Effect of Pretreatment Blood Pressure on Outcomes in Thrombolysed Acute Ischemic Stroke Patients: A Systematic Review and Meta-analysis

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Background: Blood pressure (BP) is an important determinant of functional outcome in acute ischemic stroke (AIS) patients treated with intravenous tissue plasminogen activator (IV-tPA). Current guidelines recommend a BP target of 185/110 mmHg before IV-tPA bolus and maintaining it at less than 180/105 mmHg for the first 24 hours. However, the effect of blood pressure on various outcome measures after systemic thrombolysis remains unclear. *Methods:* Following a systematic search of Medline and EMBASE, all observational studies reporting effect of pretreatment BP on 90-day functional outcome as measured by the modified Rankin Scale (mRS) and/ or incidence of symptomatic intracranial hemorrhage (sICH) in AIS patients receiving thrombolytic therapy were included. *Results:* Of 2181 studies screened, 26 studies, involving 38,937 subjects, met inclusion criteria. Higher prethrombolysis systolic BP was significantly-associated with poorer 90-day functional outcome (Mean difference 3.87 mmHg; 95% confidence interval [CI] 1.18-6.56) and increased incidence of sICH (Mean difference 5.31; 95% CI 2.22-8.40). When studies were stratified by different cut-offs for functional outcome (mRS 0-1 versus 0-2) and definitions of sICH used (Randomized controlled trials or SITS-MOST), there was no significant difference in mean difference between the subgroups. *Conclusions:* Our data showed that higher prethrombolysis SBP was associated with poorer outcomes in thrombolysed acute ischemic stroke patients. This may suggest that more aggressive lowering of BP below the current recommendations prior to thrombolysis could be beneficial. The effect of early BP trends after tPA infusion could not be evaluated due to limited available data. Ongoing randomized clinical trials, like ENCHANTED, may provide further insights into the current guidelines and optimal BP levels.

Key Words: Acute ischaemic stroke—clinical outcomes—blood pressure—thrombolysis

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Introduction

The optimal control of blood pressure (BP) in patients with acute ischaemic stroke (AIS) treated with intravenously-administered tissue plasminogen activator (IV-tPA) remains debatable. While current guidelines suggest that a BP should be reduced below to 185/110 mmHg before initiating thrombolysis, the exact extent to which the BP may be lowered is unclear.[1] This question is of particular interest as the therapeutic approach towards AIS becomes more aggressive to reduce mortality as well as long-term disability of this dreaded condition.[2] While elevated BP is the predominant modifiable risk factor,[3] up to 75% AIS patients present with high BP at presentation (Systolic BP > 160 mmHg), which persists for hours to days.[4] Various explanations for a raised BP at presentation include the compensatory need to increase cerebral perfusion pressure, pain, stress, persistent inflammatory state, and pre-existing poorly controlled hypertension.[5]

Cerebral autoregulation is believed to be impaired during first few days of AIS, leading to a more linear relationship between mean arterial pressure and cerebral perfusion pressure.[6] Accordingly, the International Stroke Trial (IST) suggested a J-shaped relationship between baseline systolic BP and stroke outcome, where extremes on both ends of the spectrum portend inferior outcomes.[7]

Current guidelines emphasize the importance of maintaining BP target of less than 185/110 mmHG before IV-tPA bolus, followed by maintaining it less than 180/105 mmHg for the first 24 hours.[8,9,46] However, the ideal target for BP levels remains a matter of debate,[1] In preclinical models, higher BP increased the risk of hemorrhagic transformation and cerebral edema in AIS.[5] However, there is a paucity of actual clinical evidence supporting either conservative or aggressive lowering of BP. A recent meta-analysis of previous 13 randomized controlled trials that evaluated the impact of antihypertensive therapy found no effect on short- or long-term patient outcomes.[10] Notably, the included studies had heterogeneous outcome measures, BP parameters, stroke types, and excluded patients on thrombolytic therapy. This meta-analysis aims to examinine the effect of prethrombolysis BP on specific outcomes (90-day mRS and sICH), in thrombolysed AIS patients.

Methodology

Search Strategy

A search was performed on Medline (Pubmed) and EMBASE using keywords relating to thrombolytic therapy (e.g., "thrombolysis" OR "thrombolytic therapy" OR "alteplase"), blood pressure (e.g., "blood pressure" OR "blood pressure reduction" OR "blood pressure lowering" OR "labetalol") and stroke (e.g., "stroke" OR "ischemic stroke" OR "cerebrovascular disease" OR "cerebrovascular accident" OR "brain infarct" OR "cerebral ischemia"). Further details of the search strategy are provided in Supplementary Table 1. Studies published up to 27th March, 2018 were reviewed by 2 independent investigators (R.T. and B.T.). Review articles or meta-analyses found during the database search were manually screened for further relevant studies. No language limits were applied.

Inclusion and Exclusion Criteria

This study examined the effect of BP on outcomes in thrombolysed AIS patients. Our inclusion and exclusion criteria are detailed in a PRISMA flowchart (Fig 1). Selected cohort studies had to meet the following inclusion criteria: (1) Subjects were diagnosed as AIS and, (2) Subjects received IV-tPA. From randomized controlled trials that compared thrombolytic therapy and a placebo, only data from the thrombolytic therapy arm was extracted (3) Studies had to report pretreatment systolic and/or diastolic BP values, in terms of mean and standard deviation. In studies, where BP was reported as median and interquartile range (IQR), we included only those with symmetrical distribution of 25th and 75th percentiles about the median. (4) Studies had to include development of sICH and 90-day functional outcome (as mRS) as endpoints.

We implemented certain strict exclusion criteria in this study. First, we excluded the reviews/meta-analyses, case reports, and preclinical studies. However, such papers were manually screened for any missing relevant references. Second, studies on nonrelated topics such as stroke detection/prognostication with imaging or biomarkers, nonthrombolytic therapies, poststroke care or stroke prevention, and characteristics/outcomes of patients not meeting thrombolysis criteria were excluded. Third, studies with endpoints that were not functional outcomes (mRS or sICH) were also excluded. Last, eligibility assessment was performed independently in an unblinded standardized manner by 2 reviewers (R.T. and B.T.). Disagreements between reviewers were resolved by consensus. The quality of each study was evaluated using the Newcastle-Ottawa quality assessment scale (NOQAS).

Data Extraction

A data extraction template was developed by 3 reviewers (R.T., B.T., and V.K.S.) and refined using a pilot of 5 studies. The details extracted from each study included first author, publication year, PMID, country of origin of the study population, size of study population, and number of patients on thrombolytic therapy. In terms of disease characteristics of the study population, the type and location of stroke, nature of thrombolytic therapy (dose, route of administration, drug type), median National Institute of Health Stroke Scale (NIHSS) score, etiopathogenic classification by the Trial of Org

Table 1. *Characteristics of the 26 included studies comparing baseline blood pressure of patients with and without post-thrombolysis good outcomes (mRS, sICH)*

Study (PMID)	Year	Country	N*	Base-line NIHSS	OTT/ min	BP measure†	mRS cut-off	No. good, bad	BP of‡ Good mRS	BP‡ of poor mRS	p§	sICH def	No. sICH, no sICH	BP‖ of sICH	BP‖ of no sICH	P#
Forlivesi[14] (29227292)	2018	Italy	200	8 (5-15)	175 (140-225)	SBP, median	0-2	132, 68	152 (26.7)	158 (24.4)	0.059					
						DBP, median			80 (12.6)	79 (11.9)	0.241					
Li[17] (29201550)	2017	China	294			SBP, mean	0-2	191, 103	152.31 (20.85)	161.72 (22.33)	0.003					
						DBP, mean			87.37 (12.37)	90/1 (12.02)	0.06					
Lokes-krawee[31] (28826584)	2017	Thailand	1172			SBP, mean	-					ECASS II	95, 923	155 (22.5)	147.2 (24.0)	0.003
						DBP, mean								84.6 (13.6)	82.5 (14.9)	0.378
Wu[24] (28579505)	2017	China	383	6.85	207	SBP, mean	0-2	253, 130	147.31 (21.72)	149.85 (22.61)	0.357					
Waltimo[37] (27529662)	2016	Finland	1868			SBP, median						ECASS II	109, 1759	157 (26.7)	155 (23.0)	0.93
Cao[12] (27000211)	2016	China	660			SBP, median	0-2	476, 184	143 (20.7)	150 (20.7)	0.001					
						DBP, median			82 (10.4)	84 (12.6)	0.548					
Jiang[16]	2016	China	198			SBP, mean	0-2	123, 75	154.4 (26.9)	157.3 (23.6)	-					
						DBP, mean			88.9 (16.2)	86.4 (14.8)	-					
Liu[30] (26892891)	2016	China	461	10 (5-16)	232.9 (93.9)	SBP, mean						ECASS II	12, 449	157.4 (19.9)	153.4 (22.6)	0.54
						DBP, mean								90 (13.0)	85.5 (14.7)	0.298
Li[29] (25891755)	2015	China	811	11 (7-16)	2.78 (2.33-3.25)	SBP, mean						ECASS II	25, 786	148.2 (16.7)	147.4 (21.3)	0.901
						DBP, mean						ECASS II		91.3 (12.9)	85.7 (12.7)	0.038
						SBP, mean						SITS	147, 797	146.8 (13.1)	147.8 (21.4)	0.828
						DBP, mean						SITS		88.8 (13.9)	85/8 (12.8)	0.422
Yan[25] (25851976)	2015	China	121	11.9 (6.6)	235.2 (88.4)	SBP, mean	0-2	58, 63	152.7 (23.9)	151.2 (23.6)	0.734					
						DBP, mean	0-2		86.1 (15.3)	85.7 (12.8)	0.867					
Huang[15] (24342312)	2013	China	101			SBP, mean	0-1	55, 46	135.5 (19.4)	148.8 (19.4)	0.003					
Strbian[22] (22762436)	2013	Finland	1427			SBP, median	0-2	126, 347	155 (23.0)	153 (23.0)	0.48					
						DBP, median	0-2		84 (13.3)	80 (15.6)	0.01					
Mazya[33] (22442178)	2012	Sweden	31,627			SBP, median						SITS	557, 29728	160 (18.5)	150 (22.2)	<0.001
						DBP, median								82 (11.9)	81 (11.9)	0.561
Martins[19] (20813552)	2011	Brazil	55			SBP, mean	0-1	23, 32	166 (36)	164 (30)	0.76					
Tvisgoulis[36] (19762689)	2009	USA	510			SBP, mean						ECASS II	31, 479	169 (29)	156 (24)	0.006
						DBP, mean								85 (21)	82 (16)	0.43
Kellert[28] (22179586)	2012	Germany	427			SBP, mean						ECASS II	10, 376	151.3 (17.5)	147.2 (16.5)	0.43
						SBP, mean								75.1 (10.4)	74.8 (9.32)	0.92
Saqqur[34] (18753474)	2008	Canada	349	16 (12-20)	134 (32)	SBP, mean						CLOTBUST	26, 323	156 (27)	157 (22)	0.73
Delgado-Mederos[13] (18550860)	2008	Spain	44 (recanalized)	15 (10-19)	194.3 (64.7)	SBP, mean	0-2	33, 11	145.7 (23.3)	150.5 (27.9)	-					
						DBP, mean			79.8 (12)	78.7 (13.2)	-					
Saqqur[21] (17290031)	2007	Canada	335	16 (3-32)	145 (68)	SBP, mean	0-2	90, 170	155 (23)	158 (23)	0.3					
Marti-Fabregas[32] (17114877)	2007	Spain	347	15	153 (41.8)	SBP, mean						ECASS	8, 339	149.3 (44.2)	153.8 (24.1)	0.61
						DBP, mean						ECASS		78 (11.3)	83.6 (14.5)	0.27
Tvisgoulis[23] (17255548)	2007	USA		16.5		SBP, mean	0-2	137, 162	154 (20)	160 (25)						
Cocho[27] (16497981)	2006	Spain	114	14 (4-26)	153 (33)	SBP, mean						ECASS II	8, 106	164.1 (15.5)	154.4 (27.7)	0.36
						DBP, mean								81.5 (13.9)	83.9 (13.4)	0.29
Yong[26] (16254220)	2005		615			SBP, mean	0-1	111, 192	157.7 (24.9)	154.0 (22.7)	0.19					
						DBP, mean			87.8 (13)	86.9 (12.2)	0.38					

Table 1 (*Continued*)

Study (PMID)	Year	Country	N*	Base-line NIHSS	OTT/ min	BP measure†	mRS cut-off	No. good, bad	BP of‡ Good mRS	BP‡ of poor mRS	p§	sICH def	No. sICH, no sICH	BP‖ of sICH	BP‖ of no sICH	P#
Molina[20] (14671245)	2004	Spain	177	16 (13-20)	134.1 (46.7)	SBP, mean	0-2	87, 90	150.4 (20.7)	160.6 (24.5)	0.005					
						DBP, mean			81.1 (12)	81.9 (19)	0.81					
Lindsberg[18](12738891)	2003	Finland	75	30.3 (10.0)	86	SBP, mean	0-2	43, 32	160 (21)	155 (28)	0.45					
						DBP, mean			92 (12)	84 (12)	0.008					
Selim[35] (12154261)	2002	USA	29	18 (5-32)	160 (20)	SBP, mean							4, 13	159 (36)	138 (20)	-

*N represents number of patients receiving thrombolytic therapy.
†All BP measurements are taken at baseline/before thrombolytic therapy.
‡Blood pressure of groups with different functional outcome (mRS), expressed in mean (SD). Where median (IQR) was provided, it was converted to mean (SD) using the method proposed by Hozo (2010).
§*P* value for comparison of BP between patients with good and poor mRS (unadjusted).
‖Blood pressure of groups with or without symptomatic intracranial hemorrhage (sICH), expressed in mean (SD).
#*P* value for comparison of BP between sICH and non-sICH patients (unadjusted).

10172 in Acute Stroke Treatment (TOAST) criteria and onset-to-treatment time. The following details on BP were extracted: mean systolic and/or diastolic BP and their standard deviation or median and inter-quartile range (IQR), time at which the BP was recorded (baseline or post-thrombolysis), and other forms of BP measurement in the study where available, for example, BP variability, maximum, minimum, standard deviation (SD), and average squared difference between successive measurements (SV). With regard to study endpoints, the number of patients, cut-offs used for mRS, and definition of symptomatic sICH (whether based on the individual randomized trial or the Safe Implementation of Thrombolysis in Stroke-Monitoring Study- SITS-MOST) were also recorded. Good functional outcome was defined by studies as either 90-day mRS 0-1 (no significant disability; able to carry out all usual duties and activities) or mRS 0-2 (slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance). Where available, outcomes of univariate and/or multivariate analysis, including *P* values, crude and/or adjusted odds ratios (OR), and 95% confidence intervals (CI) were recorded.

Statistical Analysis

Pooled analysis and construction of forest plots were performed with RevMan v.5.3 (Copenhagen, Denmark). Due to significant between-study heterogeneity, a random-effects model was used. As BP is a continuous variable, all calculations were performed using the mean difference (MD), defined as the difference in BP between patients with good and poor outcome.

When the studies reported BP as median and IQR, Hozo's method[11] was used to decide if these values should be included and then convert them to mean and SD. First, the distance of the 25th and 75th quartile from the median was calculated, and studies were included only if both quartiles showed a symmetrical distance from the median (implying less variance). Then, the median was assumed to be the mean, and SD was derived by dividing IQR by 1.35 (since each quartile is equivalent to 0.68 SD).

Heterogeneity between studies was also assessed using statistical tests. For the χ^2 test (Cochrane Q test), heterogeneity was considered to be present if the *P* value was less than .1 and χ^2 value was bigger than the degrees of freedom (df = number of studies included minus 1). Substantial heterogeneity was defined as an I^2 value of 50% and above. Finally, the tau-squared test was used as an estimate of between-study variance, with a value above one suggesting substantial statistical heterogeneity. Funnel plots were constructed to assess for publication and selection bias. Finally, a posthoc sensitivity analysis was performed, by removing studies reporting BP as median and IQR. Our

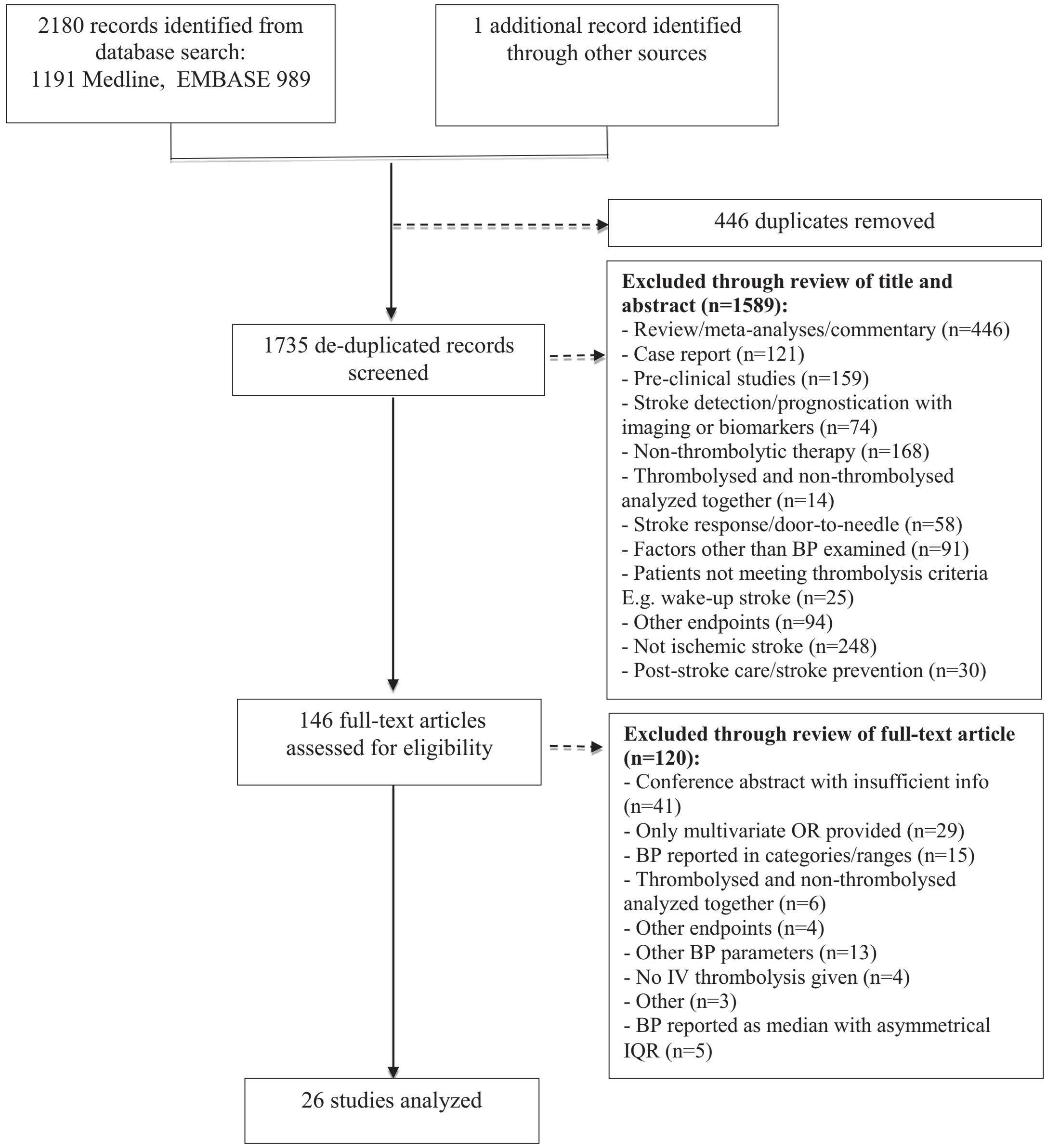


Figure 1. *PRISMA flowchart detailing inclusion and exclusion criteria.*

findings would be considered valid if removal of such studies did not significantly affect pooled mean differences.

In order to determine if covariates like age and baseline NIHSS influenced outcomes, we performed random-effects meta-regression by modeling the log odds (i.e., logit) of good mRS or sICH as a function of the summary-level baseline characteristics in included studies, using a mixed-effects linear specification of beta-regression models. Logits and study-level standard errors were calculated as follows:

$$\text{Log odds} = \ln\left(\frac{Numerator}{Denominator - Numerator}\right)$$

$$SE = \sqrt{\frac{1}{Denominator} + \frac{1}{Denominator - Numerator}}$$

The odds ratio was calculated as the exponentiated form of the beta coefficients, which represent the difference in logits per unit change in the covariate.

Results

Meta-analysis: Effect of BP on Functional Outcome

A total of 2181 articles from Medline, EMBASE, and other sources were screened. Of these, 26 cohort studies involving 38,973 subjects met the inclusion criteria. While 15 of the included studies reported impact of prethrombolysis BP on 90-day mRS,[12-26] 11 studies reported the risk of developing sICH haemorrhage.[27-37] The characteristics of included studies and their patient populations are presented in Table 1.

A higher baseline systolic BP (SBP) was found to be associated with poor functional outcome at 3 months, with a mean difference of 3.87 (95% CI 1.18-6.56; *P* value .005) between BP of patients with and without poor mRS (Fig 2). When studies were stratified based on cut-off for optimal mRS (0-1 versus 0-2), there was no difference between subgroups (P = .87, I^2 = 0%). Six out of 15 of the studies reported an inverse association between high SBP and poor functional outcome, including a posthoc analysis of the thrombolytic therapy arm of the European Cooperative Acute Stroke Study-1 (ECASS-1) trial.[26] Substantial heterogeneity was observed between studies (Cochrane Q 35.72, P = .0007, I^2 = 61%), although no publication bias was seen by the funnel plot.

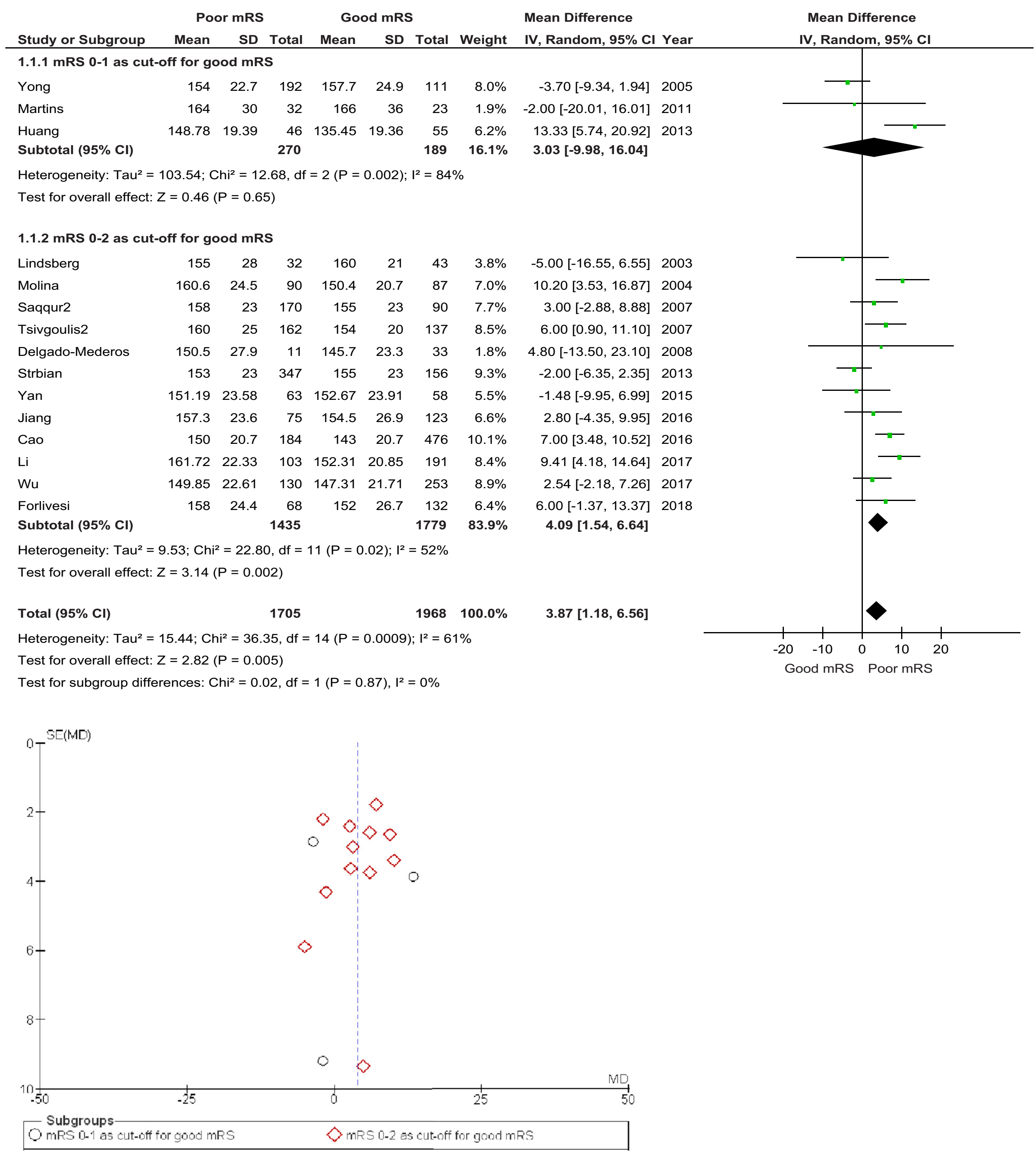
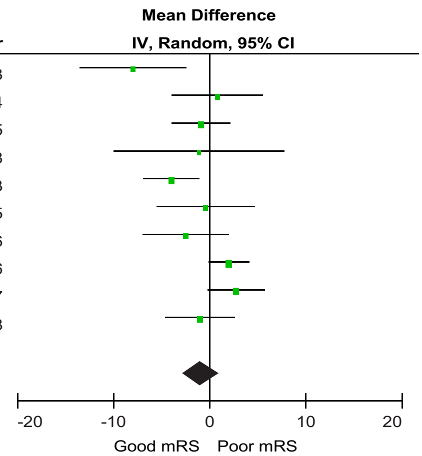


Figure 2. *Forest plot showing effect of baseline systolic blood pressure (SBP) on 90-day functional outcome (mRS).*

Study or Subgroup	Poor mRS Mean	Poor mRS SD	Poor mRS Total	Good mRS Mean	Good mRS SD	Good mRS Total	Weight	Mean Difference IV, Random, 95% CI	Year
Lindsberg	84	12	32	92	12	43	7.3%	-8.00 [-13.49, -2.51]	2003
Molina	81.9	19	90	81.1	12	87	8.7%	0.80 [-3.87, 5.47]	2004
Yong	86.9	12.2	192	87.8	13	111	12.4%	-0.90 [-3.87, 2.07]	2005
Delgado-Mederos	78.7	13.2	11	79.8	12	33	3.8%	-1.10 [-9.91, 7.71]	2008
Strbian	80	15.6	347	84	13.3	126	12.7%	-4.00 [-6.84, -1.16]	2013
Yan	85.69	12.84	63	86.12	15.29	58	8.0%	-0.43 [-5.48, 4.62]	2015
Jiang	86.4	14.8	75	88.9	16.2	123	9.2%	-2.50 [-6.91, 1.91]	2016
Cao	84	12.6	184	82	10.4	476	14.6%	2.00 [-0.05, 4.05]	2016
Li	90.1	12.02	103	87.37	12.37	191	12.5%	2.73 [-0.18, 5.64]	2017
Forlivesi	79	11.9	68	80	12.6	132	11.0%	-1.00 [-4.55, 2.55]	2018
Total (95% CI)			**1165**			**1380**	**100.0%**	**-0.91 [-2.85, 1.03]**	

Heterogeneity: Tau² = 5.61; Chi² = 24.59, df = 9 (P = 0.003); I² = 63%
Test for overall effect: Z = 0.92 (P = 0.36)



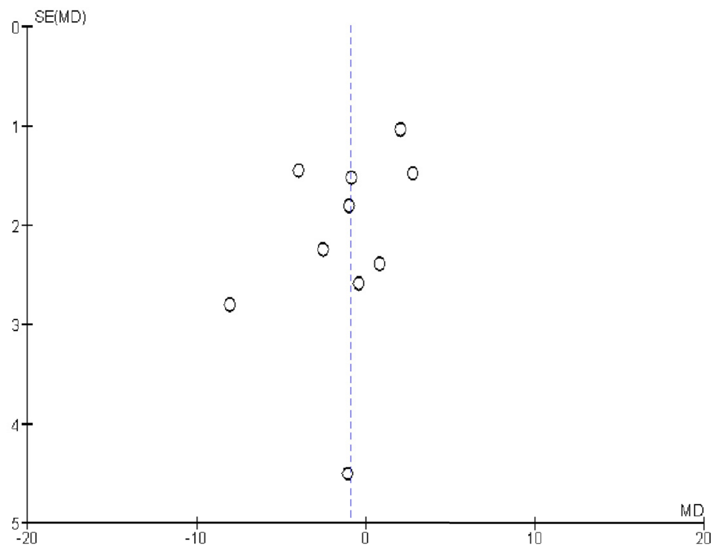


Figure 3. *Forest plot showing effect of baseline diastolic blood pressure (DBP) on 90-day functional outcome (mRS).*

Diastolic BP (DBP) was not associated with functional outcome at 3 months (MD −0.91; 95% CI −2.85-1.03; *P* value .36; Fig 3). Substantial heterogeneity was also observed between studies reporting on DBP ($I^2 = 63\%$).

Meta-analysis: Effect of BP on sICH

Higher baseline SBP was associated with increased risk of developing sICH (Fig 4). Amongst studies using the RCT definition of sICH (e.g., ECASS I/II or National Institute of Neurological Disorders and Stroke-NINDS definitions), a mean difference of 5.1 mmHg (95% CI 2.26-7.95; *P* value .0004) was observed between patients with and without sICH (Fig 3). Only 2 studies used the SITS-MOST definition of sICH, with a pooled mean difference of 5.07 mmHg (95% CI −5.61-15.76; *P* value .36). A large study by Mazya et al[33] which included 30,285 patients from the SITS-ISTR registry found a strong association between higher prethrombolysis SBP and sICH (MD 10.00 mmHg; 95% CI 8.44-11.56). However, the other study in the subgroup[29] reported no association between SBP and sICH (MD −0.96; 95% CI −7.96-6.04).

No difference between subgroups was observed ($P = 1.00$, $I^2 = 0\%$) when studies were stratified according to the definition of sICH (RCT vs SITS-MOST). Moderate heterogeneity was observed between studies ($I^2 = 61\%$), and the funnel plot was symmetrical suggesting no publication bias.

A weaker association between baseline DBP and sICH was observed, with studies using the RCT definition, reporting a mean difference of 1.95 mmHg (95% CI −0.39-4.30; *P* value .03) (Fig 5). Only the 2 earliest studies[27,32] reported an inverse relationship between baseline DBP and sICH. Little to no heterogeneity was observed between studies ($I^2 = 0\%$) and there was no publication bias based on the funnel plot.

Meta-regression and Sensitivity Analysis

Three variables tested (age, onset-to-treatment time (OTT), and NIHSS) did not show any significant association with functional outcomes measured by mRS, or sICH in the meta-regression analysis (Supplemental Material – Figure S1).

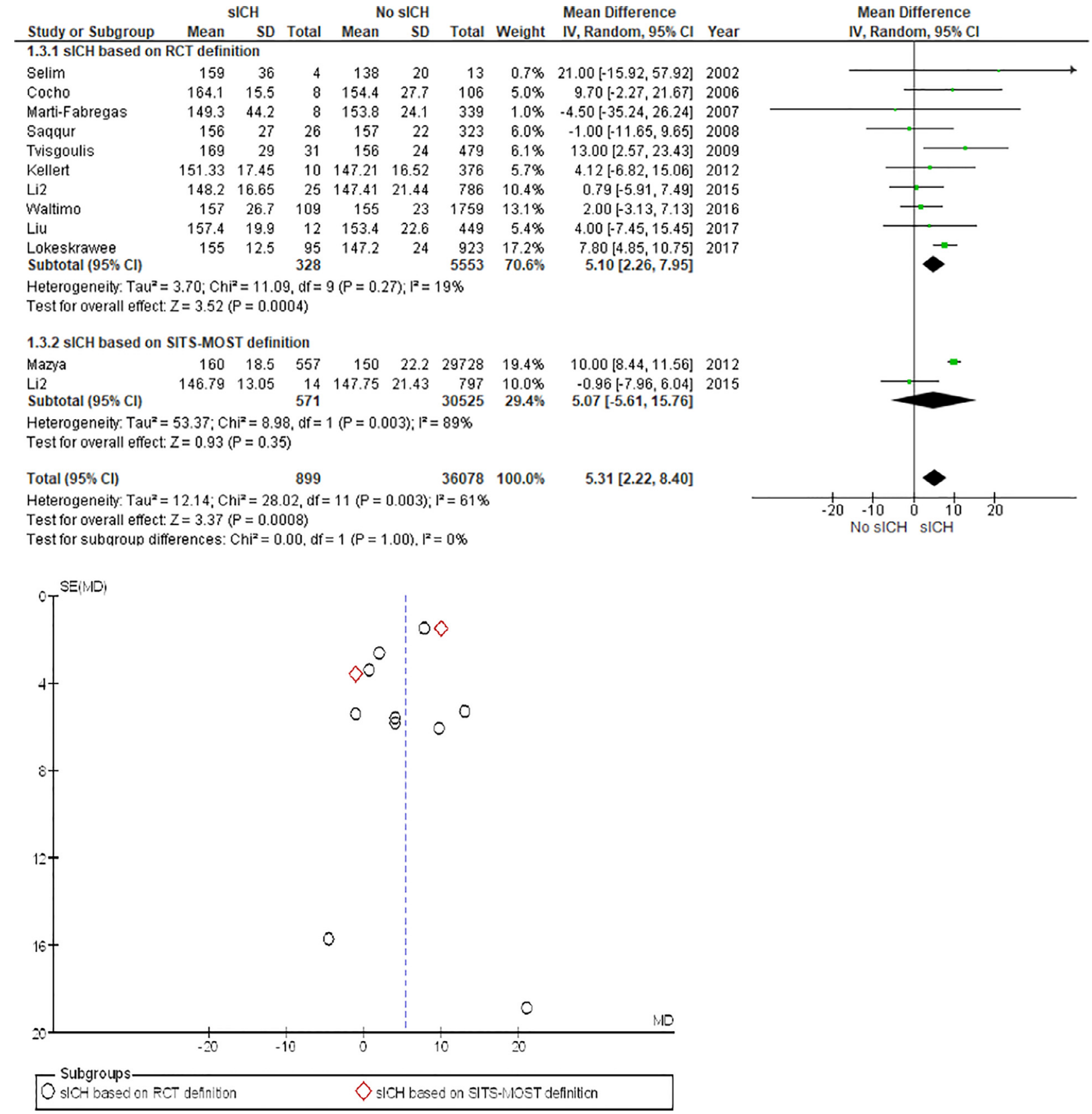


Figure 4. *Forest plot showing effect of baseline systolic blood pressure (SBP) on risk of development of symptomatic intracranial hemorrhage (sICH) post-thrombolysis.*

Although several studies reported BP values as median and IQR instead of mean and standard deviation (implying substantial variance in the cohort), they were included in our pooled analysis due to their high quality. The method proposed by Hozo et al[11] was used to convert the BP values in these studies to mean and SD. A posthoc sensitivity analysis was performed to ascertain if removal of such values affected mean differences (Table 3). Our sensitivity analysis found that excluding studies with median/IQR values did not significantly-affect the pooled mean differences, thus validating our findings. For instance, all studies reporting on the effect of baseline SBP on mRS (n = 15) had a pooled mean difference of 3.87 (95% CI 1.18-6.56), while mean difference remained at 3.98 (95% CI 0.80-7.16) after 3 studies reporting median/IQR values were removed.

Assessment of Study Quality

Majority of included studies were found to be of moderate to high quality on NOQAS (Table 2). Most studies scored well for representativeness of exposed cohort, selection of nonexposed cohort, ascertainment of exposure (measurement of BP), length of follow-up, and adequacy of follow-up. However, several studies failed to report the

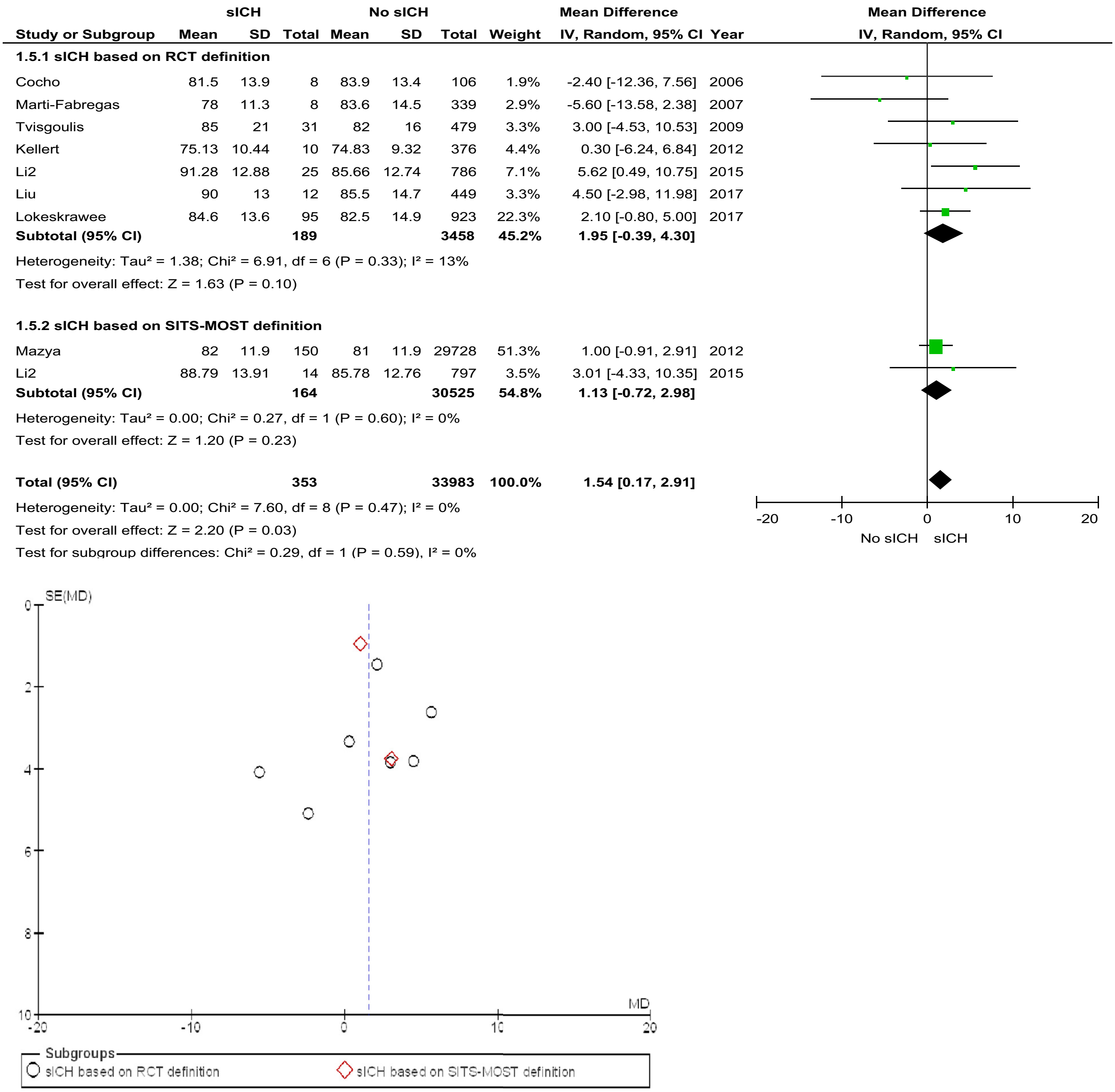


Figure 5. *Forest plot showing effect of baseline diastolic blood pressure (DBP) on sICH.*

method of assessment of outcome. There was also poor comparability between subjects among various studies since the study populations with various comorbidities (e.g., DM, hypertension, atrial fibrillation) were included, and none of the studies matched or stratified the cohorts.

Discussion

Our meta-analyses demonstrated that increased pretreatment systolic BP is associated with poorer functional outcome and an increased risk of sICH in thrombolysed AIS patients. Previously, Willmot et al[38] found a similar association between SBP and death/dependency, but that study pooled only two studies involving AIS patients. Other meta-analyses have explored the effect of antihypertensive therapy on stroke outcomes.[10] Furthermore, they included even the studies where patients did not receive thrombolysis, or those where no difference in prethrombolysis BP was seen between the 2 arms.

The mechanism through which prethrombolysis BP influences stroke outcomes is not well-understood.[39] It is possible that higher BP (and consequently cerebral perfusion pressure/hyperperfusion) leads to increased cerebral edema and hemorrhagic transformation, similar to the observations from animal models.[5]

The evidence for diastolic BP lowering is less clear as it did not show any association with functional outcomes.

Table 2. *Studies were evaluated using the Newcastle Ottowa Scale for assessing quality of Nonrandomized Studies (NOQAS)*

		Selection				Comparability	Outcome		
Study ID	Yr	Representa-tiveness of exposed cohort*	Selection of non exposed cohort†	Ascertainment of exposure‡	Outcome of interest not present at start§	Comparability‖	Assessment of outcome#	Length of follow-up**	Adequacy of follow-up^x
Forlivesi[14]	2018	A	A	A	A	B	D	A	A
Li[17]	2017	A	A	A	A	B	A	A	B
Lokeskrawee[31]	2017	A	A	A	A	B	A	A	B
Wu[24]	2017	A	A	A	A	B	A	A	A
Waltimo[37]	2016	A	A	A	A	B	A	A	A
Cao[12]	2016	A	A	A	A	B	B	A	A
Jiang[16]	2016	A	A	A	A	C	B	A	A
Liu[30]	2016	A	A	A	A	B	A	A	A
Li[29]	2015	A	A	A	A	C	A	A	A
Yan[25]	2015	A	A	A	A	A	A	A	A
Huang[15]	2013	A	A	D	A	C	D	A	A
Strbian[22]	2013	A	A	A	A	B	A	A	A
Mazya[33]	2012	A	B	A	A	B	A	A	A
Martins[19]	2011	A	A	A	A	C	B	A	A
Tsivgoulis[36]	2009	A	A	A	A	B	B	A	A
Kellert[28]	2012	A	A	A	A	B	A	A	A
Saqqur[34]	2008	A	A	A	A	B	A	A	A
Delgado-Mederos[13]	2008	A	A	A	A	B	D	A	A
Saqqur[21]	2007	A	A	A	A	B	B	A	A
Marti-Fabregas[32]	2007	A	A	A	A	A	B	A	A
Tsivgoulis[23]	2007	A	A	A	A	B	B	A	A
Cocho[27]	2006	A	A	A	A	C	D	A	A
Yong[26]	2005	A	A	A	A	A	A	A	A
Molina[20]	2004	A	A	A	A	C	B	A	A
Lindsberg[18]	2003	A	A	A	A	B	A	A	A
Selim[35]	2002	A	A	A	A	B	A	A	A

*Representativeness of the exposed cohort: A, truly representative; B, somewhat representative; C, selected group of users e.g., nurses, volunteers; D, no description of the derivation of the cohort.

†Selection of the nonexposed cohort: A, drawn from the same community as the exposed cohort; B, drawn from a different source; C, no description of the derivation of the nonexposed cohort.

‡Ascertainment of exposure: A, secure record; B, structured interview; C, written self-report; D, no description.

§Demonstration that outcome of interest was not present at start of study: A, yes; B, no.

‖Comparability of cohorts: A, study cohorts had similar baseline NIHSS; B, study cohorts were similar for other factors potentially affecting functional outcome like baseline mRS, age, gender, comorbidities; C, study cohorts were not comparable / unknown.

#Assessment of outcome: A, independent blind assessment; B, record linkage; C, self report; D, no description.

**Was follow-up long enough for outcomes to occur: A, yes (follow-up at least 3 months/90 days); B, no.

^xAdequacy of follow up of cohorts: A, complete follow up with all subjects accounted for; B, subjects lost to followup unlikely to introduce bias; C, follow-up rate less than 70% and no description of those lost; D, no statement.

Table 3. *Sensitivity analysis was performed by excluding studies reporting median and IQR values for BP*

Inclusion	MD* for SBP, mRS	n	MD for SBP, sICH	n	MD for DBP, mRS	n	MD for DBP, sICH	n
All studies, including those with asymmetrical median	3.89 (1.25, 6.62)	16	4.58 (1.36, 7.81)	14	−0.91 (−2.85, 1.03)	10	1.74 (0.48, 3.01)	9
Included studies, with symmetrical median	3.87 (1.18, 6.56)	15	5.28 (2.32, 8.23)	11	−0.91 (−2.85, 1.03)	10	1.54 (0.17, 2.91)	8
Removal of any study reporting median/IQR	3.98 (0.80, 7.16)	12	4.71 (1.36, 8.06)	9	−0.95 (−3.41, 1.51)	7	2.10 (0.14, 4.06)	7

*MD stands for mean difference (95% confidence interval).

However, a weak association was observed between DBP and sICH.

Previously, the Intensive blood pressure reduction in acute cerebral hemorrhage trial (INTERACT-2)[40] and the Intracerebral Hemorrhage Acutely Decreasing Arterial Pressure Trial (ICH-ADAPT)[41] trials demonstrated that aggressive BP-lowering with a target of SBP less than 150 mmHg improved functional outcome and reduced hematoma growth in patients with ICH. However, similarly robust evidence does not exist for AIS patients, with current recommendations based off expert opinion and the results from thrombolysis trials in myocardial infarction.[42,43] More recently, observational data from large patient cohorts in the SITS register linked higher SBP with poorer functional outcomes[44,45] and higher sICH,[33] with the most favorable outcomes observed in patients with prethrombolysis SBP of 141-150 mmHg.

High prethrombolysis BP may also be a marker of stroke severity rather than an actual causal factor of sICH or poor mRS.[46] The same studies comparing the effect of BP on stroke outcomes have shown that baseline NIHSS,[24,27,36] blood glucose,[14,22,37] dehydration,[17] hyperthermia,[14] Body Mass Index (BMI),[24] age,[37] and previous stroke/transient ischemic attack[22] are independently-associated with short- and long-term outcomes on multivariate analysis.

Our findings suggest that while current guidelines[47] recommend lowering prethrombolysis BP to below 185 mmHg, it may be prudent that lower SBP targets are set and achieved in clinical practice for better functional outcomes and a lower incidence of sICH. Our study demonstrated that even very small differences in the prethrombolysis BP values lead to significant differences in the functional outcome (insert numbers here) as well as sICH. This appears reassuring since a BP reduction of small magnitude may be acceptable by the stroke neurologists. The ongoing Enhanced Control of Hypertension and Thrombolysis stroke study (ENCHANTED), the largest ever clinical trial for systemic thrombolysis in AIS, aims to address the impact of early intensive BP lowering in thrombolysed AIS patients. However, the prethrombolysis optimal BP level would still remain elusive.

Limitations

The scope of our meta-analysis included studies that reported prethrombolysis SBP or DBP values. Therefore, we did not include other BP parameters such as maximum, minimum, standard deviation (SD), average squared difference of successive BP values (SV), and other variability coefficients. Additionally, several studies[24,37] have reported that post-thrombolysis SBP may be a more robust predictor for sICH and poor mRS than prethrombolysis SBP. However, owing to the heterogeneity and limited availability of such studies, we were unable to examine the impact of BP trends after thrombolysis on functional outcomes and sICH. Second, apart from the ongoing ENCHANTED trial,[48] we could not find any other study that examines the effect of different extents of BP reduction on AIS outcome measures. Therefore, we could include only the observational cohort studies and registries. Inclusion of such studies in our meta-analysis did not ensure comparable patient cohorts by adjusting for confounders or matching patients based on comorbidities. Third, despite our strict inclusion and exclusion criteria, included studies had moderate heterogeneity. Since crude BP values were used, we could not account for between-study differences in age, ethnicity, stroke protocol, onset-to-treatment time, as well as the covariates mentioned in the previous paragraph. The quality of poststroke rehabilitation might also have influenced the functional outcome at 3 months. Fourth, we included only the 2 widely-used endpoints in this meta-analysis−90-day functional outcome (mRS) and development of sICH. Studies with other measurements of stroke outcome such as change in NIHSS from baseline, recanalization, early neurological deterioration, and hemorrhagic transformation solely based on imaging were excluded.

Conclusion

In conclusion, higher prethrombolysis systolic BP is associated with poorer functional outcomes and increased incidence of symptomatic intracranial hemorrhage in thrombolysed acute ischemic stroke patients. This supports the case for more aggressive lowering of BP prior to thrombolysis. Perhaps, large well designed prospective studies and randomized trials are required to establish the optimal pretreatment BP targets for a safer and effective systemic thrombolysis.

Supplementary Materials

Supplementary data to this article can be found online at doi:10.1016/j.jstrokecerebrovasdis.2018.12.008.

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