

Supplementary materials

Supplementary Table 1 Search Strategy

1. cerebrovascular disorders/ or basal ganglia cerebrovascular disease/ or brain ischemia/ or exp brain infarction/ or hypoxia-ischemia, brain/ or carotid artery diseases/ or carotid artery thrombosis/ or carotid artery, internal, dissection/ or intracranial arterial diseases/ or cerebral arterial diseases/ or infarction, anterior cerebral artery/ or infarction, middle cerebral artery/ or infarction, posterior cerebral artery/ or exp "Intracranial Embolism and Thrombosis"/ or exp stroke/ or vertebral artery dissection/
2. (isch?emi\$ adj6 (stroke\$ or apoplex\$ or cerebral vasc\$ or cerebrovasc\$ or cva or attack\$)).tw.
3. 1 or 2
4. thrombolytic therapy/
5. fibrinolytic agents/ or plasmin/ or plasminogen/ or tissue plasminogen activator/ or exp plasminogen activators/ or urokinase-type/ or plasminogen activator/
6. fibrinolysis/
7. (thromboly\$ or fibrinoly\$ or recanaliz\$ or recanaliz\$).tw.
8. ((clot\$ or thrombus) adj5 (lyse or lysis or dissolve\$ or dissolution)).tw.
9. (tPA or t-PA or rtPA or rt-PA or plasminogen or plasmin or alteplase or actilyse).tw.
10. (anistreplase or streptodornase or streptokinase or urokinase or pro?urokinase or rpro?uk or lumbrokinase or duteplase or lanoteplase or pamiteplase or reteplase or saruplase or staphylokinase or streptase or tenecteplase or desmoteplase or retevase).tw.
11. 4 or 5 or 6 or 7 or 8 or 9 or 10
12. 3 and 11

Supplementary Table 2 Characteristics of studies included in the review

Publication	Origin	TPA dose, mg/kg	No. of cases	Age, years	Baseline NIHSS: median (range)	Onset to treatment time in minutes	mRS2-6 at 3 months, n(%) (95%CI)	Death, n(%) (95%CI)	sICH per NINDS	sICH per SISTS-MOST	sICH per ECASS, n (%) (95% CI)
NINDS 1995 ¹ (Part 1 and 2)	USA	0.9	312	68 (11)	14 (1–37)	119.7	179/312(57.4) (51.9-62.9)	53/312(17) (12.8-21.2)	20/312(6.4) (3.7–9.1)		
SITS-MOST study group 2007 ²	European Union members in 2002, including Norway and Iceland	0.9	6483	68 (59–75)	12 (8–17)	136 (33)	3750/6136(61.1) (59.9-62.3)	701/6218(11.3) (10.5–12.1)	468/6438(7.3) (6.7–7.9)	107/6444(1.7) (1.4–2.0)	296/6442(4.6) (4.1–5.1)
Suwanwela et al 2006 ³	Thailand	0.6	2	65(12)	18 (9–32)	130 (45–180)					
		0.9	32		20 (8–32)	138 (55–180)	17/32(53.1) (35.8-70.4)				
Yamaguchi et al 2006 ⁴	Japan	0.6	103	70.9 (9.8)	15 (5–30)	150.5	65/103(63.1) (53.8-72.4)	10/103(9.7) (4.0-15.4)		6/103 (5.8) (1.3–10.3)	
Padma et al 2007 ⁵	India	0.9	54	66	14(8-22)	170.8		1/54(1.8) (-1.7-5.3) *	0/54 (0) (0–5 4)		
Yoneda et al 2007 ⁶	Japan	0.6	20	68(14)	19(5-37)	136(87-180)	15/20(75) (56-94)	3/20(15) (-0.6-30.6)		1/20(5) (-4.6-14.6)	
Sharma et al 2008 ⁷	India	0.9	32	66 (38–78)	14(8-22)	150 (93–248)	Average mRS=1.2	1/31 (3.2) (-3.0-9.4)	2/32 (6.3) (-2.1-14.7)		
Hsu et al 2009 ⁸	Taiwan	0.9	43	63 (13)	18 (6–32)	134 (30–224)	29/43(67) (52.9-81.1)	4/43(9.3) (0.6-18.0)	2/43 (4.7) (-1.6-11.0)		
Salam et al 2009 ⁹	India	0.6-0.9	57	62(35-78)	12(5-21)	140 (55–185)	mRS≤2: 29/57 (50.9) (38.0–63.6)	7/57(12) (3.6-20.4)	1/57 (1.7) (-1.7-5.1)		
Toyoda et al 2009 ¹⁰	Japan	0.6	600	72(12)	13(7.3-19)	145(121-166)	401/600(66.8) (63.0-70.6)	43/600(7.2) (5.4-9.5)		1.3 (0.7-2.6)	
Boddu et al 2010 ¹¹	India	0.9	72	53(12.3)	11(7-23)	152(28)	38/72(52.8) (41.3-64.3)**	6/72(8.3) (1.9-14.7)**	4/72 (5.5) (0.2-10.8)		

Chao et al 2010 ¹²	Taiwan	0.72±0.07	116	66.7(13.3)	14.9±6.0	141.6±34.9	68/116(58.6) (49.6-67.6)	8/116(6.9) (2.3-11.5)	6/116(5.2) (1.2-9.2)	2/116(1.7) (-0.7-4.1)	3/116(2.6) (-0.3-5.5)
		0.90±0.02	125	64.9(11.7)	15.9±5.6	137.5±39.4	78/125(62.4) (53.9-70.9)	16/125(12.8) (6.9-18.7)	13/125(10.4) (5.0-15.8)	7/125(5.6) (1.6-9.6)	10/125(8.0) (3.2-12.8)
Lau et al 2010 ¹³	Hong Kong	0.9	17	71	16(9-23)	144(42)	8/17(47.1) (23.4-70.8)	1/17(5.9) (-5.3-17.1)			
Mori et al 2010 ¹⁴	Japan	0.6	58	70.3(11.5)	12(5-22)	132(24)	31/58(53.4) (39.6-65.6)	1/58(1.7) (-17-5.1)			
Nakagawara et al 2010 ¹⁵	Japan	0.6	7492	72(65-79)	15(9-20)	133(110-160)	3313/4944(67.0) (65.7-68.3)	985/7492(13.1) (12.4-13.9)			259/7492(3.5) (3.1-3.9)
Nguyen et al 2010 ¹⁶	Vietnam	0.6-0.86	48	57(13)	10.5(5.7)	141(33)	21/48(43.7) (29.7-57.7)	1/48 (2.1) (-2.0-6.2)		1/48 (2.1) (-2.0-6.2)	
		0.9	73	58(14)	12(7)	145(33)	48/73(65.7) (54.8-76.6)	9/73(12.5) (4.9-20.1)		4/73 (5.5) (0.3-10.7)	
Sharma et al 2010 ¹⁷	Singapore	0.5-0.71	48	55(12)	12(10)	165(30)	31/48(64.6) (51.1-78.1)	5/48(10.4) (1.8-19.0)		7/48 (14.5) (4.5-24.5)	
		0.9	82	62(13)	15(11)	155(47)	34/82(41.5) (30.8-52.2)	11/82(13.4) (6.0-20.8)		1/82 (1.2) (-1.2-3.6)	
Wasay et al 2010 ¹⁸	Pakistan	0.9	21	62(27-77)	Not available	169(95-200)		4/21(19) (2.2-35.8)			
Zhou et al 2010 ¹⁹	China	0.6-0.7	23	69.8(8.6)	12.6(6.8)	170.3(43.9)	15/23(65.2) (45.7-84.7)	4/23(17.4) (1.9-32.9)	1/23(4.3) (-4.0-12.6)		1/23(4.3) (-4.0-12.6)
		0.8	31	72.9(8.7)	12.7(5.0)	174.3(45.2)	19/31(61.3) (44.2-78.4)	5/31(16.1) (3.2-29.0)	3/31(9.7) (-0.7-20.1)		1/31(3.2) (-3.0-9.4)
		0.9	51	72.7(10.7)	13.0(6.3)	153.5(53.0)	25/51(49) (35.3-62.7)	6/51(11.8) (2.9-20.7)	5/51(9.8) (1.6-18.0)		2/51(3.9) (-1.4-9.2)
Chen et al 2012 ²⁰	Taiwan	<0.85	105	67.9(12.8)	13.3(6.2)	144(41)	56/95(59) (49.1-68.9)	7/95(7.4) (2.1-12.7)	5/105(4.8) (0.7-8.9)	4/105(3.8) (0.1-7.5)	
		≥0.85	156	67.9(12.3)	13.1(6.3)	141(39)	90/146(61.6) (53.7-69.5)	12/146(8.2) (3.7-12.7)	4/156(2.6) (0.1-5.1)	2/156(1.3) (-0.5-3.1)	
Koga et al 2012 ²¹	Japan	0.6	600	81.7(8.6)	Not available	Not available	336/532(63.1) (59.0-67.2)	43/600(7.2) (5.1-9.3)		16(2.7%)	
Muengtaweepo ngsa et al 2012 ²²	Thailand	0.9	100	65	15(3-34)	160(60-270)	58/100(58) (48.3-67.7)	14/100(14) (7.2-20.8)		2/100(2) (-0.7-4.7)	

Pan et al 2012 ²³	China	<0.75	31	63.8(9.3)	8.7(4.6)	185.3(54.4)	15/31(48.4) (30.8-66.0)	1/31(3.2) (-3.0-9.4)	3/31(9.1) (-1.0-19.2)		
		0.75-0.90	33	64.5(7.7)	9.2(5.0)	190.4(62.2)	13/33(39.4) (22.7-56.1)	1/33(3.0) (-2.8-8.8)	5/33(16.1) (3.6-28.6)		
		0.9	19	65.7(9.3)	11.1(5.8)	177.2(44.0)	8/19(42.1) (19.9-64.3)	2/19(5.3) (-4.8-15.4)	2/19(10.5) (-3.3-24.3)		
Chao et al 2014 ²⁴	Taiwan	0.6	181	70.1(10.9)	14.4(6.1)	147.7(41.7)	90/146(61.6) (53.7-69.5)	14/181(7.7) (3.8-11.6)	10/181 (5.5) (2.2-8.8)	5/181(2.8) (0.4-5.1)	10/181(5.5) (2.2-8.8)
		0.7	199	70.1(10.9)	14.7(6.4)	140.4(36.7)	112/156(71.8) (64.7-78.9)	19/199 (9.6) (5.5-13.7)	10/199 (5.0) (2.0-8.1)	4/199 (2.0) (0.1-4.0)	6/199 (3.0) (0.6-5.4)
		0.8	202	66.9(13.5)	15.2(6.5)	145.5(36.0)	125/171(73.1) (66.5-79.7)	18/202 (8.9) (5.0-12.8)	12/202 (5.9) (2.7-9.2)	5 /202(2.5) (0.3-4.6)	11/202 (5.5) (2.3-8.6)
		0.9	422	66.1(12.0)	15.0(7.7)	137.3(57.3)	243/367(66.2) (61.4-71.0)	35/422 (8.3) (5.7-10.9)	31/422 (7.4) (4.9-9.8)	7/422 (1.7) (0.4-2.9)	21/422 (5.0) (2.9-7.1)
Liao et al 2014 ²⁵	China	0.5-0.7	75	62(52-71)	10(7-17)	175.2(151.1-190.8)	43/74(58.1) (46.9-69.3)	14/74(5.4) (0.3-10.5)			
		0.7-0.85	131	68(57-73)	10(6-15)	175.8(139.8-199.8)	66/127(52.0) (43.3-60.7)	11/127(8.7) (3.8-13.6)	12/131(9.2) (4.3-14.1)	5/131(3.8) (0.5-7.1)	11/131(8.4) (3.6-13.2)
		0.85-0.95	678	63(55-72)	11(7-15)	167.4(139.8-195.0)	307/665(46.2) (42.4-50.0)	49/666(7.4) (5.4-9.4)	33/678(4.9) (3.3-6.5)	11/678(1.6) (0.7-2.5)	21/678(3.1) (1.8-13.2)
Rha et al 2012 ²⁶	South Korea, China, India, and Singapore	0.9	591	64(55-72)	12(8-17)	130(105-160)	332/579(57.3) (53.3-61.3)	59/579(10.2) (7.7-12.7)	51/586(8.7) (6.4-11.0)	11/587(1.9) (0.8-3.0)	33/585(5.6) (3.7-7.5)
Takayanagi et al 2014 ²⁷	Japan	0.6	87	71.7(11.5)	16.8(9.1)	142.6(30.1)	66/87(75.9) (66.9-84.9)	14/87(16.1) (8.4-23.8)			
Kim et al 2015 ²⁸	Korea	0.6	450	69.0(12.7)	13.9(7.0)	126(54)	304/450(67.6) (63.3-71.9)	57/450(12.7) (9.6-15.8)		38/450(8.4) (5.8-11.0)	
		0.9	1076	68.2(12.3)	10.5(6.0)	126(54)	696/1076(64.7) (61.8-67.6)	151/1076(14.0) (11.9-16.1)		69/1076(6.4) (4.9-7.9)	
ENCHANTED(Asian) 2016 ²⁹	Asian	0.6	1043	64.1(11.8)	9(5-14)	174(132-216)	527/1024 (51.5) (48.4-54.6)	87/1043 (8.3) (6.6-10.0)	62/1043(5.9) (4.5-7.3)	10/1043(1.0) (0.4-1.6)	
		0.9	1036	64.3(11.4)	9(5-14)	168(126-210)	500/1020 (49.0) (45.9-52.1)	92/1036 (8.9) (7.2-10.6)	88/1036(8.5) (6.8-10.2)	23/1036(2.2) (1.3-3.1)	
ENCHANTED 2016 ²⁹		0.6	1607	68 (58-76)	8 (5-14)	170(125-218)	855/1607 (53.2) (50.8-55.6)	140/1654 (8.5) (7.2-9.8)	98/1654 (5.9) (4.8-7.0)	17/1654 (1.0) (0.5-1.5)	
		0.9	1599	67 (58-76)	8 (5-14)	170(127-219)	817/1599 (51.1) (48.6-53.6)	170/1599 (10.3) (8.8-11.8)	131/1643 (8.0) (6.7-9.3)	35/1643 (2.1) (1.4-2.8)	

*outcome at 1 month **outcome at 12 months

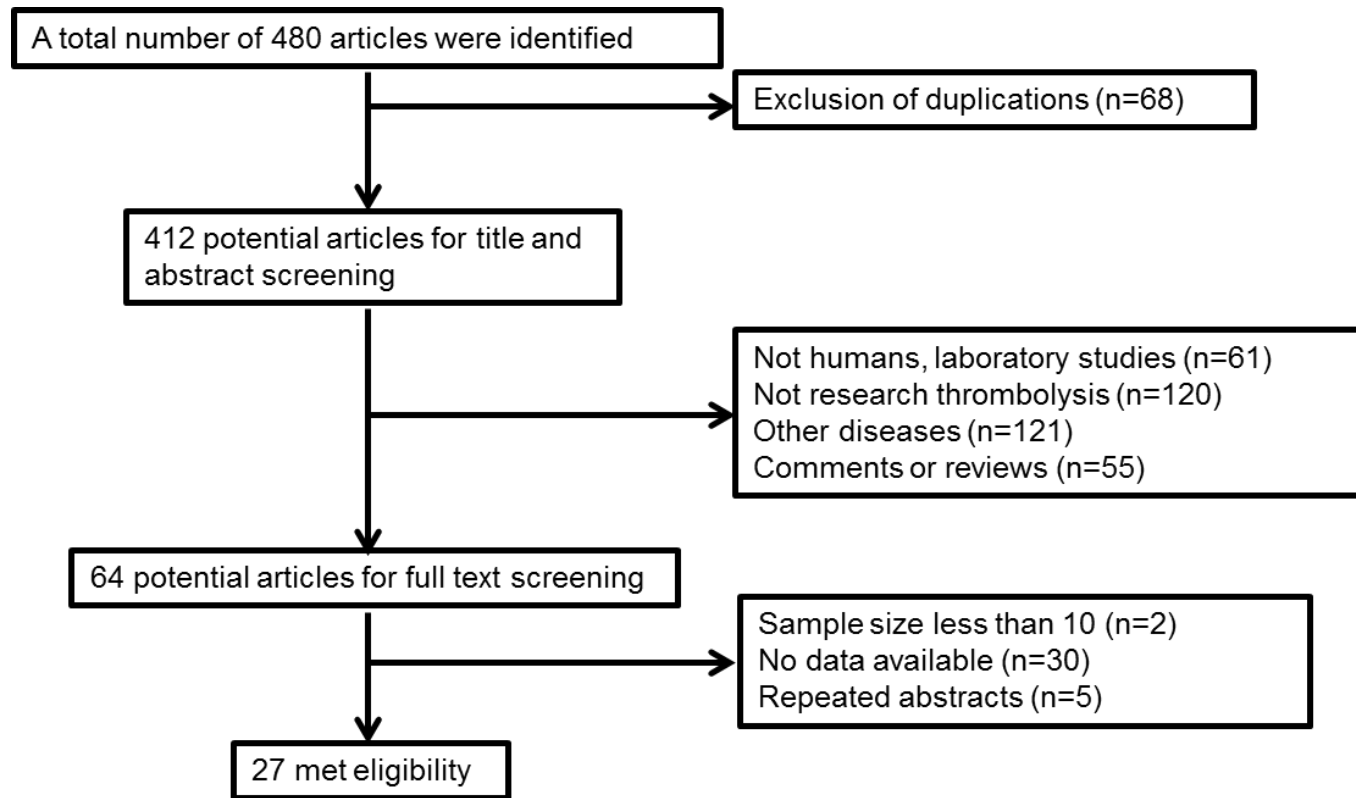
rtPA: recombinant tissue plasminogen activator; NIHSS: National Institutes of Health Stroke Scale; mRS: modified Rankin Scale; sICH: symptomatic intracranial hemorrhage; NINDS: National Institute of Neurological Disorders and Stroke; SITS-MOST: Safe Implementation of Thrombolysis in Stroke-Monitoring Study; ECASS: European Cooperative Acute Stroke Study.

Supplementary Table 3 Quality assessment of the included studies

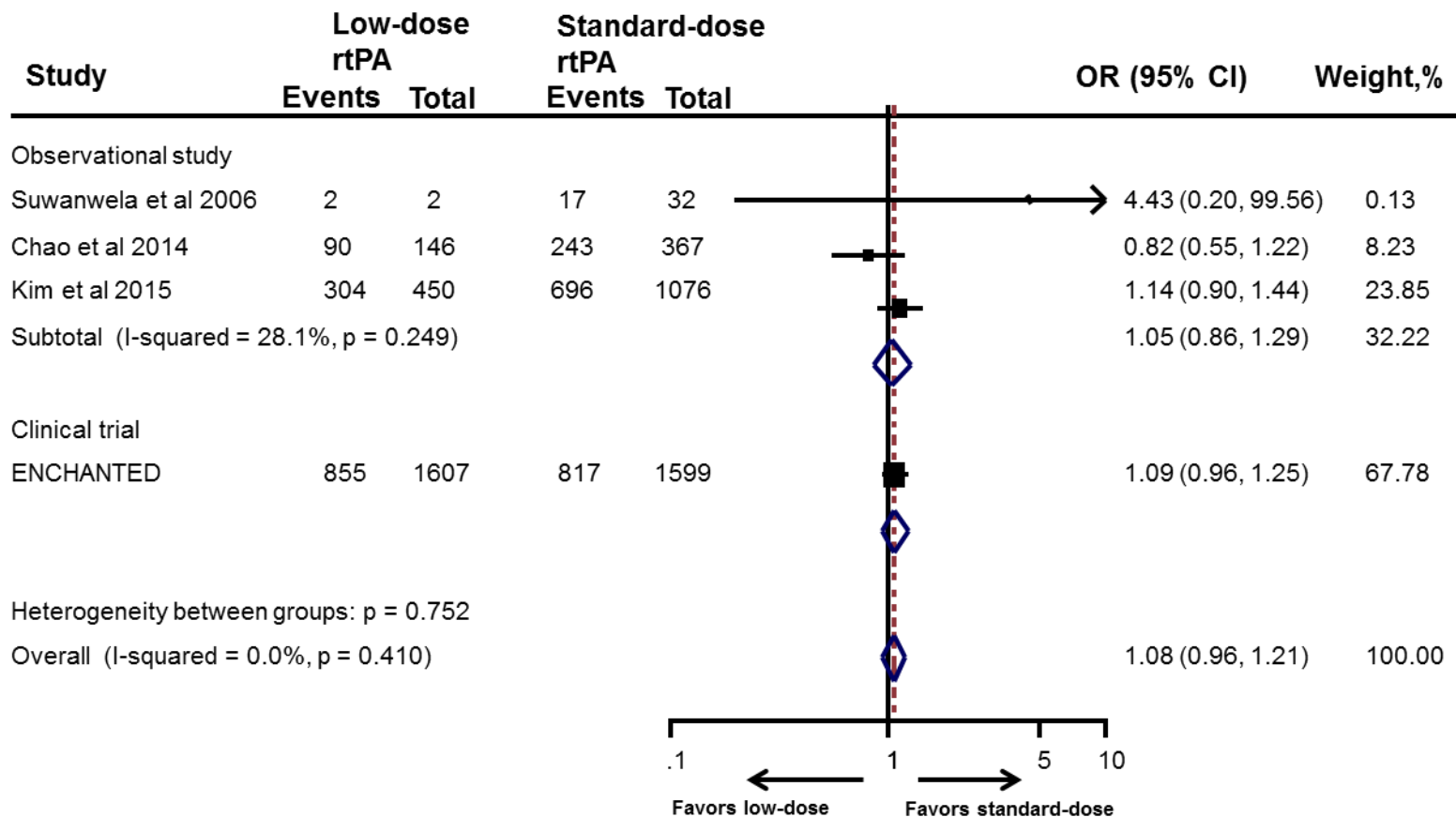
Publications	Selection				Comparability	Outcome		
Observational studies	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure to implants	Demonstration that outcome of interest was not present at start of study		Assessment of outcome	Follow-up long enough for outcomes	Adequacy of follow up of cohorts
Suwanwela et al 2006 ³	0	*	*	*	0	*	*	0
Yamaguchi et al 2006 ⁴	*	0	*	*	0	*	*	*
Padma et al 2007 ⁵	0	0	*	*	0	0	*	0
Yoneda et al 2007 ⁶	0	0	*	*	0	*	*	*
Sharma et al 2008 ⁷	0	0	*	*	0	*	*	*
Hsu et al 2009 ⁸	0	0	*	*	0	*	*	*
Salam et al 2009 ⁹	0	0	*	*	0	*	*	0
Toyoda et al 2009 ¹⁰	*	0	*	*	0	*	*	*
Boddu et al 2010 ¹¹	0	0	*	*	0	*	*	*
Chao et al 2010 ¹²	*	*	*	*	**	*	*	*
Lau et al 2010 ¹³	0	0	*	*	0	*	*	0
Mori et al 2010 ¹⁴	*	0	*	*	0	*	*	*
Nakagawara et al 2010 ¹⁵	*	0	*	*	0	*	*	0
Nguyen et al 2010 ¹⁶	*	*	*	*	**	*	*	*
Sharma et al 2010 ¹⁷	*	*	*	*	0	*	*	*
Wasay et al 2010 ¹⁸	0	0	*	*	0	*	0	0
Zhou et al 2010 ¹⁹	0	*	*	*	*	*	*	*
Chen et al 2012 ²⁰	*	0	*	*	0	*	*	*
Koga et al 2012 ²¹	*	0	*	*	0	*	*	*
Muengtaweepongsa et al 2012 ²²	0	0	*	*	0	*	*	*
Pan et al 2012 ²³	0	0	*	*	0	*	*	*
Chao et al 2014 ²⁴	*	*	*	*	**	*	*	*

Liao et al 2014 ²⁵	*	*	*	*	*	*	*	*
Rha et al 2012 ²⁶	*	0	*	*	0	*	*	*
Takayanagi et al 2014 ²⁷	0	0	*	*	0	*	*	*
Kim et al 2015 ²⁸	*	*	*	*	0	*	*	*
Clinical trial	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias	
ENCHANTED ²⁹	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk	

ENCHANTED: The ENhanced Control of Hypertension And Thrombolysis stroke stuDy

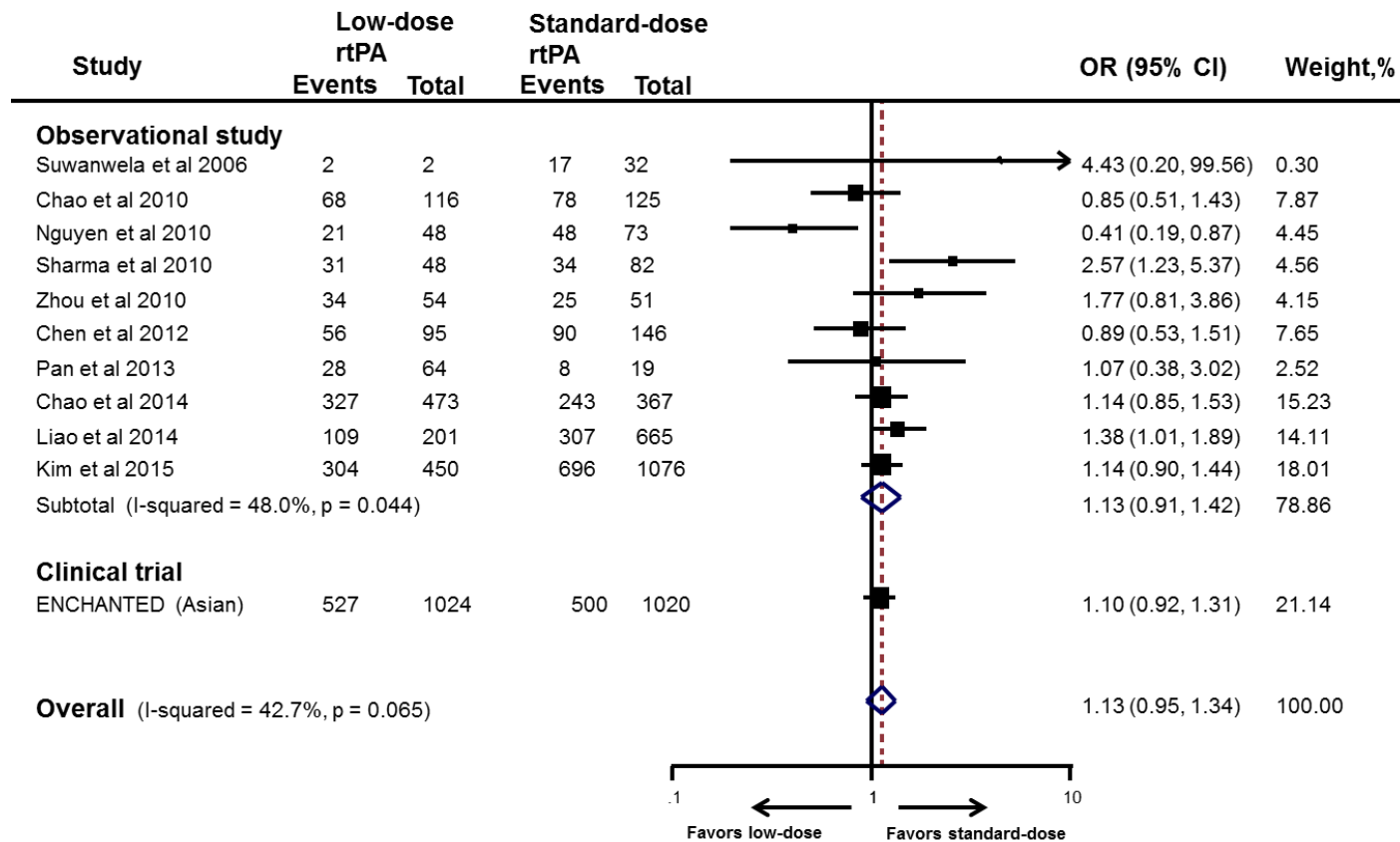


Supplementary Figure 1 Flow chart of literature search



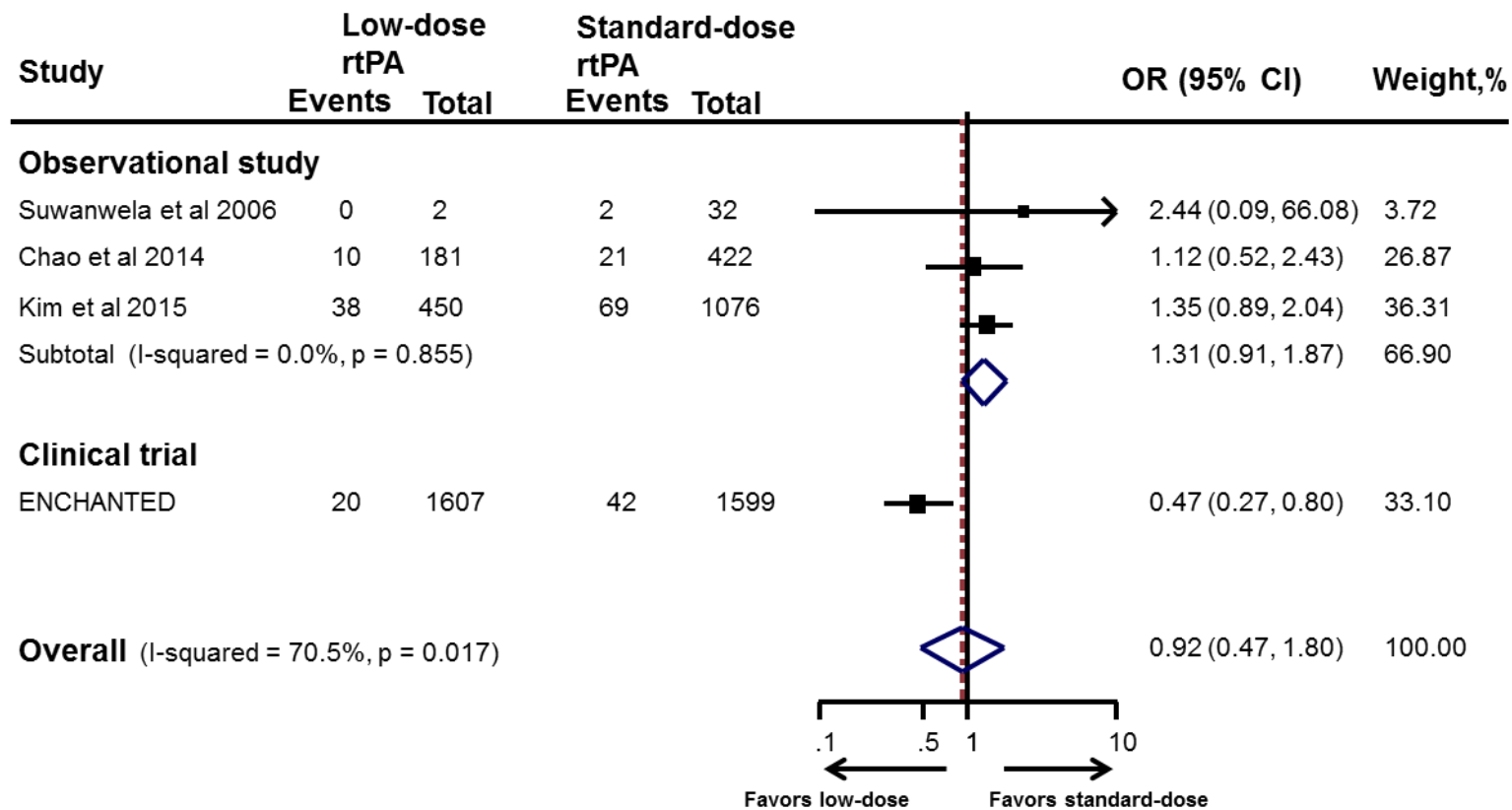
Supplementary Figure 2 Association between the rtPA dose and death or disability in studies with only low-dose rtPA of 0.6mg/kg and standard-dose of 0.9mg/kg

Footnote: CI: confidence interval, ENCHANTED: ENhanced Control of Hypertension And Thrombolysis stroke study, OR: odds ratio, rtPA: recombinant tissue plasminogen activator



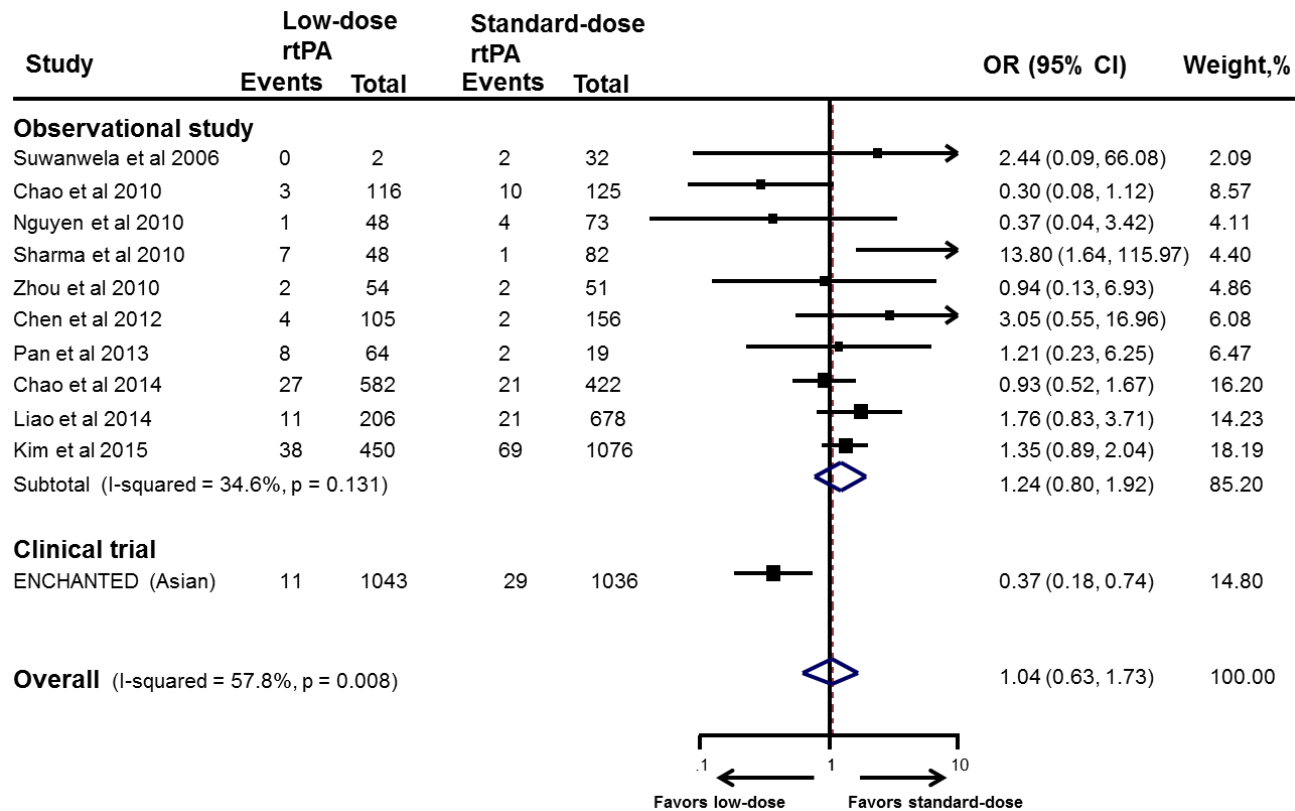
Supplementary Figure 3 Association between the rtPA dose and death or disability in studies in only Asian countries

Footnote: CI: confidence interval, ENCHANTED: ENhanced Control of Hypertension And Thrombolysis strokeE study, OR: odds ratio, rtPA: recombinant tissue plasminogen activator



Supplementary Figure 4. Association between the rtPA dose and symptomatic intracranial hemorrhage in studies with only low-dose and standard-dose rtPA

Footnote: CI: confidence interval, ENCHANTED: ENhanced Control of Hypertension And Thrombolysis stroke study, OR: odds ratio, rtPA: recombinant tissue plasminogen activator



Supplementary Figure 5 Association between the rtPA dose and symptomatic intracranial hemorrhage in studies in only Asian countries

Footnote: CI: confidence interval, ENCHANTED: ENhanced Control of Hypertension And Thrombolysis strokE study, OR: odds ratio, rtPA: recombinant tissue plasminogen activator

1. Tissue plasminogen activator for acute ischemic stroke. The national institute of neurological disorders and stroke rt-pa stroke study group. *The New England journal of medicine*. 1995;333:1581-1587
2. Wahlgren N, Ahmed N, Davalos A, Ford GA, Grond M, Hacke W, et al. Thrombolysis with alteplase for acute ischaemic stroke in the safe implementation of thrombolysis in stroke-monitoring study (sits-most): An observational study. *Lancet*. 2007;369:275-282
3. Suwanwela NC, Phanthumchinda K, Likitjaroen Y. Thrombolytic therapy in acute ischemic stroke in asia: The first prospective evaluation. *Clin Neurol Neurosurg*. 2006;108:549-552
4. Yamaguchi T, Mori E, Minematsu K, Nakagawara J, Hashi K, Saito I, et al. Alteplase at 0.6 mg/kg for acute ischemic stroke within 3 hours of onset: Japan alteplase clinical trial (j-act). *Stroke; a journal of cerebral circulation*. 2006;37:1810-1815
5. Padma MV, Singh MB, Bhatia R, Srivastava A, Tripathi M, Shukla G, et al. Hyperacute thrombolysis with iv rtpa of acute ischemic stroke: Efficacy and safety profile of 54 patients at a tertiary referral center in a developing country. *Neurol India*. 2007;55:46-49
6. Yoneda Y, Yamamoto S, Hara Y, Ohta K, Matsushita M, Yamamoto D, et al. Post-licensed 1-year experience of systemic thrombolysis with tissue plasminogen activator for ischemic stroke in a japanese neuro-unit. *Clin Neurol Neurosurg*. 2007;109:567-570
7. Sharma SR, Sharma N. Hyperacute thrombolysis with recombinant tissue plasminogen activator of acute ischemic stroke: Feasibility and effectivity from an indian perspective. *Ann Indian Acad Neurol*. 2008;11:221-224
8. Hsu YC, Sung SF, Ong CT, Wu CS, Su YH. Intravenous thrombolytic therapy for acute ischemic stroke: The experience of a community hospital. *Acta Neurol Taiwan*. 2009;18:14-20
9. Salam KA, Ummer K, Kumar VG, Noone ML, Laila A, Ragini J. Intravenous thrombolysis for acute ischemic stroke: The malabar experience 2003 to 2008. *J Clin Neurosci*. 2009;16:1276-1278
10. Toyoda K, Koga M, Naganuma M, Shiokawa Y, Nakagawara J, Furui E, et al. Routine use of intravenous low-dose recombinant tissue plasminogen activator in japanese patients: General outcomes and prognostic factors from the samurai register. *Stroke; a journal of cerebral circulation*. 2009;40:3591-3595
11. Boddu DB, Srinivasarao Bandaru VC, Reddy PG, Madhusudan M, Rukmini MK, Suryaprabha T, et al. Predictors of major neurological improvement after intravenous thrombolysis in acute ischemic stroke: A hospital-based study from south india. *Neurol India*. 2010;58:403-406
12. Chao AC, Hsu HY, Chung CP, Liu CH, Chen CH, Teng MM, et al. Outcomes of thrombolytic therapy for acute ischemic stroke in chinese patients: The taiwan thrombolytic therapy for acute ischemic stroke (tth-ais) study. *Stroke*. 2010;41:885-890
13. Lau AY, Soo YO, Graham CA, Woo WK, Wong EH, Leung H, et al. An expedited stroke triage pathway: The key to shortening the door-to-needle time in delivery of thrombolysis. *Hong Kong Med J*. 2010;16:455-462
14. Mori E, Minematsu K, Nakagawara J, Yamaguchi T, Sasaki M, Hirano T, et al. Effects of 0.6 mg/kg intravenous alteplase on vascular and clinical outcomes in middle cerebral artery occlusion: Japan alteplase clinical trial ii (j-act ii). *Stroke; a journal of cerebral circulation*. 2010;41:461-465

15. Nakagawara J, Minematsu K, Okada Y, Tanahashi N, Nagahiro S, Mori E, et al. Thrombolysis with 0.6 mg/kg intravenous alteplase for acute ischemic stroke in routine clinical practice: The japan post-marketing alteplase registration study (j-mars). *Stroke; a journal of cerebral circulation*. 2010;41:1984-1989
16. Nguyen TH, Truong AL, Ngo MB, Bui CT, Dinh QV, Doan TC, et al. Patients with thrombolysed stroke in vietnam have an excellent outcome: Results from the vietnam thrombolysis registry. *Eur J Neurol*. 2010;17:1188-1192
17. Sharma VK, Tsivgoulis G, Tan JH, Wong LYH, Ong BKC, Chan BPL, et al. Feasibility and safety of intravenous thrombolysis in multiethnic asian stroke patients in singapore. *Journal of Stroke and Cerebrovascular Diseases*. 2010;19:424-430
18. Wasay M, Barohi H, Malik A, Yousuf A, Awan S, Kamal AK. Utilization and outcome of thrombolytic therapy for acute stroke in pakistan. *Neurol Sci*. 2010;31:223-225
19. Zhou XY, Wang SS, Collins ML, Davis SM, Yan B. Efficacy and safety of different doses of intravenous tissue plasminogen activator in chinese patients with ischemic stroke. *Journal of Clinical Neuroscience*. 2010;17:988-992
20. Chen CH, Hsieh CY, Lai TB, Chuang MT, Chen WL, Sun MC. Optimal dose for stroke thrombolysis in asians: Low dose may have similar safety and efficacy as standard dose. *Journal of Thrombosis and Haemostasis*. 2012;10:1270-1275
21. Koga M, Shiokawa Y, Nakagawara J, Furui E, Kimura K, Yamagami H, et al. Low-dose intravenous recombinant tissue-type plasminogen activator therapy for patients with stroke outside european indications: Stroke acute management with urgent risk-factor assessment and improvement (samurai) rtpa registry. *Stroke*. 2012;43:253-255
22. Muengtaweepongsa S, Dharmasaroja P, Kummark U. Outcomes of intravenous thrombolytic therapy for acute ischemic stroke with an integrated acute stroke referral network: Initial experience of a community-based hospital in a developing country. *J Stroke Cerebrovasc Dis*. 2012;21:42-46
23. Pan SM, Liu JF, Liu M, Shen S, Li HJ, Dai LH, et al. Efficacy and safety of a modified intravenous recombinant tissue plasminogen activator regimen in chinese patients with acute ischemic stroke. *Journal of Stroke and Cerebrovascular Diseases*. 2013;22:690-693
24. Chao AC, Liu CK, Chen CH, Lin HJ, Liu CH, Jeng JS, et al. Different doses of recombinant tissue-type plasminogen activator for acute stroke in chinese patients. *Stroke*. 2014;45:2359-2365
25. Liao X, Wang Y, Pan Y, Wang C, Zhao X, Wang DZ, et al. Standard-dose intravenous tissue-type plasminogen activator for stroke is better than low doses. *Stroke*. 2014;45:2354-2358
26. Rha JH, Shrivastava VP, Wang Y, Lee KE, Ahmed N, Bluhmki E, et al. Thrombolysis for acute ischaemic stroke with alteplase in an asian population: Results of the multicenter, multinational safe implementation of thrombolysis in stroke-non-european union world (sits-new). *International Journal of Stroke*. 2014;9 Suppl A100:93-101
27. Takayanagi S, Ochi T, Hanakita S, Suzuki Y, Maeda K. The safety and effectiveness of low-dose recombinant tissue plasminogen activator (0.6 mg/kg) therapy for elderly acute ischemic stroke patients (\geq 80 years old) in the pre-endovascular era. *Neurol Med Chir (Tokyo)*. 2014;54:435-440

28. Kim BJ, Han MK, Park TH, Park SS, Lee KB, Lee BC, et al. Low-versus standard-dose alteplase for ischemic strokes within 4.5 hours: A comparative effectiveness and safety study. *Stroke*. 2015;46:2541-2548
29. Anderson CS, Robinson T, Lindley RI, Arima H, Lavados PM, Lee TH, et al. Low-dose versus standard-dose intravenous alteplase in acute ischemic stroke. *The New England journal of medicine*. 2016;374:2313-2323