Ischemic Stroke Management Update

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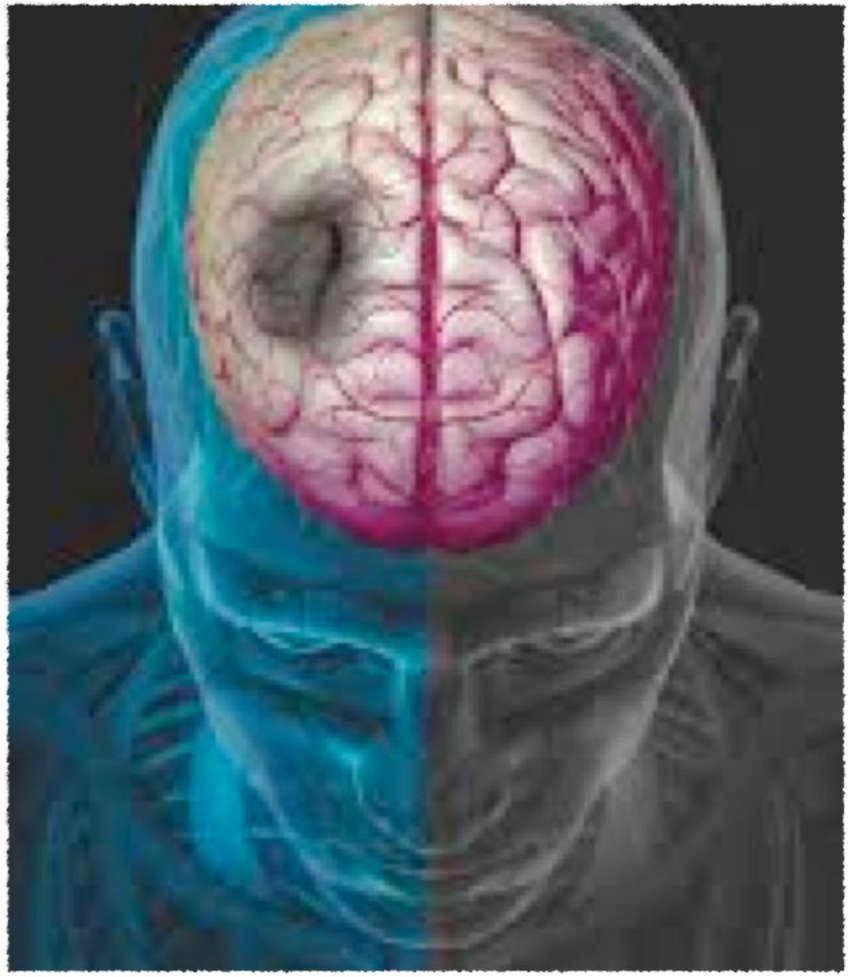
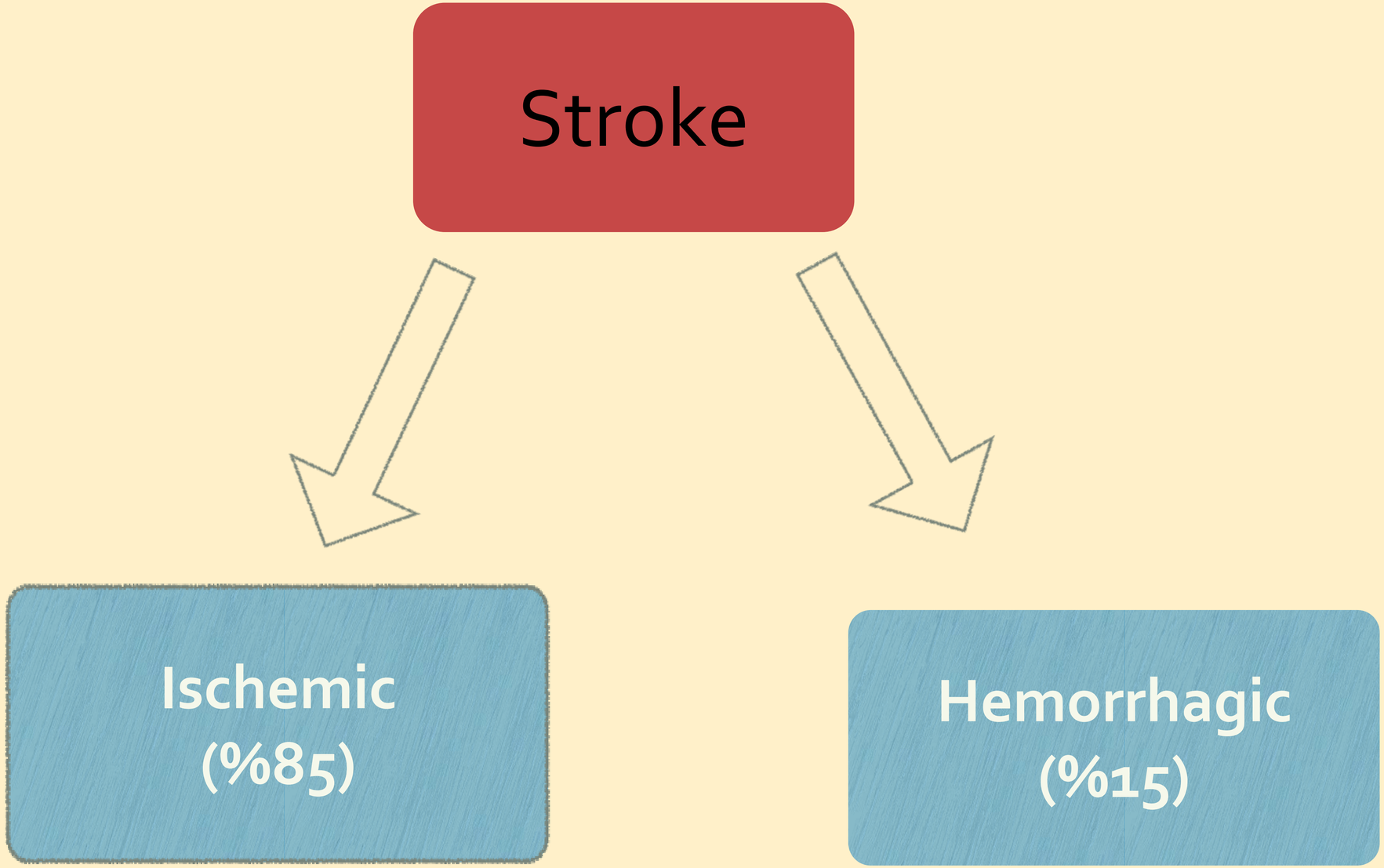
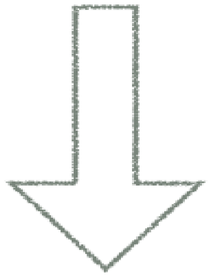



Stroke
Ischemic
(%85)
Hemorrhagic
(%15)

Ischemic Stroke

Clinical Challenges for ED Physicians



1. Blood Pressure Management
2. Thrombolytic Therapy

Blood Pressure Management

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

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

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

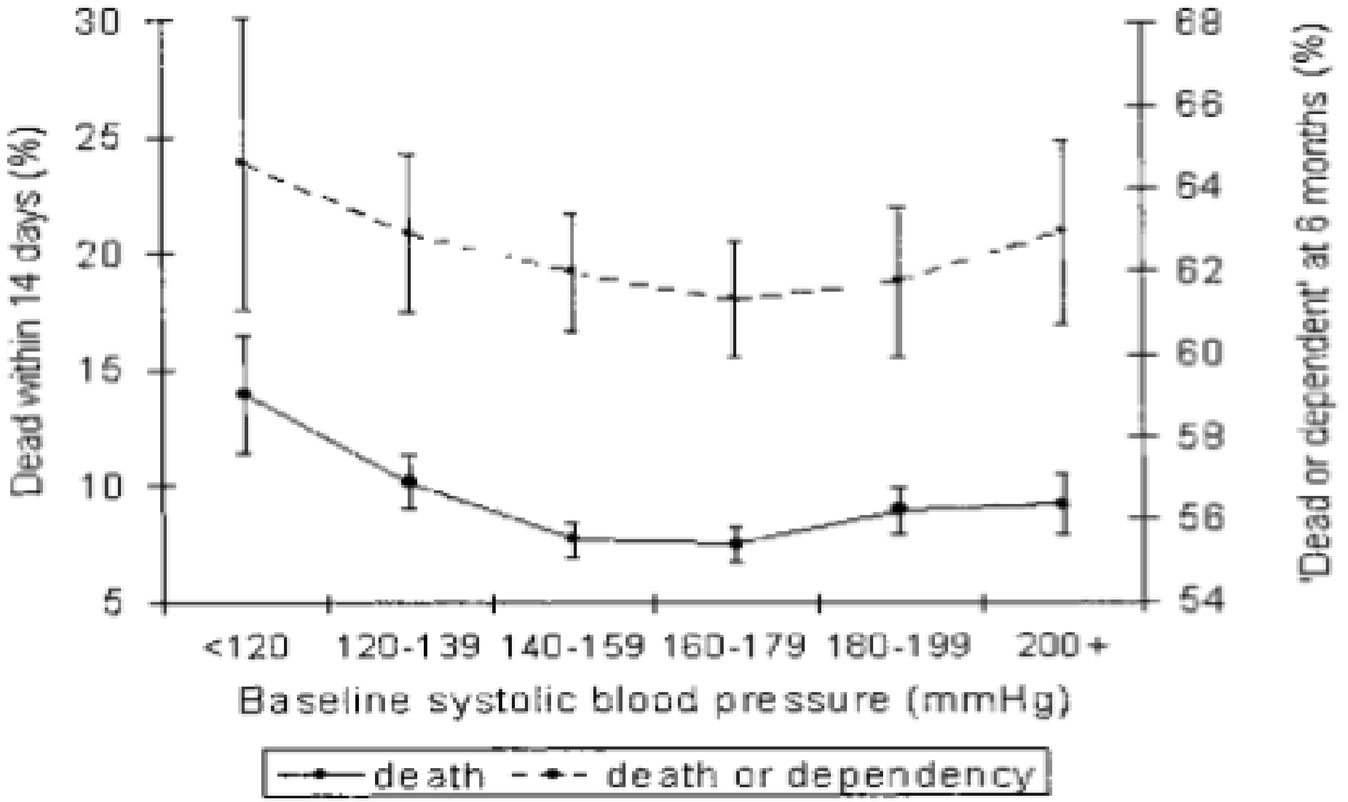
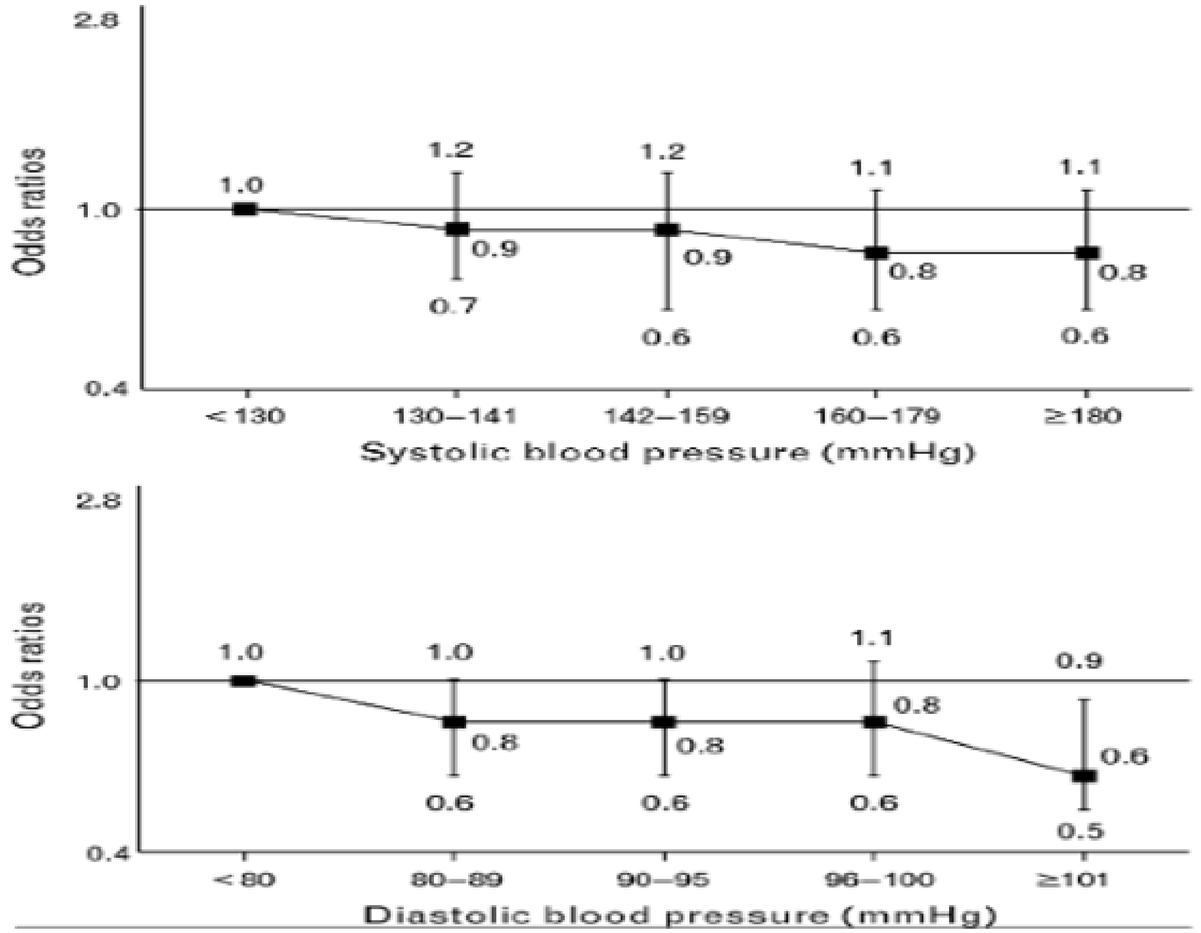


Figure 2. Proportion of patients who died within 14 days (solid lines) or were dead or dependent at 6 months (dashed lines) by baseline SBP. Circles and squares indicate the mean percent-

Zhang Y, Reilly KH, Tong W, et al. Blood Pressure and Clinical Outcome Among Patients with Acute Ischemic Stroke in Inner Mongolia, China. J Hypertens. 2008;26:1446-1452.

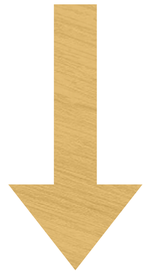


Multiple-adjusted odds ratios and 95% confidence interval of death/disability by the quintiles of systolic blood pressure (top panel) and diastolic blood pressure (lower panel) among ischemic stroke patients.

Normotensive stroke patients in acute setting

vs

Hypertensive stroke patients in acute setting



Is opposite true?

Better outcome

Poor outcome

Stroke
JOURNAL OF THE AMERICAN HEART 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

Stroke. 2013;44:870-947; originally published online January 31, 2013;
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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
JOURNAL OF THE 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

Hypertension. 2009;54:775-781; originally published online August 3, 2009;
doi: 10.1161/HYPERTENSIONAHA.109.133538
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0194-911X. Online ISSN: 1524-4563

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.

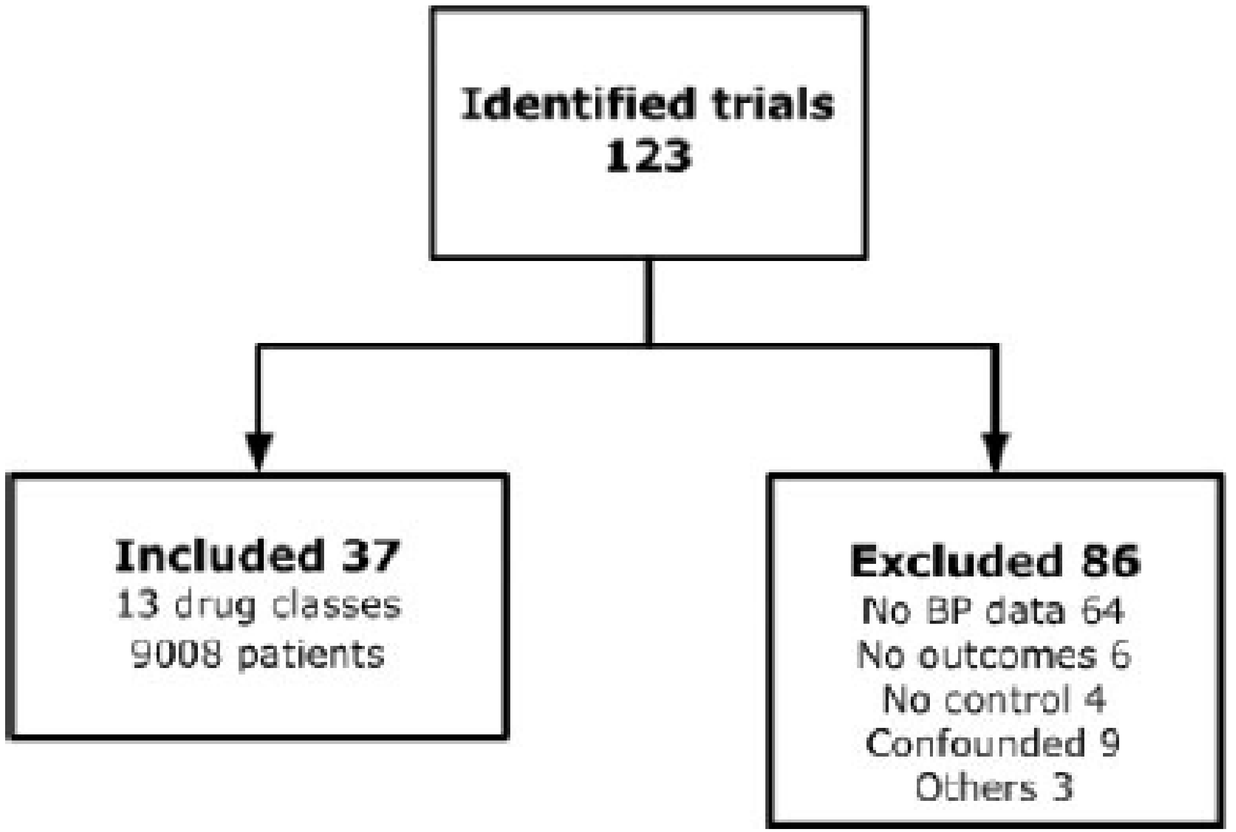
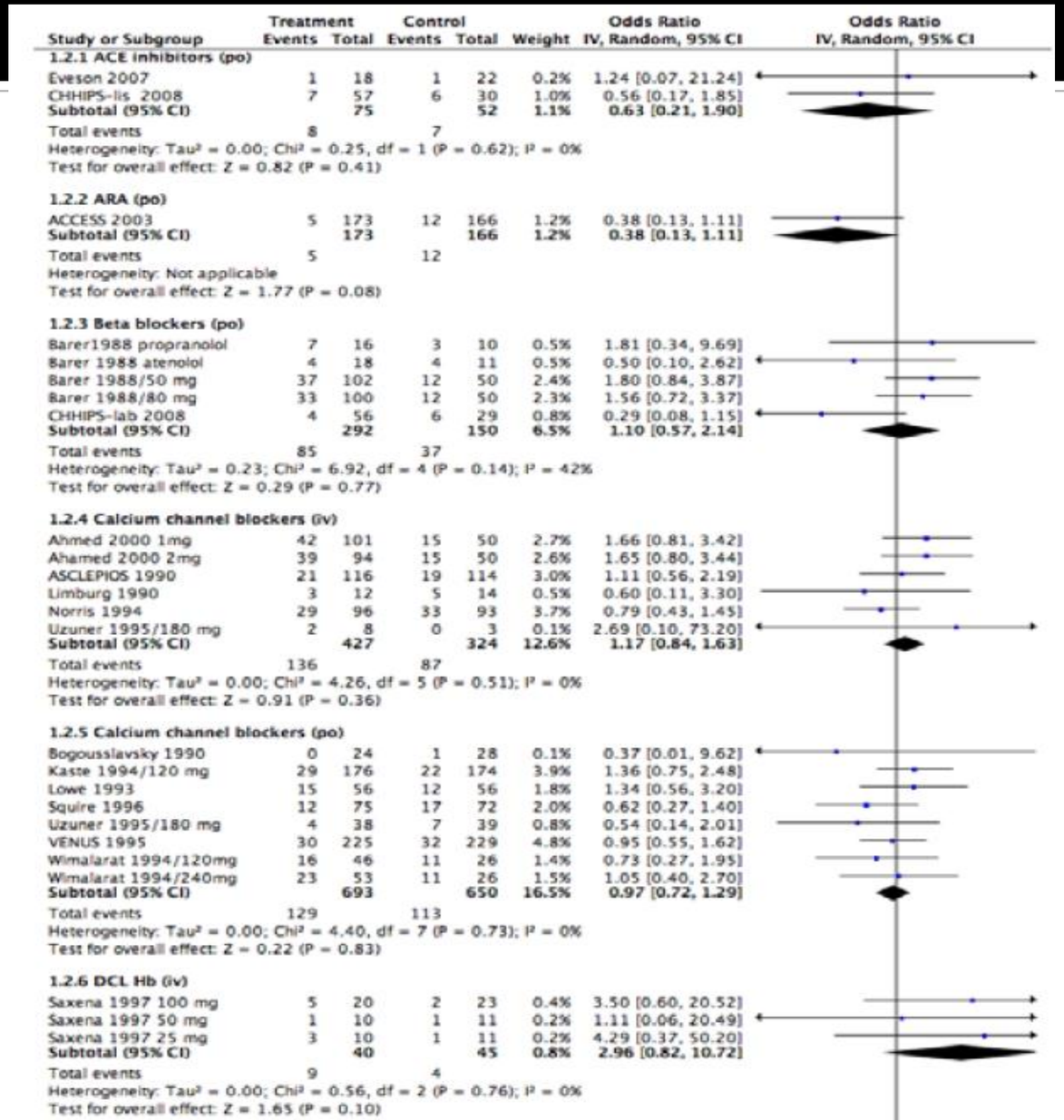
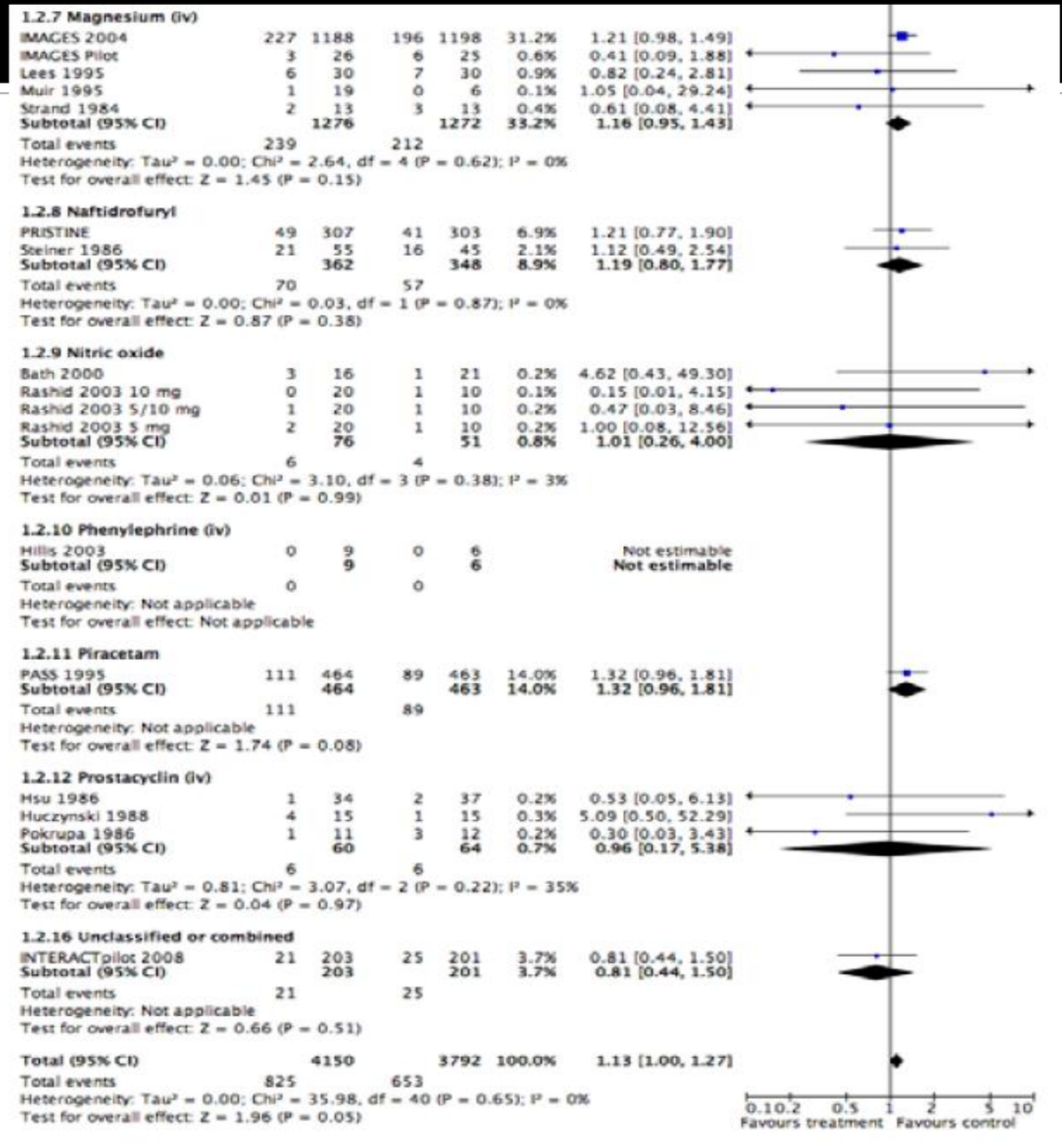
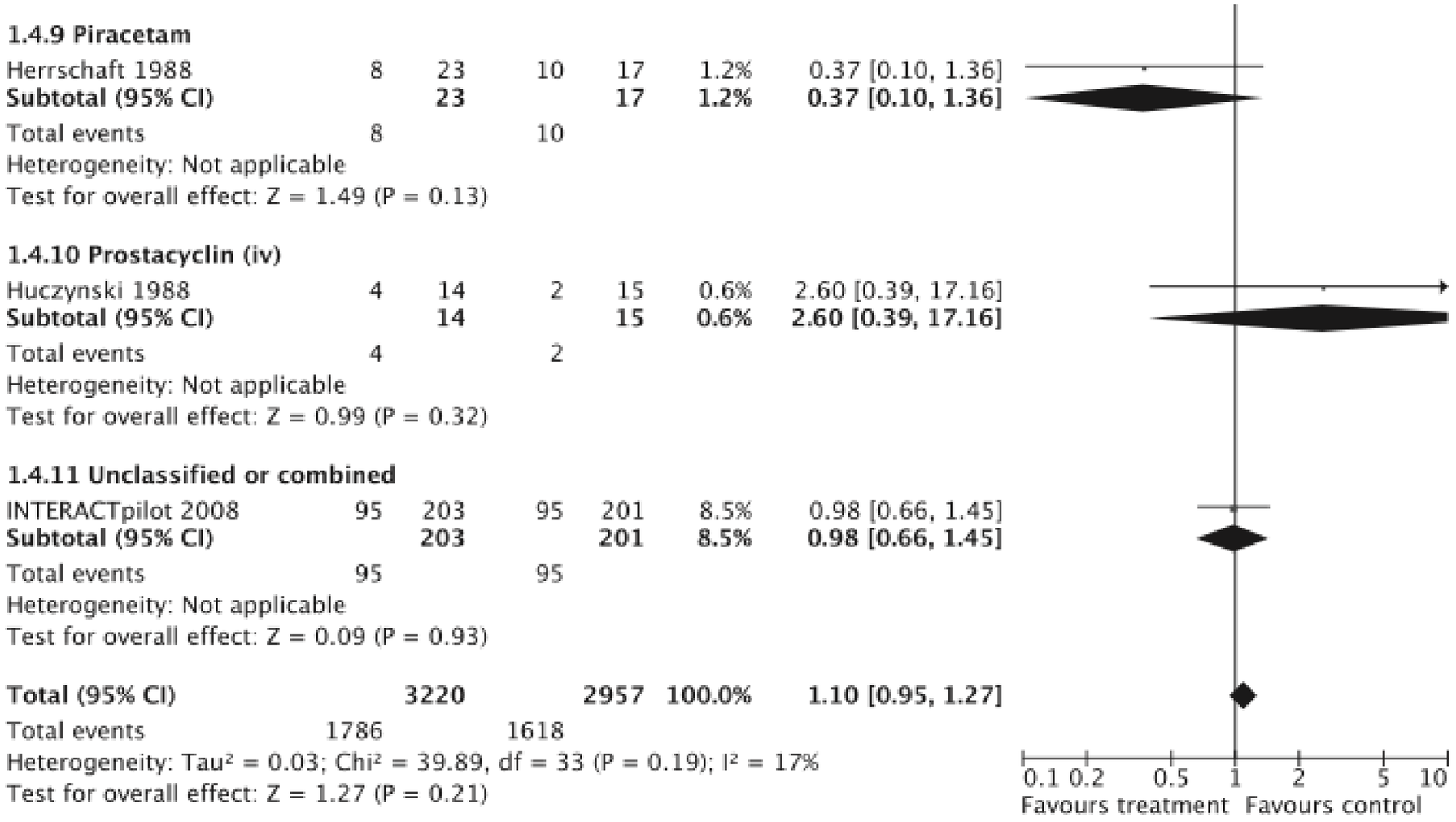


Figure 1. Search process for relevant studies.

Death Within One Month






1.4.9 Piracetam
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)
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
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

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.

Supplemental content at jama.com

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.

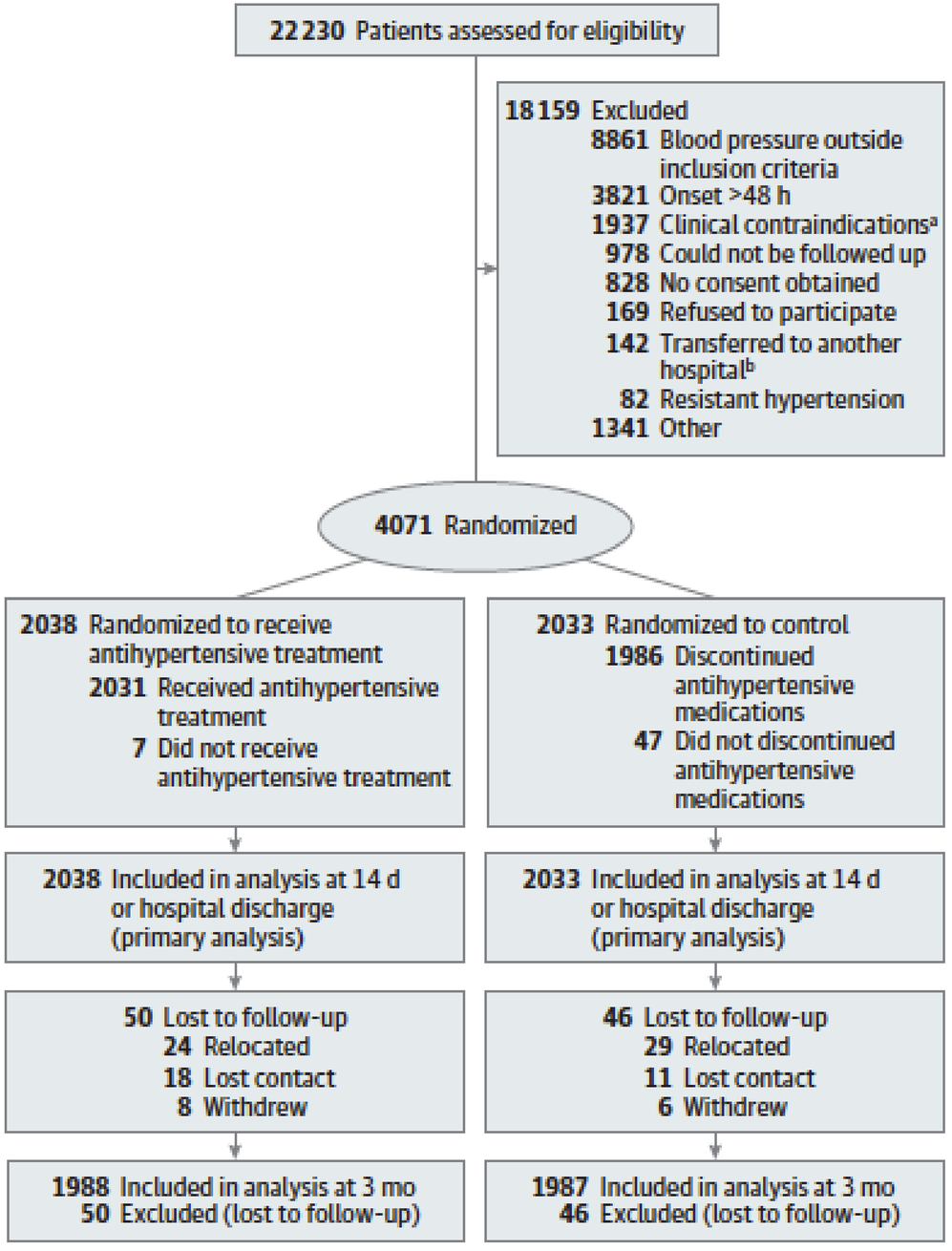


Table 1. Baseline Characteristics of the Trial Participants

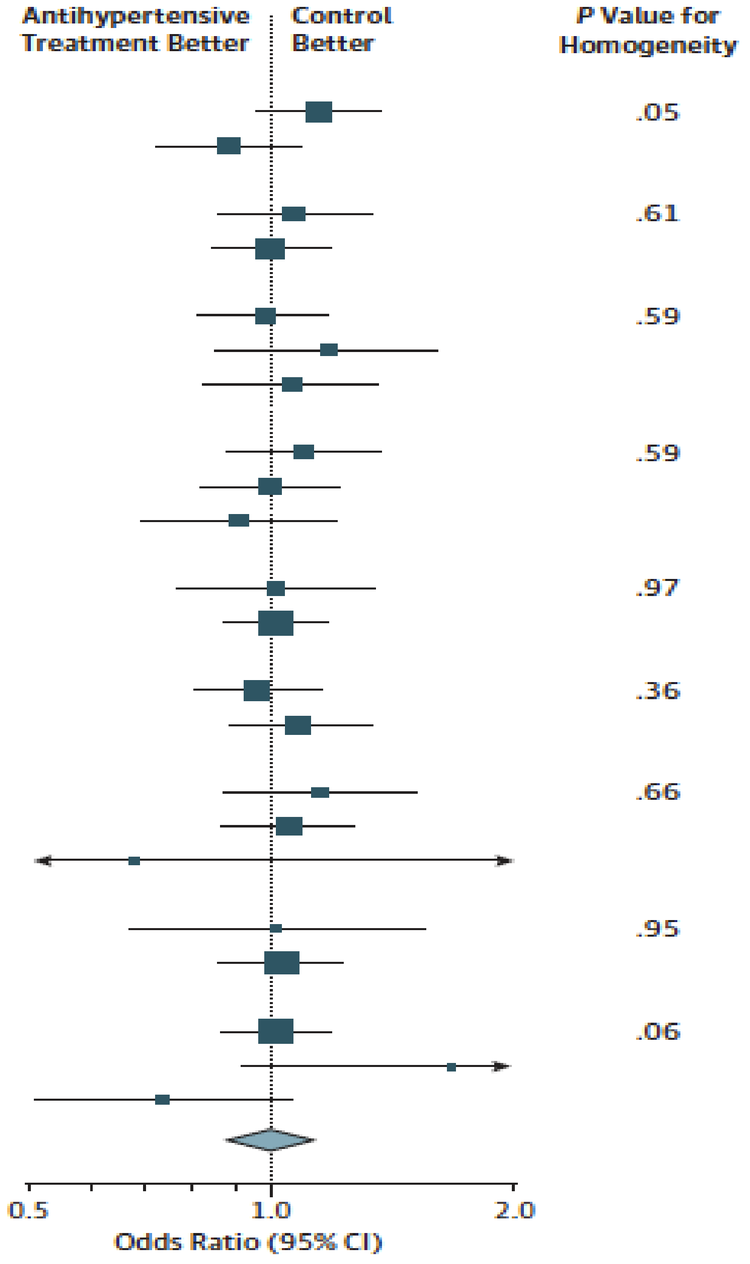
Characteristics	Antihypertensive Treatment (n = 2038)	Control (n = 2033)
Age, mean (SD), y	62.1 (10.8)	61.8 (11.0)
Men, No. (%)	1317 (64.6)	1287 (63.3)
Time from onset to randomization, mean (SD), h	15.3 (12.9)	14.9 (13.0)
Blood pressure at entry, mean (SD), mm Hg		
Systolic	166.7 (17.3)	165.6 (16.5)
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 Total, No.	Antihypertensive Treatment Events, No. (%)	Control Total, No.	Control Events, No. (%)	Odds Ratio (95% CI)	P Value for Homogeneity
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)	



Limitations

- Did not enrolled patients 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 over giving up the anti-hypertensive drugs or not administering an anti-hypertensive medication.
- 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≤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.

Lancet 2011; 377: 741–50

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See Comment page 696

Department of Internal Medicine (E C Sandset MD, E Berge MD), **Department of Haematology** (E C Sandset), and **Department of Cardiology** (E Berge), **Oslo University Hospital Ullevål, and Institute of Clinical Medicine, University of Oslo** (E C Sandset), **Oslo, Norway; Stroke Trials Unit, Division of Stroke, University of Nottingham, Nottingham, UK** (Prof P M W Bath FRCP); **Department of Neurology, Bispebjerg Hospital, and University of Copenhagen, Copenhagen, Denmark** (Prof G Boysen DMSc); **Faculty of Medicine, Vilnius University, and Department of Neurology, Vilnius University Santariskiu Klinikos Hospital, Vilnius, Lithuania** (D Jatuzis MD); **Department of Neurology, Tartu University Hospital, Tartu, Estonia** (J Kõrv MD); **Department of Internal Medicine, St Josefs Hospital, Cloppenburg,**

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**

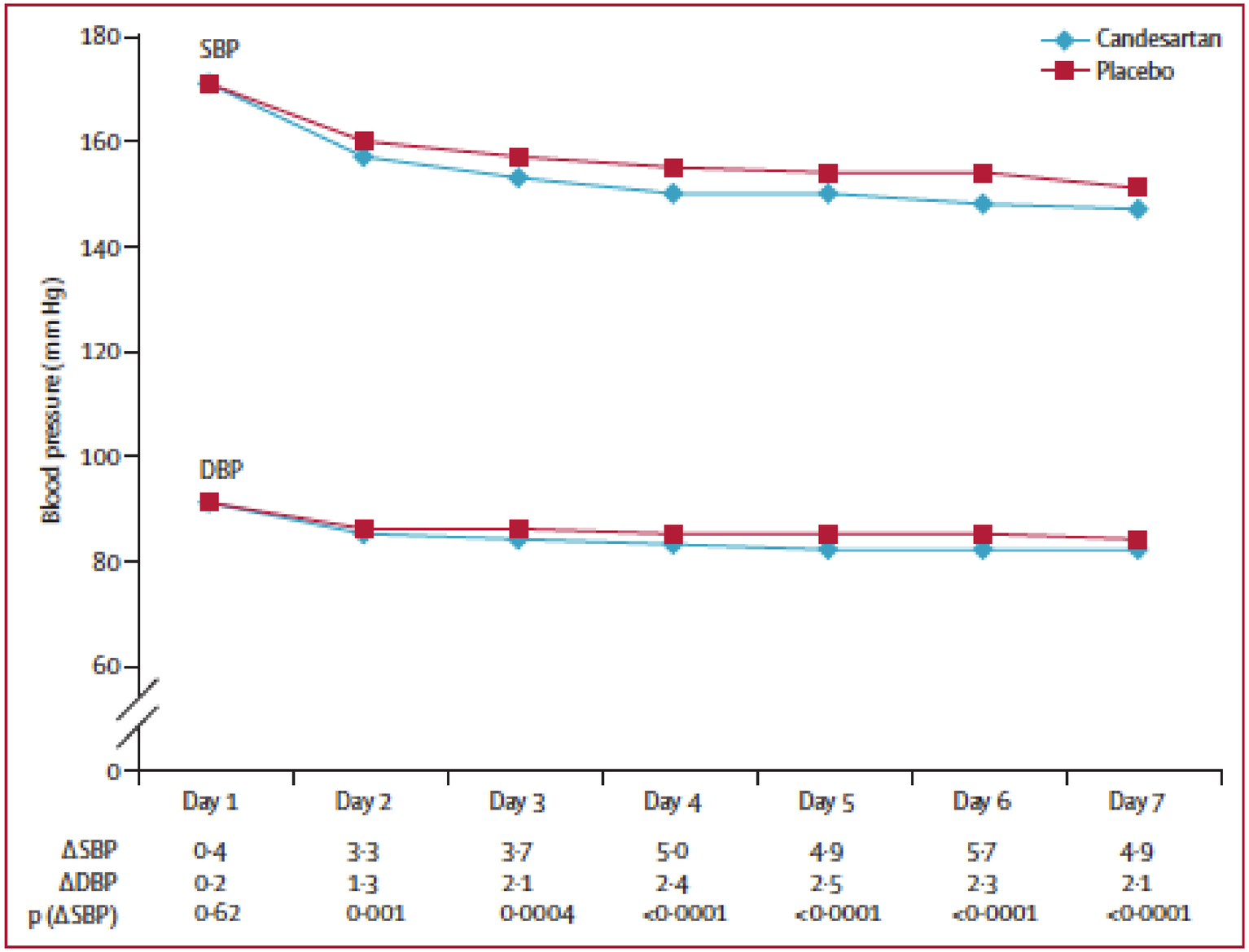


Figure 2: **Blood pressure during 7 days' treatment**

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=982)	Placebo (n=974)	p value
SSS score at 7 days	51 (38–56)	51 (41–56)	0·13
Barthel index at 6 months	100 (80–100)	100 (85–100)	0·47

Data are median (IQR) or p value. Analysis was by the Mann-Whitney *U* test.
SSS=Scandinavian Stroke Scale.

Table 4: **Secondary clinical outcomes**

	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**

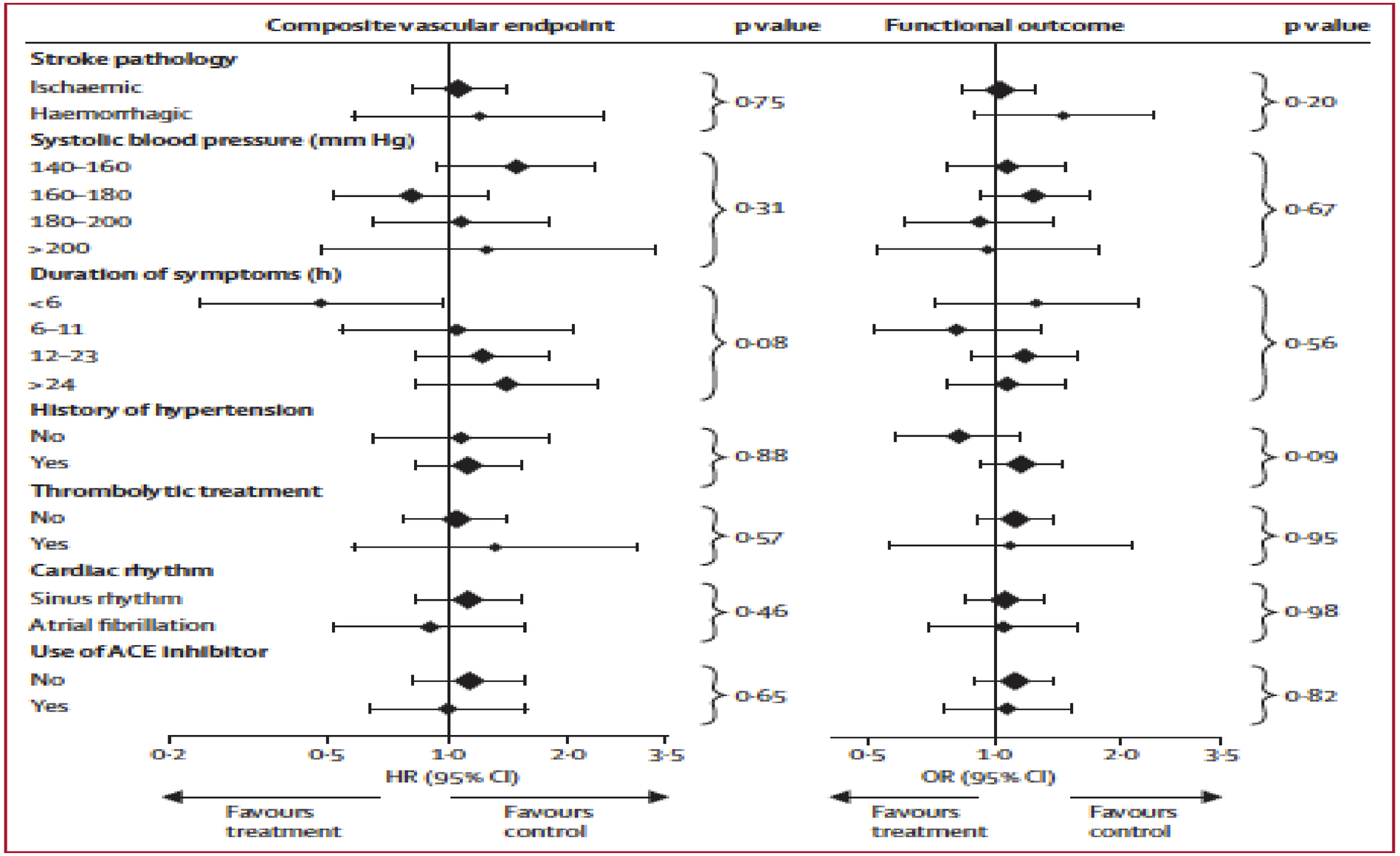


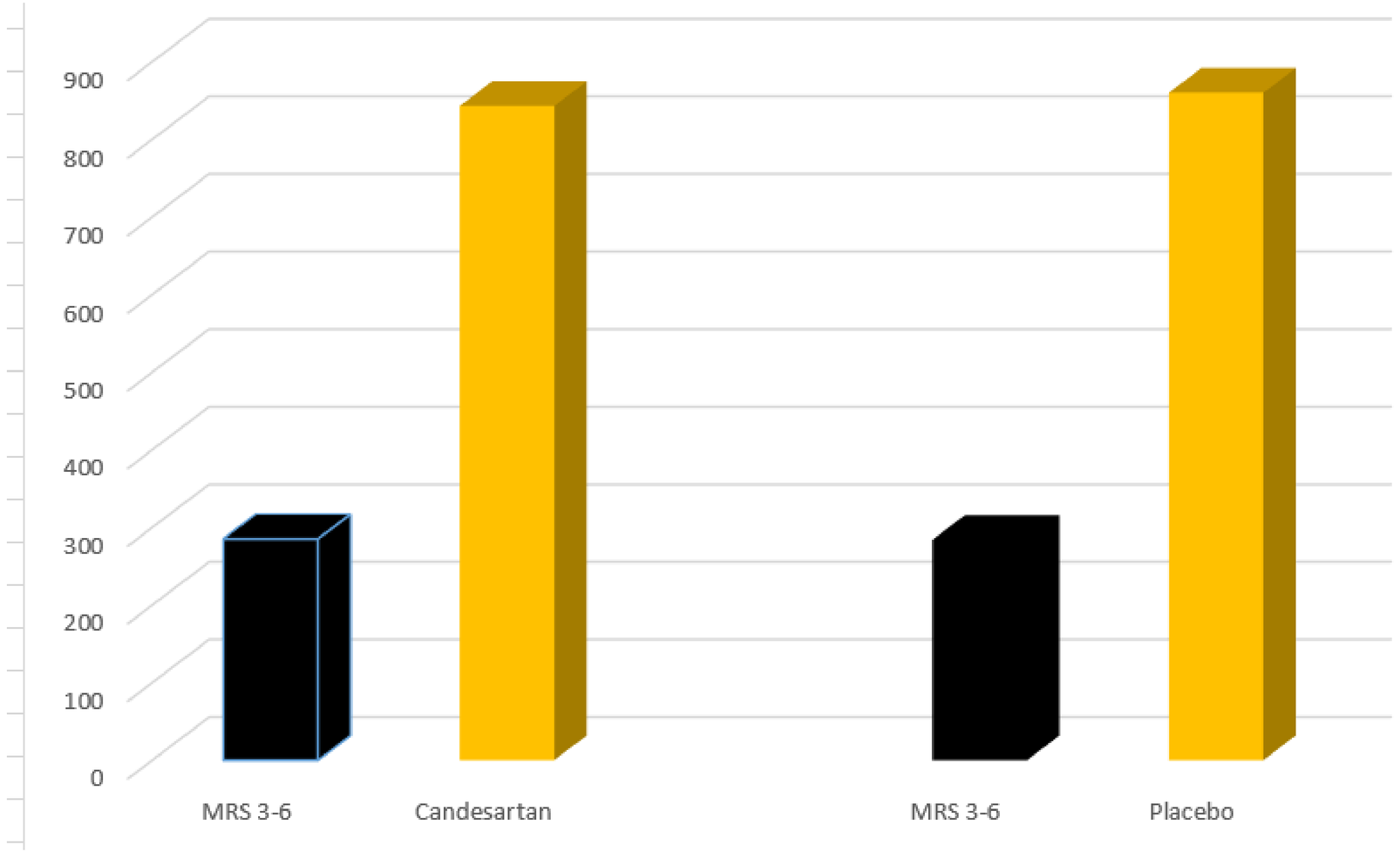
***Figure 5*: Subgroup analysis of effects on the composite vascular endpoint during 6 months' follow-up and functional outcome at 6 months**

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 the candesartan and placebo groups to draw a conclusion.

Analysis of Ischemic Stroke Patients in SCAST Trial



33.8%

33%

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 an oral or intravenous antihypertensive

Controversies on t-PA?

BMJ

BMJ 2013;347:f5215 doi: 10.1136/bmj.f5215 (Published 29 August 2013)

HEAD TO HEAD

Do risks outweigh benefits in thrombolysis for stroke?

Simon Brown and **Stephen Macdonald** argue that patients with stroke should not be given thrombolysis outside clinical trials, but **Graeme Hankey** says the benefits are clear in carefully selected patients

The Skeptics' Guide to EM

SGEM#85: Won't Get Fooled Again (tPA for CVA)

American College of Emergency Physicians

NEUROLOGY/CLINICAL POLICY

Clinical Policy: Use of Intravenous tPA for the Management of Acute Ischemic Stroke in the Emergency Department

This clinical policy is the result of a collaborative project of the American College of Emergency Physicians and the American Academy of Neurology.

Development Panel

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Robert L. Wears, MD, MS (Methodologist; Department of Emergency Medicine, University of Florida, Jacksonville, FL)

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American College of Emergency Physicians

CRITICAL QUESTIONS

1. **Is IV tPA safe and effective for acute ischemic stroke patients if given within 3 hours of symptom onset?**
2. **Is IV tPA safe and effective for acute ischemic stroke patients treated between 3 to 4.5 hours after symptom onset?**

Patient Management Recommendations

Level A recommendations. In order to improve functional outcomes, IV tPA should be offered to acute ischemic stroke patients who meet National Institute of Neurological Disorders and Stroke (NINDS) inclusion/exclusion criteria and can be treated within 3 hours after symptom onset.*

Level B recommendations. In order to improve functional outcomes, IV tPA should be considered in acute ischemic stroke patients who meet European Cooperative Acute Stroke Study (ECASS) III inclusion/exclusion criteria and can be treated between 3 to 4.5 hours after symptom onset.*

*The effectiveness of tPA has been less well established in institutions without the systems in place to safely administer the medication.

AHA/ASA Guideline

Guidelines for the Early Management of Patients With Acute Ischemic Stroke

A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

The American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists.

Endorsed by the American Association of Neurological Surgeons and Congress of Neurological Surgeons

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

Recommendations

1. **Intravenous rtPA (0.9 mg/kg, maximum dose 90 mg) is recommended for selected patients who may be treated within 3 hours of onset of ischemic stroke *(Class I; Level of Evidence A)*. Physicians should review the criteria outlined in** Tables 10 and11 **(which are modeled on those used in the NINDS Trial) to determine the eligibility of the patient. A recommended regimen for observation and treatment of patients who receive intravenous rtPA is described in** Table 12. (Unchanged from the previous guideline[13])
2. **In patients eligible for intravenous rtPA, benefit of therapy is time dependent, and treatment should be initiated as quickly as possible. The door-to-needle time (time of bolus administration) should be within 60 minutes from hospital arrival *(Class I; Level of Evidence A)*.** (New recommendation)
3. **Intravenous rtPA (0.9 mg/kg, maximum dose 90 mg) is recommended for administration to eligible patients who can be treated in the time period of 3 to 4.5 hours after stroke onset *(Class I; Level of Evidence B)*. The eligibility criteria for treatment in this time period are similar to those for people treated at earlier time periods within 3 hours, with the following additional exclusion criteria: patients >80 years old,**

Clinical Policy: Use of Intravenous tPA for the Management of Acute Ischemic Stroke in the Emergency Department
DRAFT January 5, 2015

From the American College of Emergency Physicians Clinical Policies Subcommittee (Writing Committee) on Use of Intravenous tPA for Ischemic Stroke:

Michael D. Brown MD, MSc (Subcommittee Chair)
John H. Burton, MD
Devorah J. Nazarian, MD
Susan B. Promes, MD, MBA

CRITICAL QUESTIONS

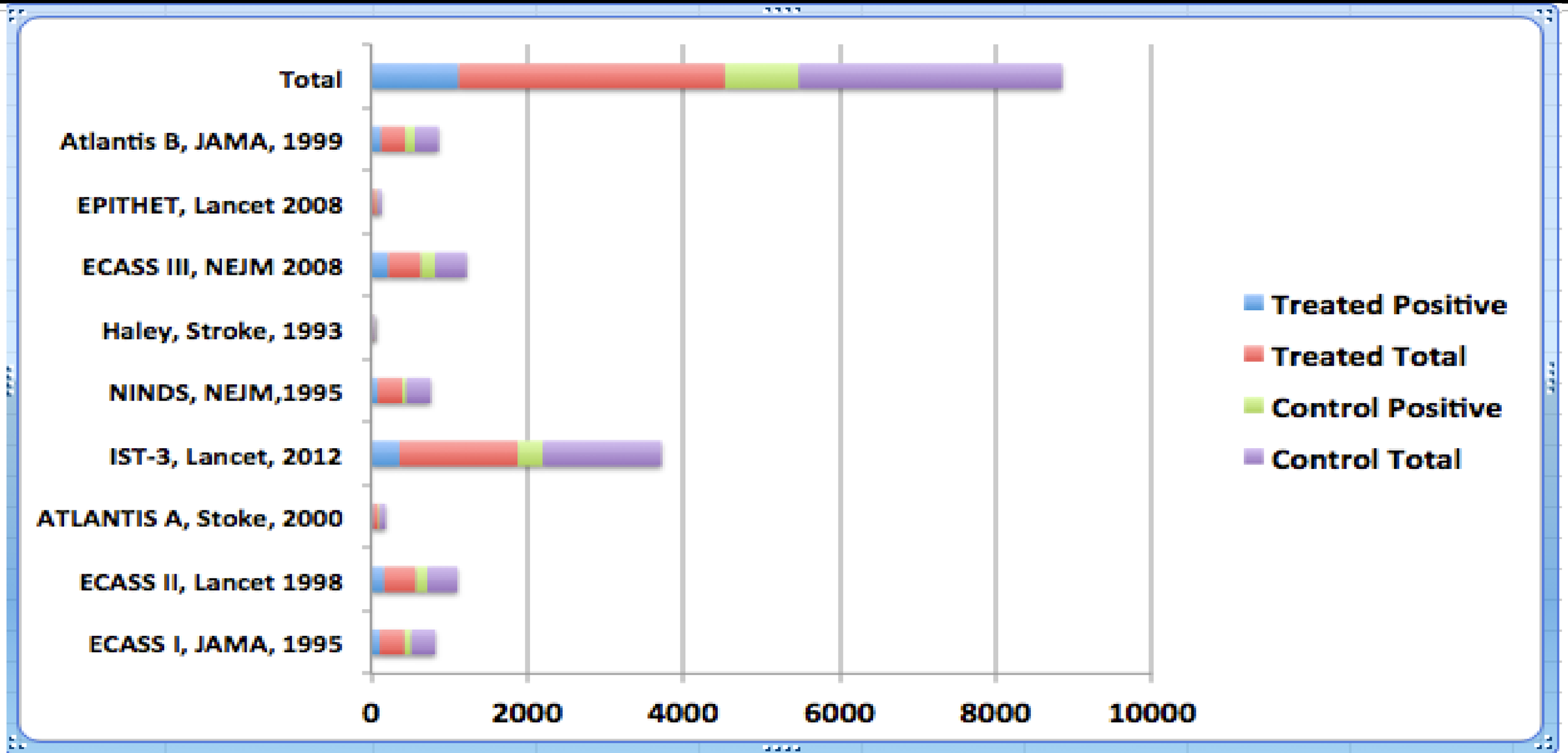
1. Is IV tPA safe and effective for acute ischemic stroke patients if given within 3 hours of symptom onset?

Patient Management Recommendations

Level A recommendations. The increased risk of symptomatic intracerebral hemorrhage (approximately 7% compared to a baseline of 1%) must be considered when deciding whether to administer IV tPA to acute ischemic stroke patients.

Level B recommendations. With a goal to improve functional outcomes, IV tPA may be given to carefully selected acute ischemic stroke patients within 3 hours after symptom onset at institutions where systems are in place to safely administer the medication.

t-PA vs Placebo Within 6 Hours



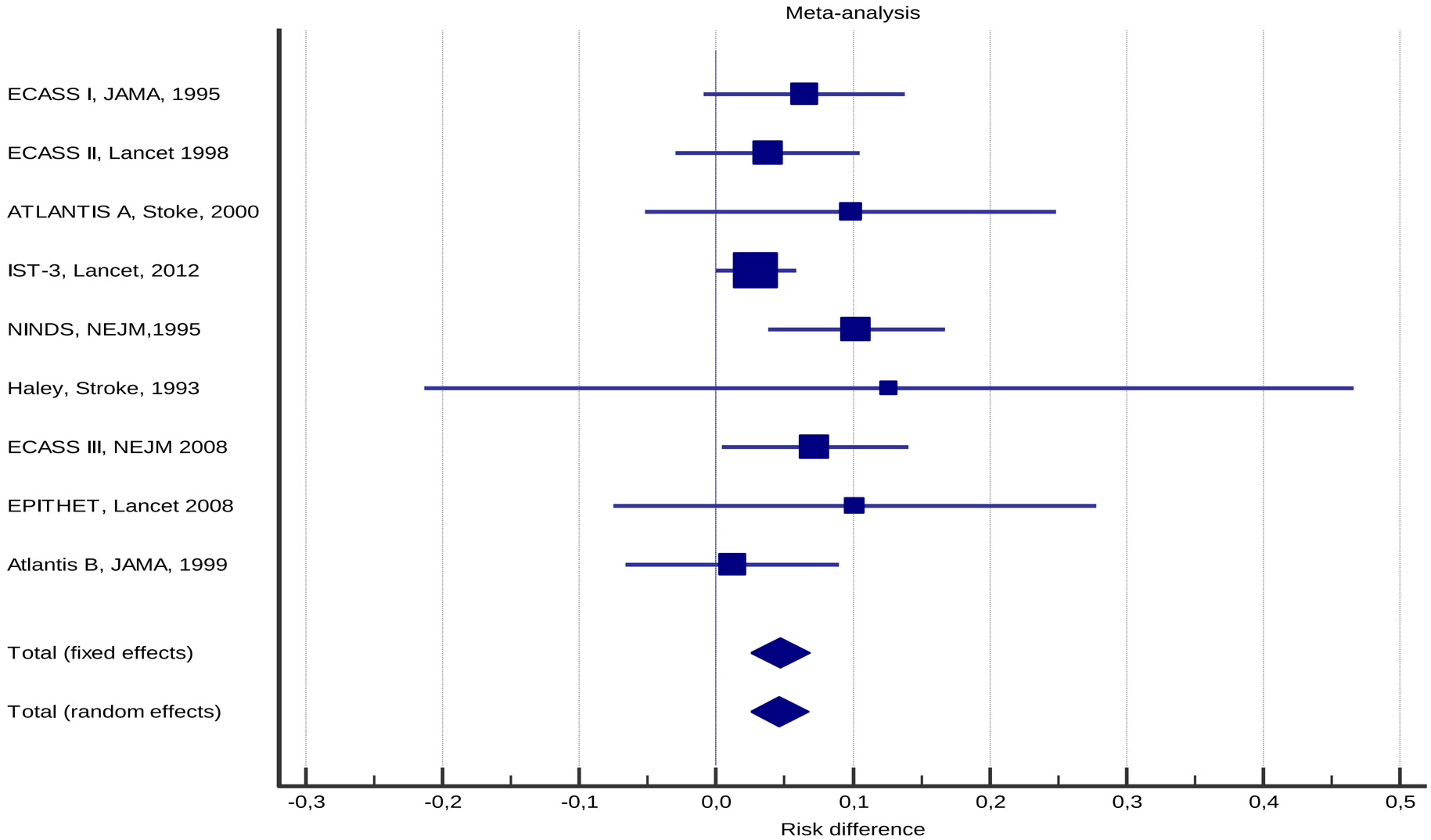
Study Qualities Regarding t-PA

Studies	Randomization	Blindness	Allocation Concealment	Intention-to-treat Analysis
NINDS, 1995	✓	✓ (only abstract)	Unclear	✓
Haley, 1993	✓	✓	✓	(–)
ATLANTIS B, 1999	✓	✓	✓	✓
ECASS III, 2008	✓	✓	✓	✓
EPITHET, 2008	✓	✓	✓	(–)
ECASS I, 1995	✓	Not reached.	Not reached.	✓
ECASS II, 1998	✓	✓	✓	✓
ATLANTIS A, 2000	✓	✓	✓	✓
IST-3, 2012	✓	Open Label	Open Label	Open Label

Limitations to the t-PA Studies

- Most of the studies are funded by the drug companies
- Patients in placebo groups received no therapy as an anti-aggregant.
- The biggest study, IST-3, so far is a pragmatic (open label) trial.
- The outcomes are dichotomized.

t-PA vs Placebo Within 6 Hours



Study	Treated_Positive	Treated_Total	Control_Positive	Control_Total
ECASS I, JAMA, 1995	112	313	90	307
ECASS II, Lancet 1998	165	409	143	391
ATLANTIS A, Stoke, 2000	25	71	18	71
IST-3, Lancet, 2012	363	1515	320	1520
NINDS, NEJM,1995	85	312	53	312
Haley, Stroke, 1993	5	14	3	13
ECASS III, NEJM 2008	219	418	182	403
EPITHET, Lancet 2008	18	52	12	49
Atlantis B, JAMA, 1999	128	307	124	306
Total	1120	3411	945	3372
	32.83%		28%	

Absolute Risk Reduction: 4.83%

Study	Treated_Hemorrhage Positive	Treated_Total	Control_Hemorrhage Positive	Control_Total
ECASS I, JAMA, 1995	62	313	20	307
ECASS II, Lancet 1998	48	407	12	386
ATLANTIS A, Stoke, 2000	8	71	0	71
IST-3, Lancet, 2012	104	1515	16	1520
NINDS, NEJM,1995	20	312	2	312
Haley, Stroke, 1993	0	14	1	13
ECASS III, NEJM 2008	22	418	9	403
EPITHET, Lancet 2008	4	52	0	49
Atlantis B, JAMA, 1999	21	307	4	306
Total	289	3409	64	3367
	8.47%		1.9%	

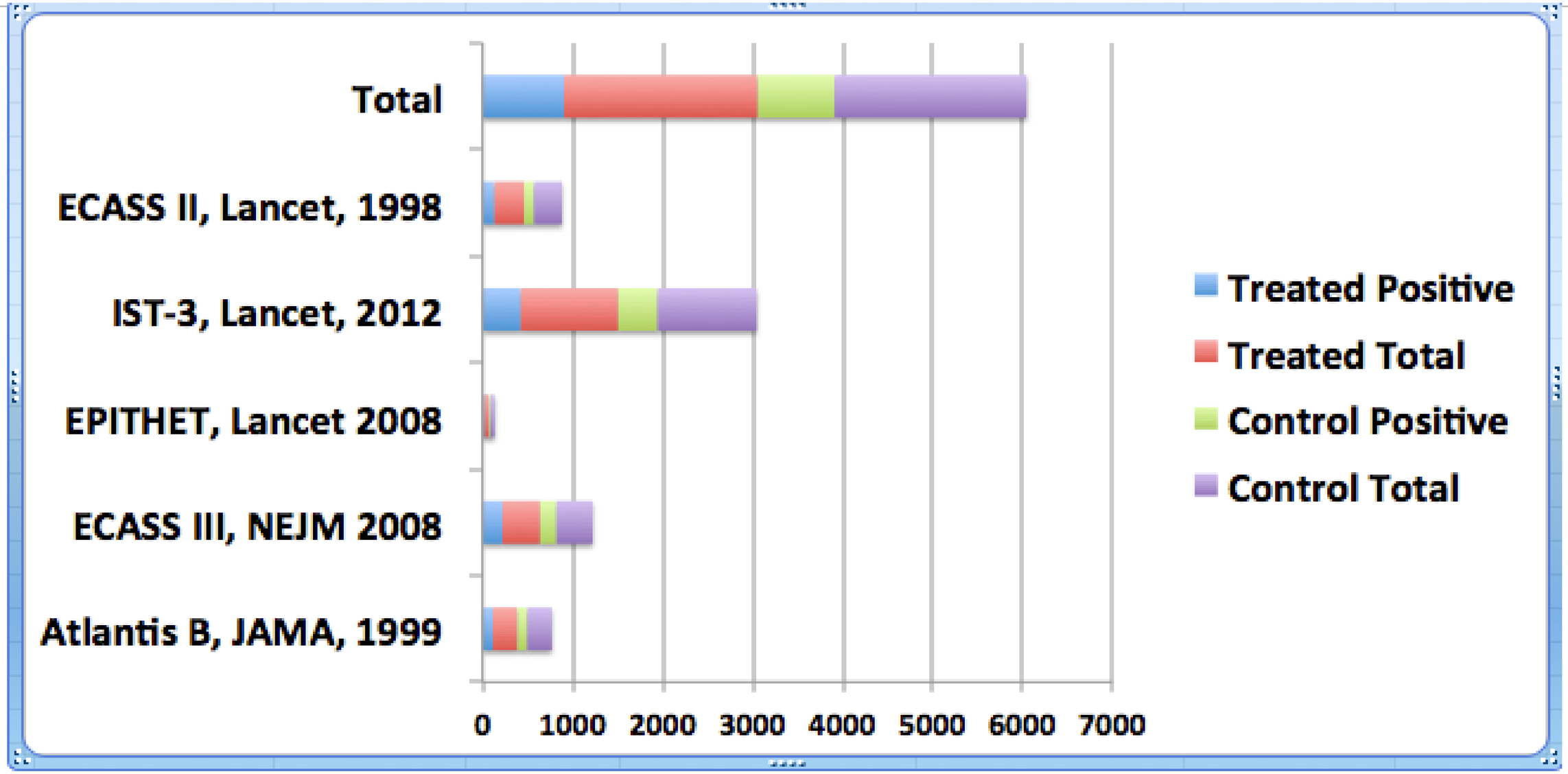
Hemorrhage Risk Difference: 6.57%

Benefit
4.83%

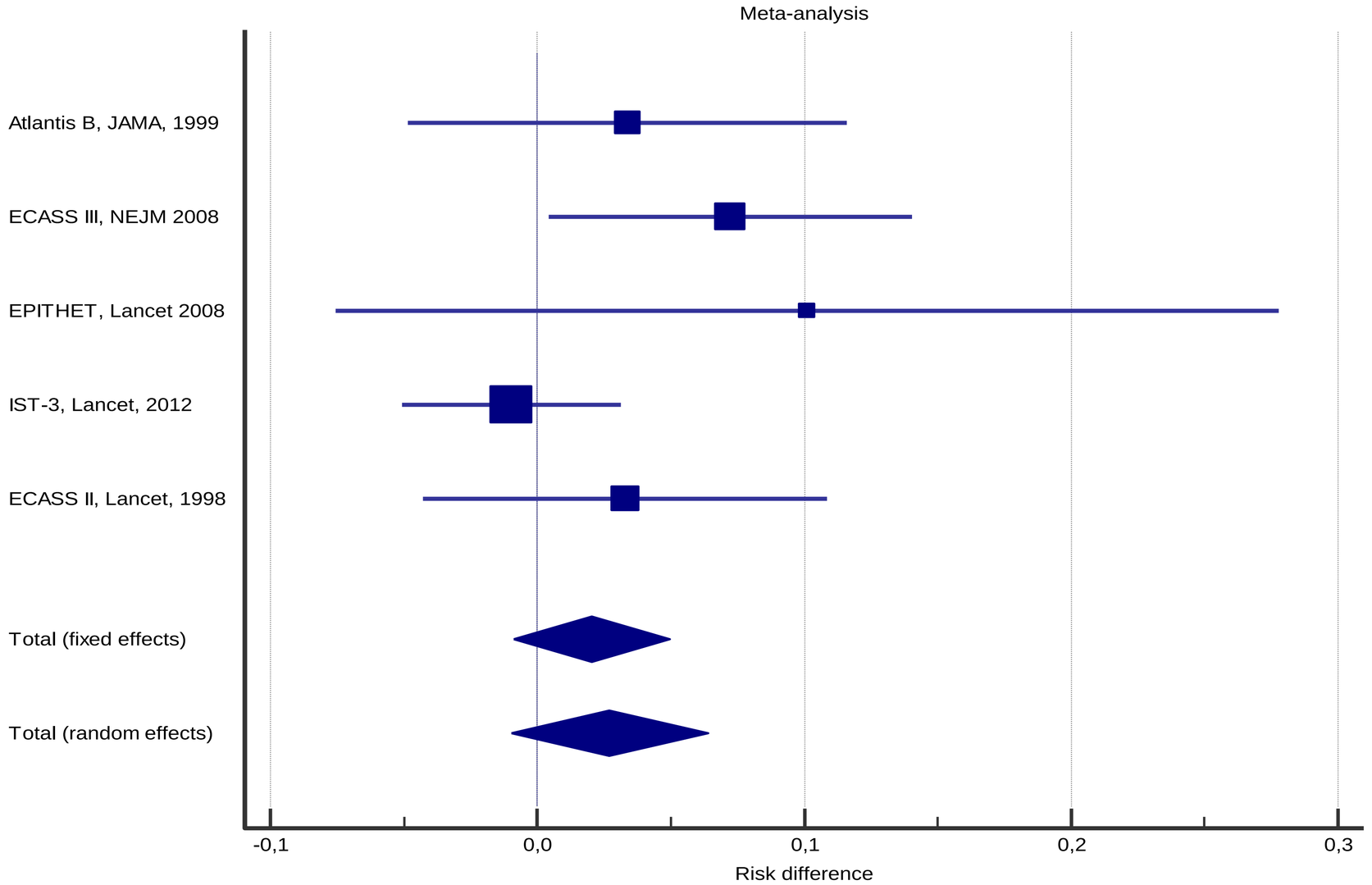
Harm
6.57%

Within 6 Hours

t-PA vs Placebo Within 3-6 Hours



t-PA vs Placebo Within 3-6 Hours



t-PA vs Placebo Within 3-6 Hours

Study	Treated_Positive	Treated_Total	Control_Positive	Control_Total
Atlantis B, JAMA, 1999	115	272	107	275
ECASS III, NEJM 2008	219	418	182	403
EPITHET, Lancet 2008	18	52	12	49
IST-3, Lancet, 2012	422	1084	439	1100
ECASS II, Lancet, 1998	131	326	114	309
Total	905	2152	854	2136
	42.05%		**39.98%**	

Absolute Risk Reduction: 2%

t-PA vs Placebo Within 3-6 Hours

Study	Sym_Hemorrhage_Positive	Treated_Total	Sym_Hemorrhage_Positive	Control_Total
Atlantis B, JAMA, 1999	19	272	3	275
ECASS III, NEJM 2008	22	418	9	403
EPITHET, Lancet 2008	4	52	0	49
IST-3, Lancet, 2012	76	1084	11	1100
ECASS II, Lancet, 1998	41	326	8	309
Total	162	2152	31	2136
	7.52%		**1.45%**	

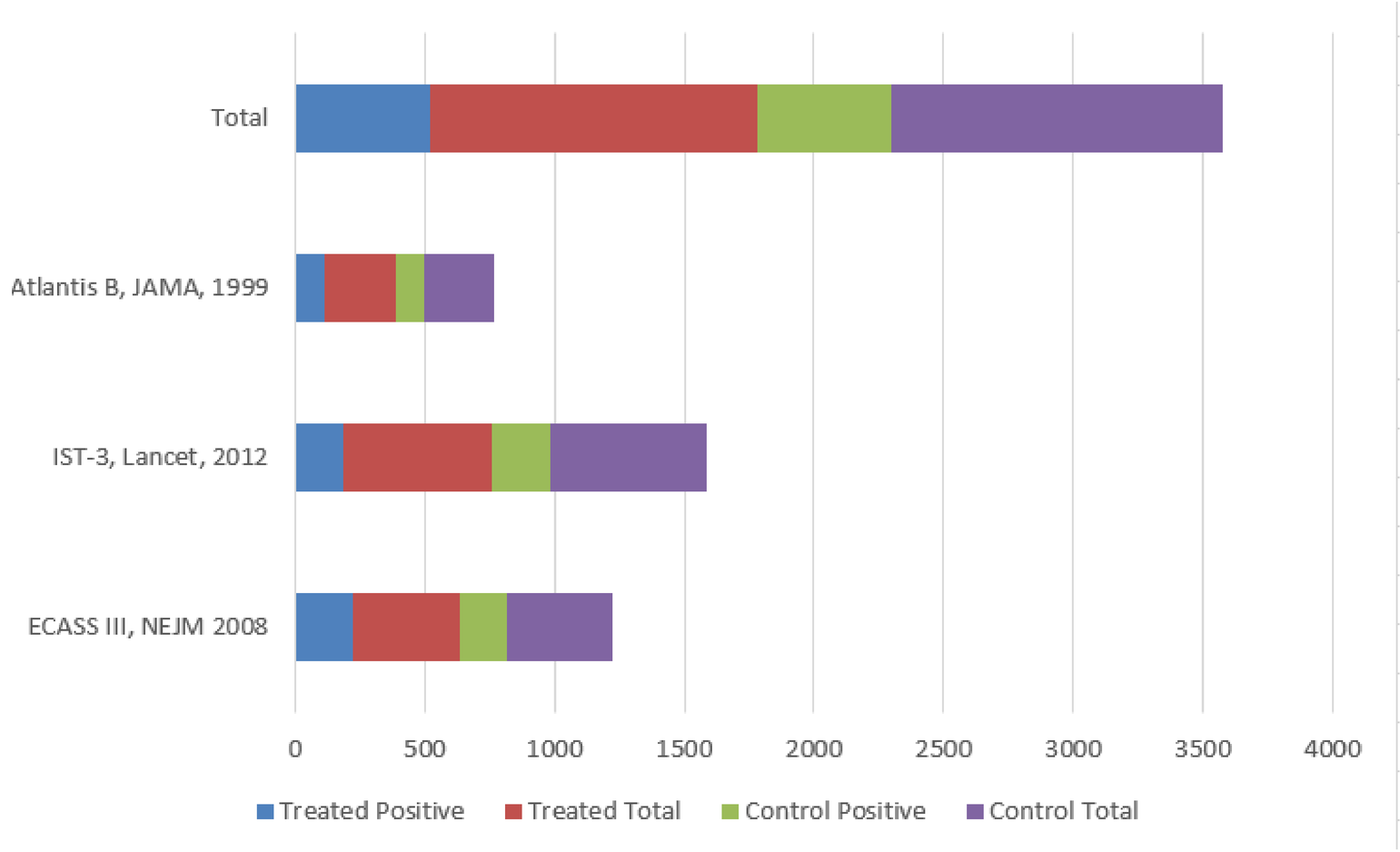
Absolute Risk Reduction: 6.07%

Benefit
2%

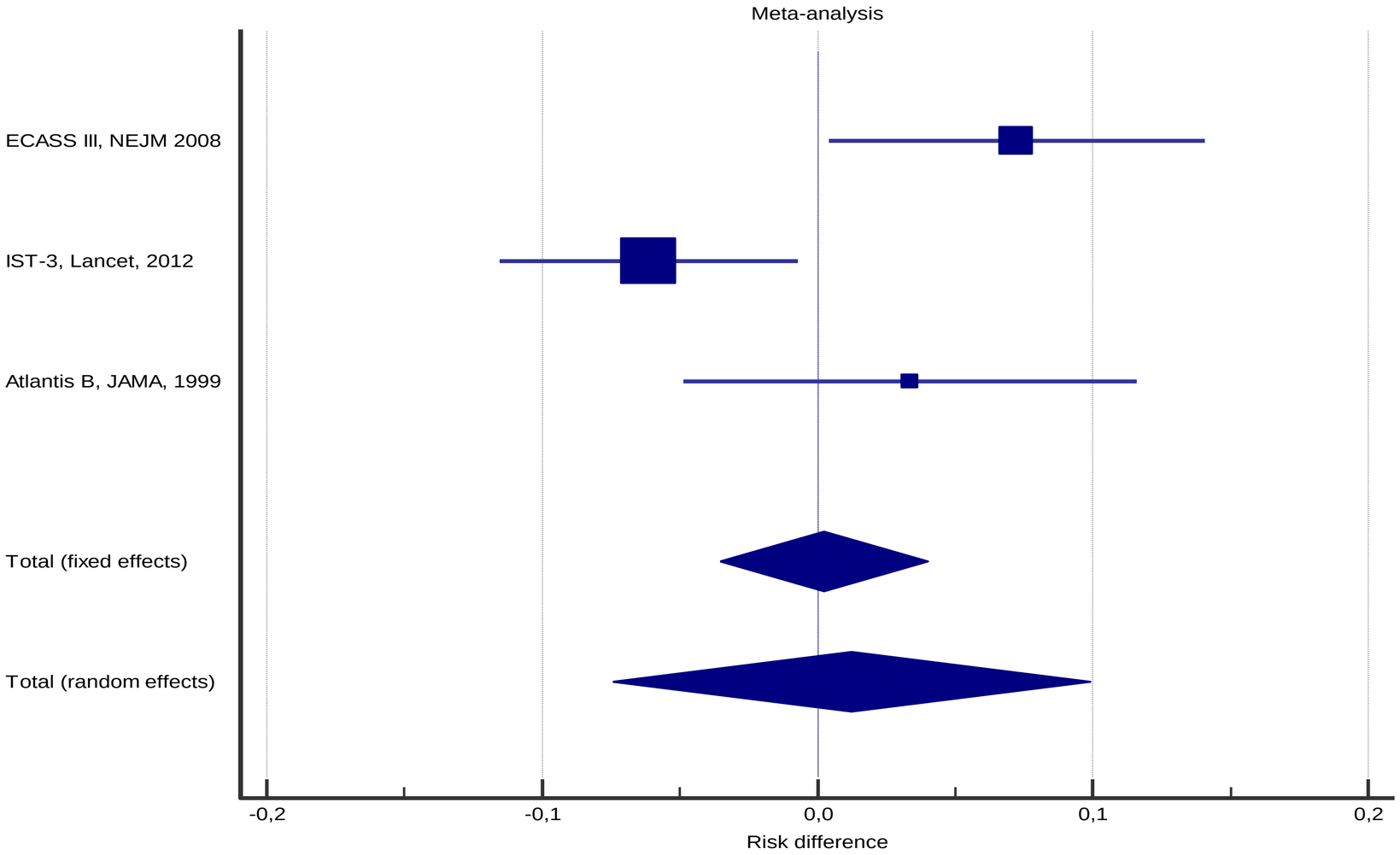
Harm
6%

Within 3-6 Hours

t-PA vs Placebo Within 3-4.5 Hours



t-PA vs Placebo Within 3-4.5 Hours



t-PA vs Placebo Within 3-4.5 Hours

Study	Treated_Positive	Treated_Total	Control_Positive	Control_Total
ECASS III, NEJM 2008	219	418	182	403
IST-3, Lancet, 2012	182	577	226	600
Atlantis B, JAMA, 1999	115	272	107	275
Total	516	1267	515	1278
	40.72%		**40.29%**	

t-PA vs Placebo Within 3-4.5 Hours

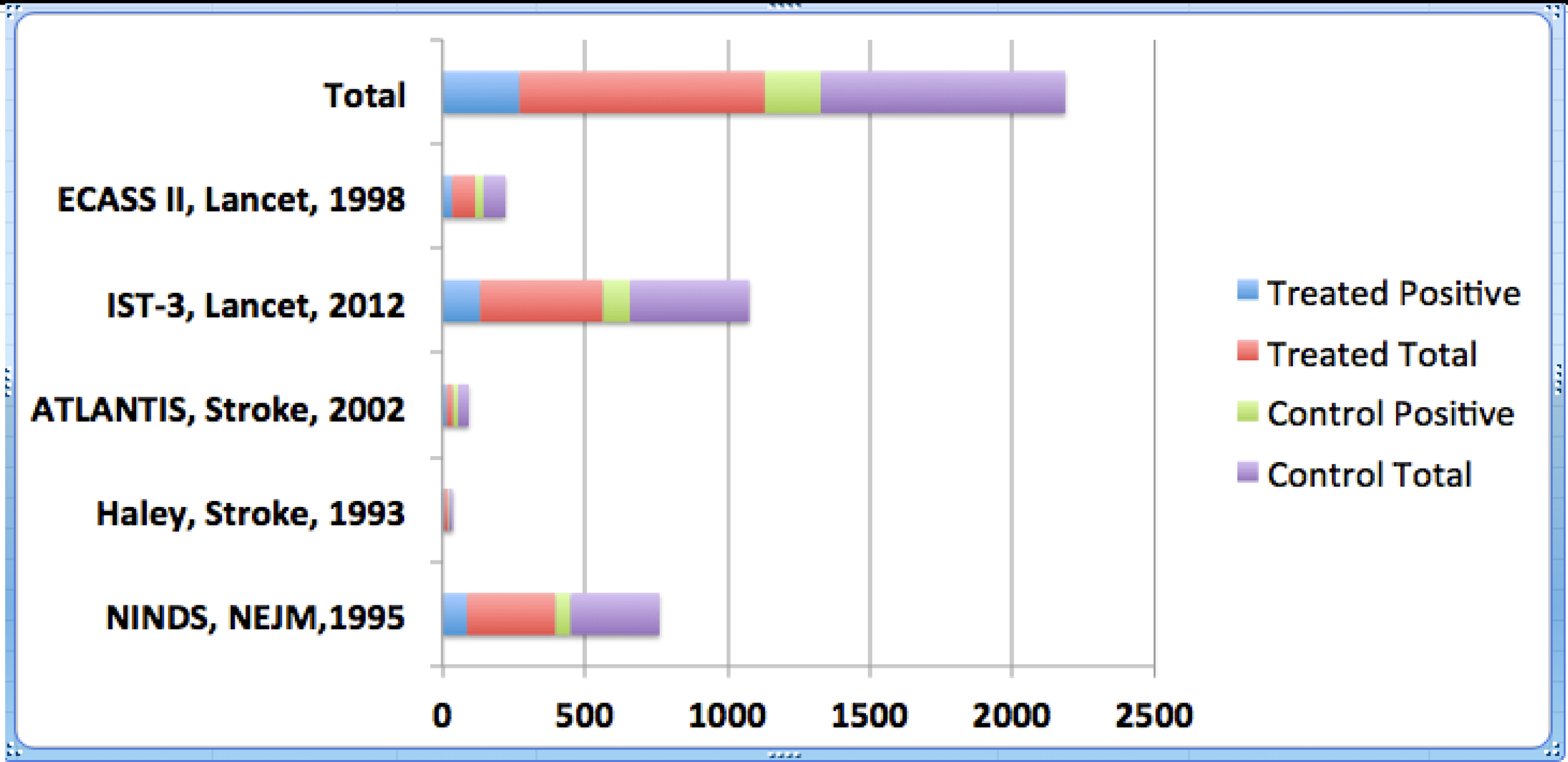
Study	Sym_Hemorrhage_Positive	Treated_Total	Sym_Hemorrhage_Positive	Control_Total
ECASS III, NEJM 2008	22	418	9	403
IST-3, Lancet, 2012	40	577	6	600
Atlantis B, JAMA, 1999	19	272	3	275
Total	81	1267	18	1278
	6.39%		**1.41%**	

Benefit
0.43%

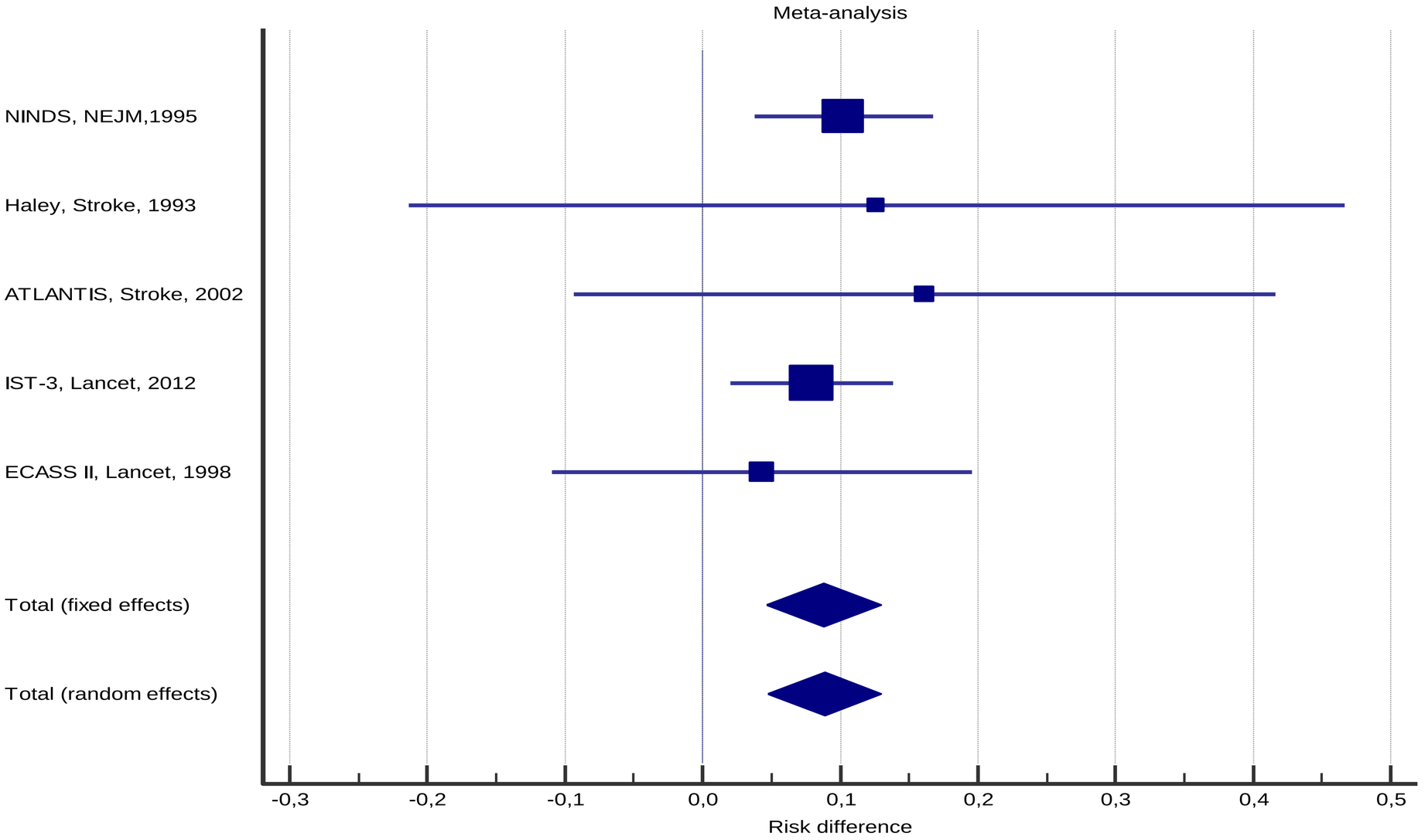
Harm
4.98%

Within 3-4.5 Hours

t-PA vs Placebo Within 3 Hours



t-PA vs Placebo Within 3 Hours



t-PA vs Placebo Within 3 Hours

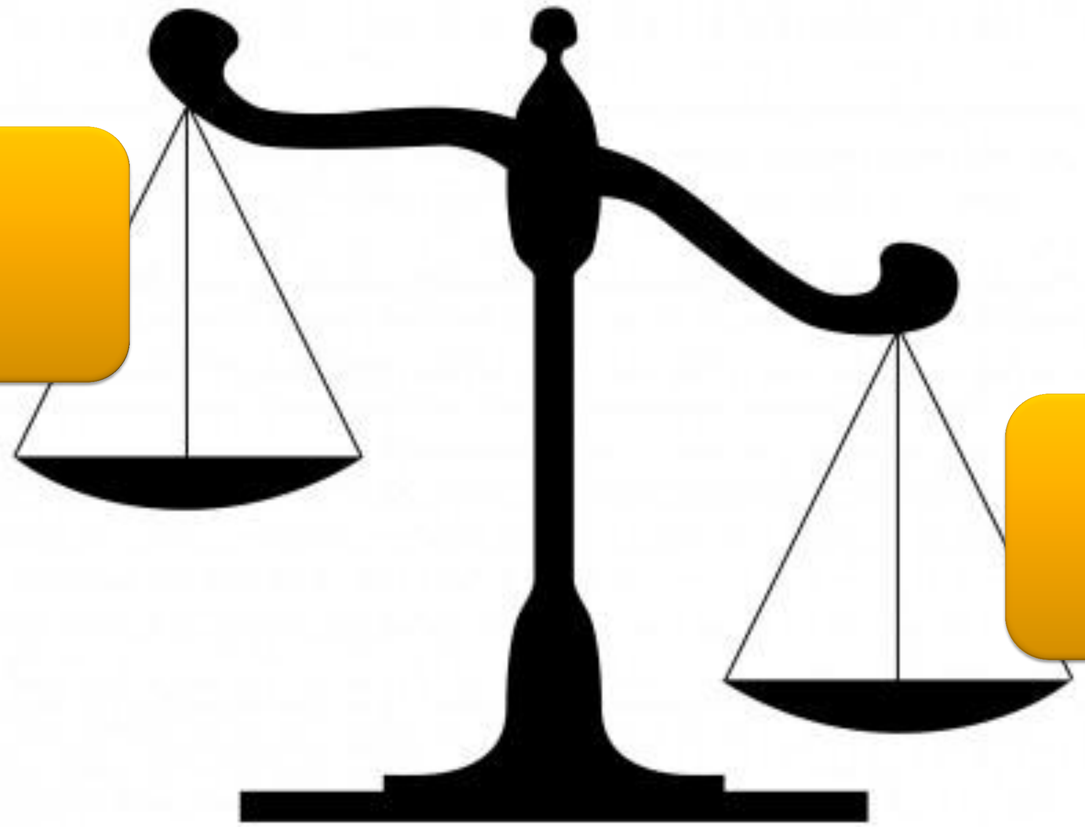
Study	Treated_Positive	Treated_Total	Control_Positive	Control_Total
NINDS, NEJM,1995	85	312	53	312
Haley, Stroke, 1993	5	14	3	13
ATLANTIS, Stroke, 2002	14	23	17	38
IST-3, Lancet, 2012	132	431	95	418
ECASS II, Lancet, 1998	34	81	29	77
Total	270	861	197	858
	31.5%		**22.96%**	

Absolute Risk Reduction: 8.5%

t-PA vs Placebo Within 3 Hours

Study	Sym_Hemorrhage_Positive	Treated_Total	Sym_Hemorrhage_Positive	Control_Total
NINDS, NEJM,1995	20	312	2	312
Haley, Stroke, 1993	0	14	1	13
ATLANTIS, Stroke, 2002	3	23	0	38
IST-3, Lancet, 2012	30	431	4	418
ECASS II, Lancet, 1998	7	81	4	77
Total	60	861	11	858
	6.96%		**1.28%**	

Symptomatic Hemorrhage Difference: 5.68%



Harm
5.68%

Benefit
8.5%

Within 3 Hours

The Real Benefit is
2.82%

You have to treat at least ***35.5*** patients for one patient to be cured.

Thanks