score ≥14	64 (32%)	61 (30%)
Median GCS score‡	14 (12–15)	14 (13–15)
GCS score <9	16 (8%)	18 (9%)
Location of haematoma§		
Lobar	18 (10%)	15 (8%)
Basal ganglia or thalamus	148 (82%)	149 (83%)
Brainstem	11 (6%)	5 (3%)
Cerebellum	4 (2%)	10 (6%)
Undetermined	..	3 (2%)
Intraventricular extension	36 (21%)	45 (26%)
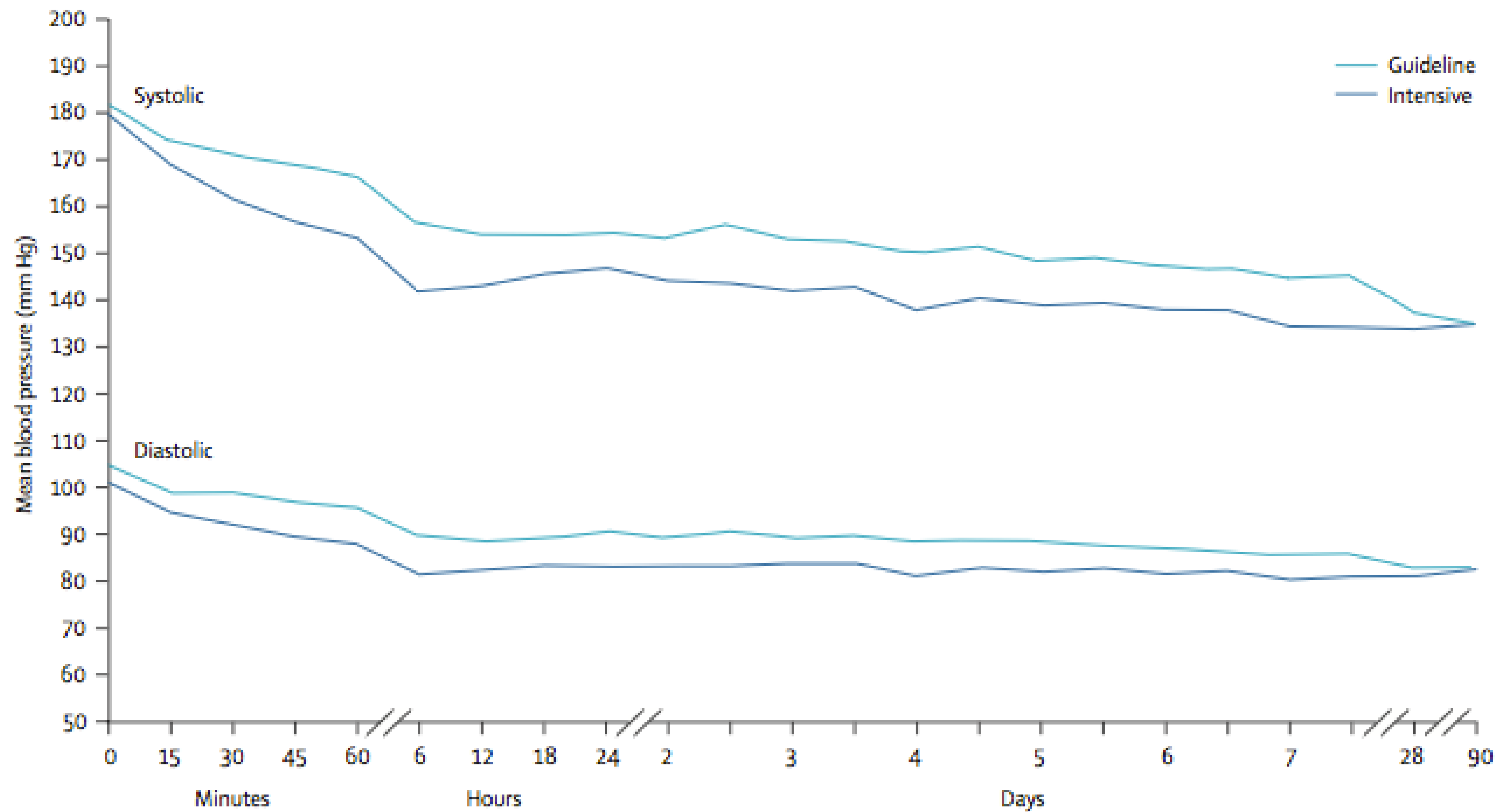
Figure 2: Mean systolic and diastolic blood pressure after randomisation

	Guideline (n=201)	Intensive (n=203)	p*
Death or dependency†	95 (49%)	95 (48%)	0·81
Death	25 (13%)	21 (10%)	0·51
Dependency	70 (36%)	74 (37%)	0·98
Median mRS score‡	2 (1–4)	2 (1–4)	0·66
Median NIHSS score§	2 (1–5)	2 (1–5)	0·97
Median Barthel index score¶	95 (65–100)	95 (65–100)	0·77
Median MMSE score‖	28 (22–30)	27 (22–30)	0·97
Median EQ5D score**	0·78 (0·59–1·00)	0·75 (0·52–1·00)	0·97
Early neurological deterioration††	30 (15%)	31 (15%)	0·94
Patients with a serious adverse event	42 (21%)	42 (21%)	0·96
Numbers of serious adverse events	61 (30%)	54 (27%)	0·40
Recurrent stroke‡‡	3 (2%)	2 (1%)	..
Acute coronary event	0 (0%)	1 (0%)	..
Other vascular events	3 (1%)	2 (1%)	..
Neurological deterioration§§	28 (14%)	23 (11%)	..
Renal failure	2 (1%)	4 (2%)	..
Non-vascular events	21 (10%)	17 (8%)	..
Pneumonia	15 (7%)	11 (5%)	..
Sepsis	2 (1%)	1 (0%)	..
Fracture	1 (0%)	0 (0%)	..
Other non-vascular events	3 (1%)	5 (2%)	..
Hypotension	4 (2%)	5 (3%)	..
Mild hypotension¶¶	0 (0%)	2 (1%)	..
Severe hypotension‖‖	4 (2%)	3 (1%)	..

- Limitations:

  - Small sample size

  - Drops in systolic blood pressure in control groups that prevents the comparison of high and low blood pressures in hemorrhagic stroke

- Conclusion:

  - Giving these patients IV anti-hypertensive agents may not contribute a better neurological outcome but tends to lower mortality with statistical insignificance.

Rapid Blood-Pressure Lowering in Patients with Acute Intracerebral Hemorrhage

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ABSTRACT

BACKGROUND

Whether rapid lowering of elevated blood pressure would improve the outcome in patients with intracerebral hemorrhage is not known.

METHODS

We randomly assigned 2839 patients who had had a spontaneous intracerebral hemorrhage within the previous 6 hours and who had elevated systolic blood pressure to receive intensive treatment to lower their blood pressure (with a target systolic level of <140 mm Hg within 1 hour) or guideline-recommended treatment (with a target systolic level of <180 mm Hg) with the use of agents of the physician's choosing. The primary outcome was death or major disability, which was defined as a score of 3 to 6 on the modified Rankin scale (in which a score of 0 indicates no symptoms, a score of 5 indicates severe disability, and a score of 6 indicates death) at 90 days. A prespecified ordinal analysis of the modified Rankin score was also performed. The rate of serious adverse events was compared between the two groups.

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*Investigators in the second Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT2) are listed in the Supplementary Appendix, available at NEJM.org.

- Patient: spontaneous intracranial hemorrhage within 6 hours, BP 150-220 mmHg

- Intervetion: achieving blood pressure level of less than 140 mmHg within 1 hour after randomization and maintaining this level for next 7 days.

  - IV and oral anti-hypertensives

- Control: Blood pressure was dropped if BP is over 180 mmHg with oral anti-hypertensives.

- Outcome: Major disability or death (Modified Rankin Score of 3-6).

Table 1. Baseline Characteristics of the Participants.*

Characteristic	Intensive Blood-Pressure Lowering (N = 1399)	Guideline-Recommended Blood-Pressure Lowering (N = 1430)
Time from onset of ICH to randomization — hr		
Median	3.7	3.7
Interquartile range	2.8–4.8	2.9–4.7
Age — yr	63.0±13.1	64.1±12.6
Male sex — no. (%)	898 (64.2)	882 (61.7)
Recruited from China — no. (%)	947 (67.7)	973 (68.0)
Blood pressure — mm Hg		
Systolic	179±17	179±17
Diastolic	101±15	101±15
NIHSS score†		
Median	10	11
Interquartile range	6–15	6–16
GCS score‡		
Median	14	14
Interquartile range	12–15	12–15
History of hypertension — no./total no. (%)	1012/1398 (72.4)	1036/1428 (72.5)
Current use of antihypertensive drugs — no./total no. (%)	627/1398 (44.8)	647/1428 (45.3)
Prior intracerebral hemorrhage — no./total no. (%)	115/1398 (8.2)	114/1428 (8.0)
Prior ischemic or undifferentiated stroke — no./total no. (%)	157/1398 (11.2)	166/1428 (11.6)
Prior acute coronary event — no./total no. (%)	39/1398 (2.8)	42/1428 (2.9)
Diabetes mellitus — no./total no. (%)	155/1398 (11.1)	150/1428 (10.5)
Use of warfarin anticoagulation — no./total no. (%)	50/1398 (3.6)	31/1428 (2.2)
Use of aspirin or other antiplatelet agent — no./total no. (%)	123/1398 (8.8)	142/1428 (9.9)
Baseline hematoma volume — ml		
Median	11	11
Interquartile range	6–19	6–20
Deep location of hematoma — no./total no. (%)§	1084/1294 (83.8)	1098/1319 (83.2)
Left hemisphere site of hematoma — no./total no. (%)	644/1294 (49.8)	669/1319 (50.7)
Intraventricular extension of hemorrhage — no./total no. (%)	371/1294 (28.7)	369/1319 (28.0)

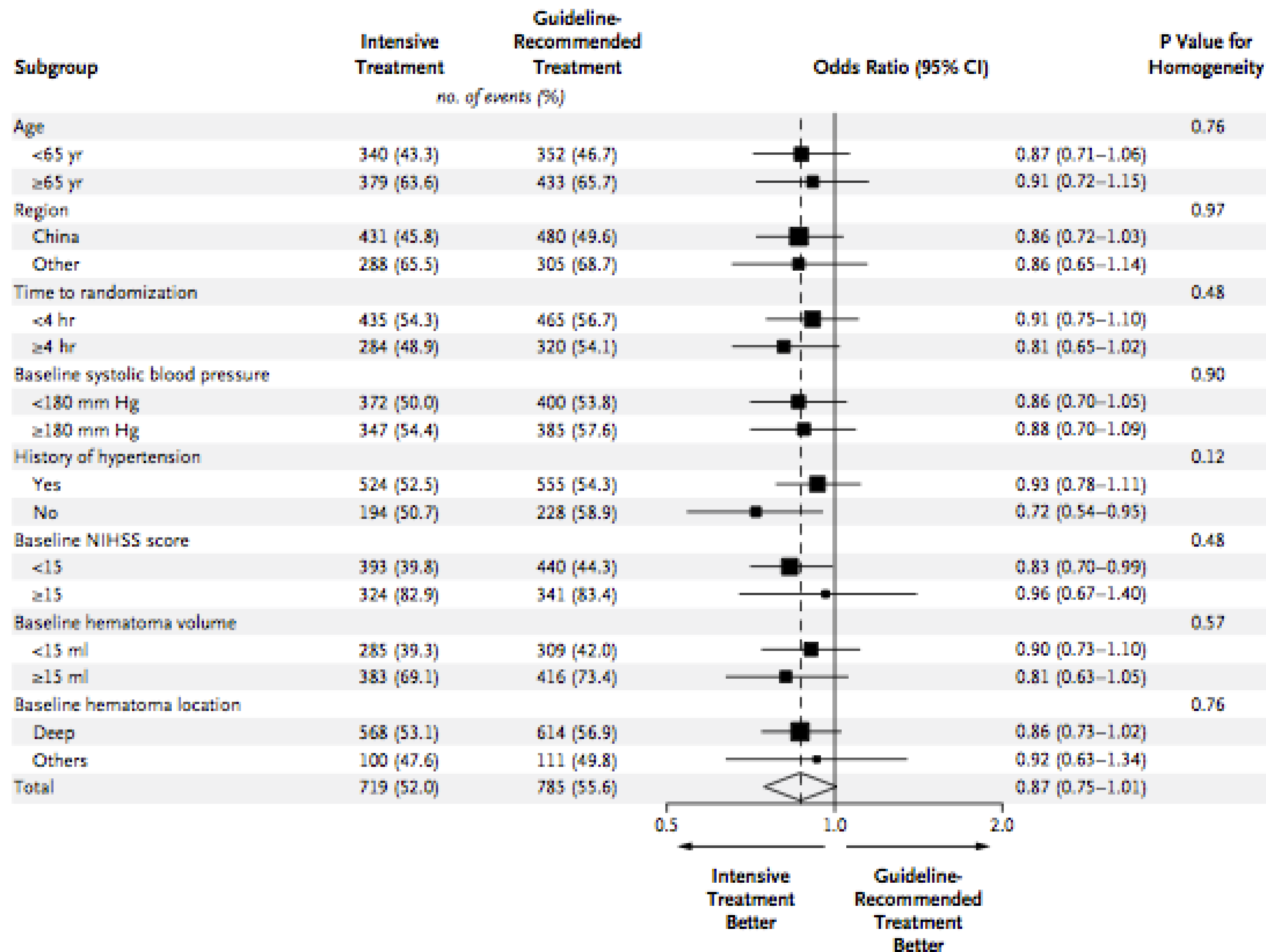Figure S2. Systolic blood pressure levels at and after randomization
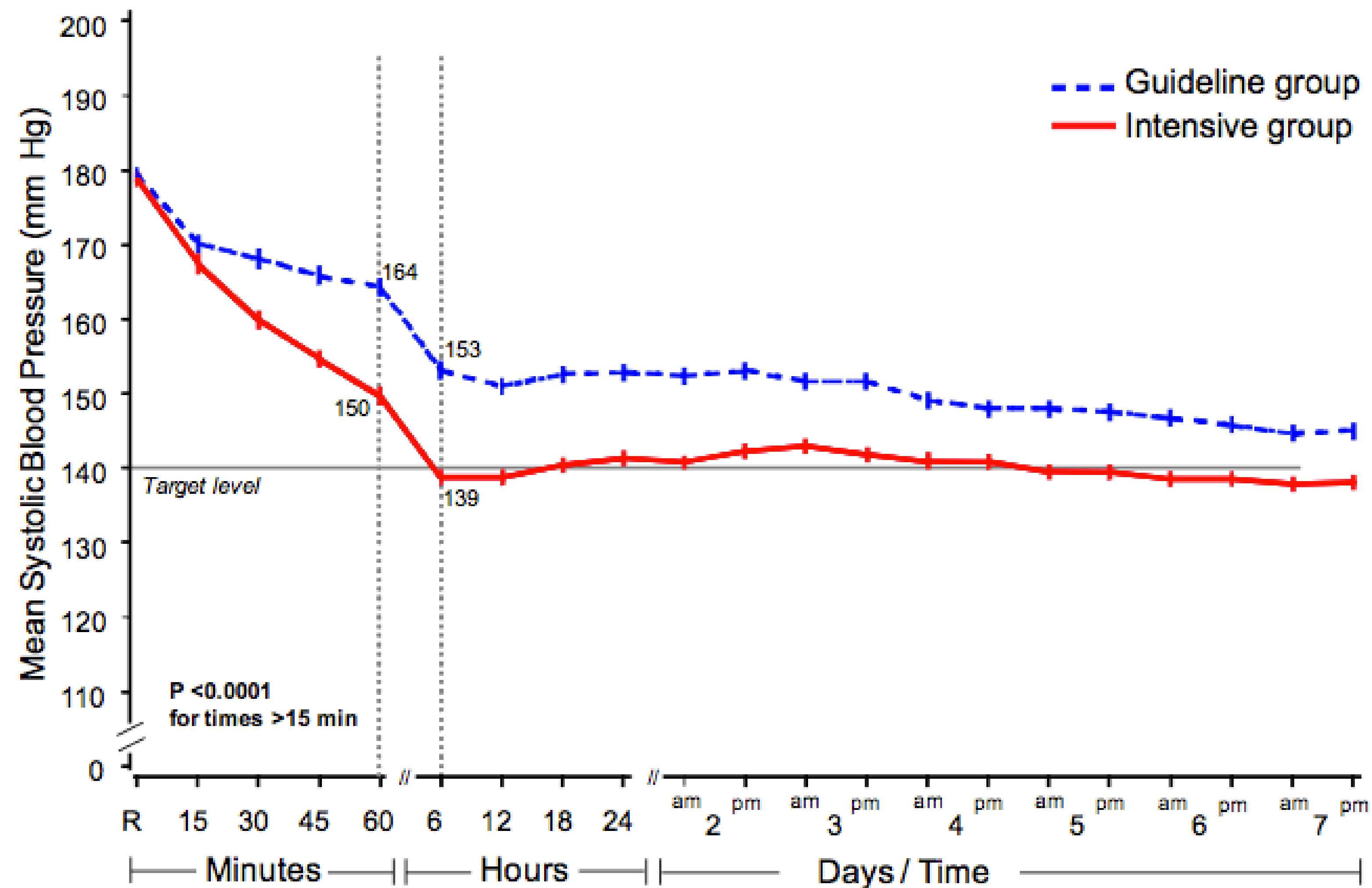
Table 3. Primary, Secondary, and Safety Outcomes at 90 Days.*

Variable	Intensive Blood-Pressure Lowering (N = 1399)	Guideline-Recommended Blood-Pressure Lowering (N = 1430)	Odds Ratio (95% CI)	P Value
Primary outcome: death or major disability — no./total no. (%)†	719/1382 (52.0)	785/1412 (55.6)	0.87 (0.75–1.01)	0.06
Secondary outcomes				
Score on the modified Rankin scale — no./total no. (%)‡			0.87 (0.77–1.00)	0.04
0: No symptoms at all	112/1382 (8.1)	107/1412 (7.6)		
1: No substantive disability despite symptoms	292/1382 (21.1)	254/1412 (18.0)		
2: Slight disability	259/1382 (18.7)	266/1412 (18.8)		
3: Moderate disability requiring some help	220/1382 (15.9)	234/1412 (16.6)		
4: Moderate–severe disability requiring assistance with daily living	250/1382 (18.1)	268/1412 (19.0)		
5: Severe disability, bed-bound and incontinent	83/1382 (6.0)	113/1412 (8.0)		
6: Death by 90 days	166/1382 (12.0)	170/1412 (12.0)		
Death — no./total no. (%)	166/1394 (11.9)	170/1421 (12.0)	0.99 (0.79–1.25)	0.96
Health-related quality of life§				
Problems with mobility — no./total no. (%)	767/1203 (63.8)	821/1231 (66.7)	0.88 (0.74–1.04)	0.13
Problems with self-care — no./total no. (%)	563/1202 (46.8)	635/1230 (51.6)	0.83 (0.70–0.97)	0.02
Problems with usual activities — no./total no. (%)	731/1203 (60.8)	814/1231 (66.1)	0.79 (0.67–0.94)	0.006
Problems with pain or discomfort — no./total no. (%)	477/1197 (39.8)	552/1227 (45.0)	0.81 (0.69–0.95)	0.01
Problems with anxiety or depression — no./total no. (%)	406/1192 (34.1)	463/1220 (38.0)	0.84 (0.72–1.00)	0.05
Overall health utility score	0.60±0.39	0.55±0.40		0.002
Living in residential care facility — no./total no. (%)	108/1222 (8.8)	114/1248 (9.1)	0.96 (0.73–1.27)	0.80
Duration of initial hospitalization — days				0.43
Median	20	19		
Interquartile range	12–35	11–33		

Subgroup	Intensive Treatment	Guideline-Recommended Treatment	Odds Ratio (95% CI)		Odds Ratio (95% CI)	P Value for Homogeneity
	no. of events (%)					
Age						0.76
<65 yr	340 (43.3)	352 (46.7)			0.87 (0.71–1.06)	
≥65 yr	379 (63.6)	433 (65.7)			0.91 (0.72–1.15)	
Region						0.97
China	431 (45.8)	480 (49.6)			0.86 (0.72–1.03)	
Other	288 (65.5)	305 (68.7)			0.86 (0.65–1.14)	
Time to randomization						0.48
<4 hr	435 (54.3)	465 (56.7)			0.91 (0.75–1.10)	
≥4 hr	284 (48.9)	320 (54.1)			0.81 (0.65–1.02)	
Baseline systolic blood pressure						0.90
<180 mm Hg	372 (50.0)	400 (53.8)			0.86 (0.70–1.05)	
≥180 mm Hg	347 (54.4)	385 (57.6)			0.88 (0.70–1.09)	
History of hypertension						0.12
Yes	524 (52.5)	555 (54.3)			0.93 (0.78–1.11)	
No	194 (50.7)	228 (58.9)			0.72 (0.54–0.95)	
Baseline NIHSS score						0.48
<15	393 (39.8)	440 (44.3)			0.83 (0.70–0.99)	
≥15	324 (82.9)	341 (83.4)			0.96 (0.67–1.40)	
Baseline hematoma volume						0.57
<15 ml	285 (39.3)	309 (42.0)			0.90 (0.73–1.10)	
≥15 ml	383 (69.1)	416 (73.4)			0.81 (0.63–1.05)	
Baseline hematoma location						0.76
Deep	568 (53.1)	614 (56.9)			0.86 (0.73–1.02)	
Others	100 (47.6)	111 (49.8)			0.92 (0.63–1.34)	
Total	719 (52.0)	785 (55.6)			0.87 (0.75–1.01)	

0.5   1.0   2.0

Intensive Treatment Better ← | → Guideline-Recommended Treatment Better

Figure 1. Effect of Early Intensive Blood-Pressure–Lowering Treatment on the Primary Outcome, According to Prespecified Subgroups.

- Limitations:

  - The dramatic decreases of blood pressure in control group

  - Inability to control the effect of oral anti-hypertensive agents in control group which results with lower blood pressure.

- Conclusion:

  - No conclusion in order to compare the prognosis of patients with high blood pressure and low blood pressure like over 180 and 140 mmHg.

  - Intense lowering tends to result with good neurological outcome but not death.

Conclusion from The Literature

- Intensive lowering the blood pressure tends to be result with good neurological outcome rather than death??

- More trials needed comparing the high BPs and intensive lowering for drawing a conclusion

- Just wait the results of ATTACH2 trial that is coming up in 2006