

Additional file

METHODS

Search strategy and study selection

To complete the search, we started by using key articles to produce relevant keyword terms. Abstracts and full-text of key articles were read to refine concepts and synonyms. A comprehensive and systematic search of electronic databases including PubMed, Embase, Web of Science, and the Cochrane Library was undertaken to identify relevant studies. The key articles were used for validating the success of the searches and the search strategies were peer-reviewed by a second librarian. Only English articles were eligible. Inclusion criteria include: (1) randomized controlled trial or observational study of adult patients with large vessel ischemic strokes; (2) studies directly comparing at least one outcome of interest between the Endovascular Thrombectomy with and without Intravenous alteplase, with odds ratio (OR) reported or clinical data which were required to calculate OR provided; (3) in English; (4) with a minimal of ten patients per treatment arm. Case reports and conference abstracts were excluded. Studies containing duplicate data were carefully evaluated, and only the one reporting data of the largest sample size was included. Studies were also excluded if they used intra-arterial pharmacotherapy only, not all patients received Endovascular Thrombectomy, or did not report data on both Endovascular Thrombectomy with and without Intravenous alteplase groups of patients. All discordant articles were adjudicated by a third reviewer.

Data extraction

The following data were collected: the first author, year of publication, study design, sample size, countries involved in the study, the use of propensity score matching method in observational study, patient characteristics like age and gender, previous disease (hypertension, diabetes and so on), National Institute of Health Stroke Scale (NIHSS) score, Alberta Stroke Program Early CT (ASPECT) score, onset-to-groin timing (OGT). The primary outcome was functional independence at 90 days (modified Rankin Scale score 0–2). The secondary outcomes were (1) successful recanalization (modified Thrombolysis in Cerebral Ischemia score 2b-3), (2) 90-day mortality, (3) symptomatic intracranial hemorrhage (sICH), (4) large or malignant middle cerebral artery infarction, (5) any procedural complications, including vessel dissection, contrast extravasation, embolization into a new territory, femoral access complications, transient vasospasms, (6) vasospasm, and (7) emboli into an uninvolved territory.

Data analysis and Statistical methods

Pooled ORs were further stratified according to prospective, retrospective, or randomized controlled trials in study designs. Subgroup analysis was conducted in studies predefined onset-to-groin timing which difference between 2 groups no more than 30 min was considered as similar. For each of studies, unadjusted and adjusted for potential confounders, the individual study effects were estimated using the fixed-effects model (Mantel-Haenszel method). Heterogeneity among studies was assessed using χ^2 and I^2 statistics. P value < 0.05 and $I^2 > 50\%$ indicate significant heterogeneity. In this case, a random-effect model was used; otherwise, a fixed effect model was performed.

Supplemental Table 1 a. Characteristics of included studies

Author(year)	Study design	Country	Propensity score matching method	Sample size (I:C)	Age (I:C) (median or mean), year	Male (I:C)	NIHSS score (I:C) (median or mean)	ASPECT score (I:C) (median or mean)	OGT (I:C) (median or mean), min	NOS score
Abilleira ³⁴ (2017)	RO	Spain	Y	599:567	68.1:68.6	309:306	17:17	NR	300:246	9
Al-Khaled ³⁵ (2018)	RO	Germany	N	92:144	68.7:69	46:62	13:13	8:8	NR	7
Alonso ³⁶ (2016)	PO	Spain	N	21:53	74:64	9:24	19:17	9:9	210:275	7
Balodis ³⁷ (2018)	PO	Latvia	N	62:84	72:72	28:38	16.5:15	NR	280:260	8
Behme ³⁸ (2016)	RO	Germany	N	27:66	74:74	9:34	17:16	NR	192:194	7
Bellwald ²⁵ (2017)	PO	Switzerland, Germany	Y	111:249	75:73	61:127	15:16	NR	194:256	9
Bourcier ³⁹ (2017)	RO	France	Y	56:85	73:68	23:55	18:18	7:7	200:240	9
Broeg-Morvay ⁴⁰ (2016)	RO	Switzerland	Y	40:156	77:73	25:82	17:15	NR	229:262	8
Casetta ²² (2019)	RO	Italy	Y	513:635	68.8:67.6	251:313	18:18	NR	210:230	7
Chalos ⁴¹ (2019)	PO	Netherlands	Y	324:1161	72:70	171:621	17:16	9:9	215:206	8
Choi ⁴² (2018)	RO	Korea	N	38:43	72.6:68.9	17:29	15:13	NR	222:205	7
Coutinho ²³ (2017)	RO	Canada	N	131:160	69:67	58:63	17:17	9:8	262:254	8
Dávalos ⁴³ (2012)	RO	European countries	N	67:74	66.4:66.2	34:45	18:17	7:7	330:290	7
Di Maria ²⁰ (2018)	PO	France	Y	531:976	67.6:67.2	272:530	16:17	7:7	244:235	9
Du ⁴⁴ (2020)	RO	China	N	57:54	66.9:65.2	32:28	18:18	9:9	198:218	8
Ferrigno ⁴⁵ (2018)	PO	France	Y	137:348	67.1:66.3	61:160	NR	8:8	251:259	8
Gariel ²¹ (2018)	post hoc RCT	France	NR	131:250	72.2:68.7	65:142	18:17	7:7	230:225	NR
Geng ⁴⁶ (2021)	PO	China	Y	5605:2069	67:68	3362:1242	16:16	NR	323:235	9
Gong ⁴⁷ (2019)	RO	China	Y	31:42	71:69	15:27	15:13	NR	216:185	8
Goyal M ² (2015)	post hoc RCT	America	NR	45:119	NR	NR	NR	NR	NR	NR
Goyal N ⁴⁸ (2019)	RO	America	N	132:287	64.3:63.7	76:143	16:16	9:10	360:223	7
Guedin ⁴⁹ (2014)	RO	France	N	40:28	64.6:69.2	15:11	15:18	NR	204:240	7
Guimaraes ⁵⁰ (2018)	RO	Portugal	N	82:152	71.9:70.9	39:70	16:16	8:8	268:245	7
Hassan ⁵¹ (2020)	RO	America	N	80:109	73.5:68.2	44:64	17.7:18.3	NR	172:181	8
Heinrichs ⁵² (2018)	PO	Germany	N	70:118	70.6:72.3	29:59	18:17	8:9	203:153.5	7

Jovin ³ (2015)	post hoc RCT	Spain	NR	33:70	NR	NR	NR	NR	NR	NR
Kass-Hout ⁵³ (2014)	RO	America	N	62:42	69.3:67.6	29:20	16:14.8	NR	122:228	7
Leker ⁵⁴ (2018)	PO	Isreal	N	111:159	67.4:68.1	58:91	16:16	NR	276:258	7
Machado ⁵⁵ (2020)	RO	Portugal	N	177:347	75:76	89:158	16:17	NR	394:250	7
Maier ⁵⁶ (2016)	PO	Germany	N	28:81	76:75	12:40	12.5:17	8:8	173.5:153	8
Maingard ⁵⁷ (2018)	RO	Australia	N	145:210	68:66	81:116	17:17	9:9	342:257	7
Merlino ⁵⁸ (2017)	PO	Italy	N	33:33	70.8:69.6	14:18	20:17.5	NR	217.8:218	7
Minnerup ⁵⁹ (2016)	PO	European countries	N	504:603	68.7:68.3	242:304	15:15	NR	294:233	8
Mulder ⁶⁰ (2016)	post hoc RCT	Netherlands	NA	30:203	NR	NR	NR	NR	NR	NR
Park ⁶¹ (2017)	RO	Korea	N	181:458	69:68	103:260	15:15	NR	296:215	7
Pfefferkorn ⁶² (2012)	RO	Germany	N	23:26	64.6:62.1	9:16	19.6:19	NR	360:360	7
Pienimaki ⁶³ (2020)	RO	Finland	N	48:58	72:69	30:37	14:16.5	9:9.5	NR	7
Rai ⁶⁴ (2017)	RO	America	N	52:38	69:63	20:20	16:18	7.5:8	NR	7
Reiff ⁶⁵ (2020)	RO	Germany	N	124:44	77.5:71	NR	16:16	8:8	348.5:310	7
Rossi ⁶⁶ (2020)	PO	European countries	N	295:255	NR	NR	16:17	NR	NR	8
Sallustio ⁶⁷ (2018)	RO	Italy	N	132:193	70.3:71.8	58:82	19:19	8:8	222.5:225	7
Smith ⁶⁸ (2006)	PO	America	N	81:30	66.5:65.4	35:13	18.8:19.6	NR	NR	8
Suzuki ¹⁹ (2021)	RCT	Japan	NR	101:103	74:76	56:72	19:17	7:8	149:158	NR
Tong ⁶⁹ (2021)	PO	China	Y	394:394	65:65	255:247	17:16	9:10	243:232	9
Wang ⁷⁰ (2017)	RO	China	Y	138:138	67:67	76:78	16:17	9:9	190.5:137	9
Weber ⁷¹ (2016)	RO	Germany	N	145:105	69.3:70.2	78:52	15:15.5	NR	210:233	7
Wee ⁷² (2017)	RO	Australia	N	29:21	71:73	16:8	15:15	NR	250:165	7
Yang ⁹ (2020)	RCT	China	NR	327:329	69:69	189:181	17:17	9:9	198:213	NR
Zha ¹⁰ (2020)	PO	China	Y	166:79	70:67	92:46	15:14	NR	NR	9
Zi ¹¹ (2021)	RCT	China	NR	116:118	70:70	66:66	16:16	8:8	200:210	NR

RO= retrospective observational study; PO= prospective observational study; RCT= randomized controlled trial; Y= yes; N= no; I= intervention group(direct thrombectomy) ;C= control group(bridging therapy); NIHSS= National Institute of Health Stroke Scale; ASPECT score= Alberta Stroke Program Early CT score; OGT= onset-to-groin timing; NOS= Newcastle-Ottawa quality assessment scale; NR= not reported

Supplemental Table 1 b. Previous disease of included patients

	Previous Disease						
Author(year)	Hypertension(I:C)	Diabetes(I:C)	Smoking(I:C)	Hyperlipidemia(I:C)	Atrial fibrillation(I:C)	Previous stroke(I:C)	Coronary heart disease(I:C)
Abilleira(2017)	382:352	96:127	110:108	233:243	244:130	87:44	87:72
Al-Khaled(2018)	71:101	18:31	16:22	36:51	50:66	32:36	22:30
Alonso(2016)	11:28	4:8	1:19	6:24	11:12	3:5	5:5
Balodis(2018)	NR	NR	NR	NR	NR	NR	NR
Behme(2016)	NR	NR	NR	NR	NR	NR	NR
Bellwald(2017)	85:171	17:42	21:47	46:98	47:85	NR	29:40
Bourcier(2017)	27:48	10:18	10:17	19:31	NR	NR	NR
Broeg-Morvay (2016)	30:100	5:28	8:33	30:83	19:61	NR	12:24
Casetta(2019)	325:418	87:83	97:151	148:166	166:177	34:17	NR
Chalos(2019)	180:562	56:197	NR	NR	141:186	NR	NR
Choi(2018)	25:29	12:7	12:18	22:29	25:22	8:5	NR
Coutinho(2017)	87:99	32:22	19:21	57:69	62:53	30:25	NR
Dávalos(2012)	NR	NR	NR	NR	NR	NR	NR
Di Maria(2018)	311:511	92:156	144:230	157:289	NR	124:117	NR
Du(2020)	33:28	12:7	15:10	NR	33:31	NR	17:10
Ferrigno(2018)	99:211	63:135	52:133	63:135	NR	43:52	NR
Gariel(2018)	90:139	27:49	14:48	46:85	NR	28:37	24:39
Geng(2021)	NR	NR	NR	NR	NR	NR	NR
Gong(2019)	19:31	7:7	NR	NR	27:20	NR	NR
Goyal M(2015)	NR	NR	NR	NR	NR	NR	NR
Goyal N(2019)	104:222	50:89	42:80	52:118	68:52	32:49	39:69
Guedin(2014)	17:11	2:2	9:6	10:10	NR	NR	NR
Guimaraes(2018)	54:104	24:30	13:17	49:79	NR	NR	NR
Hassan(2020)	75:87	45:38	4:13	NR	NR	NR	NR
Heinrichs(2018)	48:91	15:26	11:20	14:34	29:61	18:19	37:42
Jovin(2015)	NR	NR	NR	NR	NR	NR	NR
Kass-Hout(2014)	42:32	16:7	13:7	17:13	24:14	NR	26:11

Leker(2018)	75:111	33:50	19:30	50:78	47:47	8:17	NR
Machado(2020)	135:260	37:74	NR	90:147	61:139	22:31	NR
Maier(2016)	23:61	9:23	7:18	10:36	15:30	NR	9:13
Maingard(2018)	NR	NR	NR	NR	NR	NR	NR
Merlino(2017)	21:26	3:7	2:4	8:6	19:16	3:3	NR
Minnerup(2016)	382:461	93:118	84:88	186:207	231:225	104:77	126:123
Mulder(2016)	NR	NR	NR	NR	NR	NR	NR
Park(2017)	116:302	50:118	NR	46:121	92:246	46:85	NR
Pfefferkorn(2012)	NR	NR	NR	NR	NR	NR	NR
Pienimaki(2020)	31:29	11:13	NR	NR	19:37	NR	7:12
Rai(2017)	38:21	15:7	12:5	27:17	24:10	NR	NR
Reiff(2020)	94:25	22:11	15:8	43:8	70:14	NR	37:7
Rossi(2020)	NR	NR	NR	NR	NR	NR	NR
Sallustio(2018)	89:145	28:22	24:26	NR	68:84	NR	NR
Smith(2006)	NR	NR	NR	NR	NR	NR	NR
Suzuki(2021)	61:61	16:17	42:54	30:37	57:64	12:14	NR
Tong(2021)	214:214	67:63	132:127	26:31	124:125	76:63	56:60
Wang(2017)	NR	NR	NR	NR	NR	15:16	NR
Weber(2016)	104:82	28:16	25:15	31:17	56:26	NR	NR
Wee(2017)	21:13	10:4	2:4	15:8	17:9	3:5	9:4
Yang(2020)	193:201	59:65	NR	NR	152:149	43:47	NR
Zha(2020)	97:43	30:7	31:23	7:2	NR	42:10	30:15
Zi(2021)	69:74	25:20	28:29	18:22	62:62	14:19	30:19

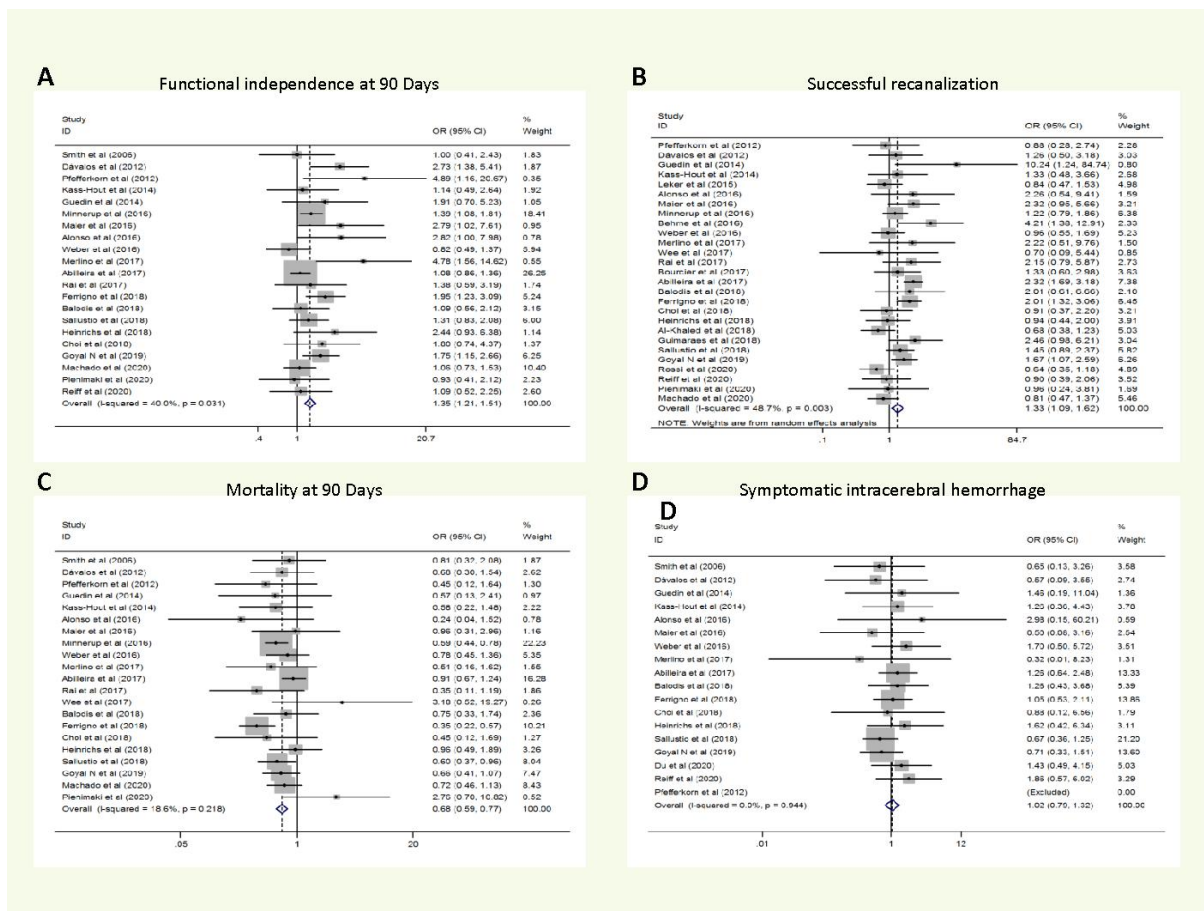
I= intervention group(direct thrombectomy) ;C= control group(bridging therapy); NR= not reported

Studies with intention-to- treat	Unique ID	Study ID	Experimental	Comparator	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall		
	Yang	NCT03469206	dMT	BT								Low risk
	Zi	ChiCTR-IOR-17013568	dMT	BT								Some concerns
	Suzuki	UMIN000021488	dMT	BT								High risk
	Gariel	NCT02523261	First-Line Contact Aspiration	First-Line Stent Retriever								
	Goyal M	NCT01778335	standard care plus endovascular treatment with the use of available thrombectomy devices	standard care								
	Jovin	NCT01692379	medical therapy and endovascular therapy	medical therapy alone								
	Mulder	ISRCTN10888758	Intraarterial treatment plus usual care	usual care alone								

Supplemental Table 2. Quality assessment of included RCTs by Cochrane Collaboration's tool

Supplemental Table 3. Publication Bias

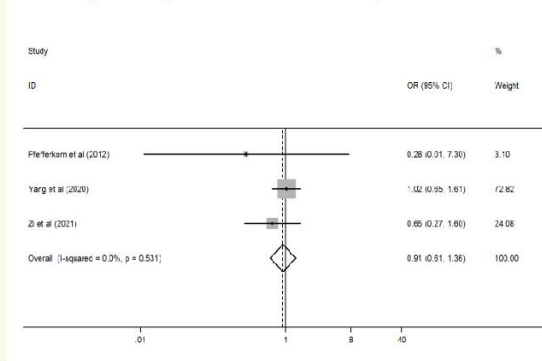
Outcome	P value, Begg's test	P value, Egger's test	Meta-trim
Functional independence at 90 Days			
Unadjusted	0.01	0.02	1.26(1.13-1.41)
PS matched	0.15	0.03	1.08(0.95-1.22)
RCTs	0.76	0.96	NR
Successful recanalization			
Unadjusted	0.28	0.75	NR
PS matched	1.00	0.65	NR
RCTs	0.13	0.19	NR
Mortality at 90 Days			
Unadjusted	0.83	0.30	NR
PS matched	0.09	0.03	0.65(0.55-0.75)
RCTs	0.45	0.40	NR
Symptomatic intracerebral hemorrhage			
Unadjusted	0.90	0.63	NR
PS matched	0.77	0.28	NR
RCTs	0.22	0.01	1.59 (1.11-2.29)
Large or malignant middle cerebral artery infarction			
Unadjusted	1.00	0.25	NR
Any procedural complications			
Unadjusted	0.30	0.15	NR
vasospasm			
PS matched	1.00	0.24	NR
emboli into an uninvolved territory			
Unadjusted	0.90	0.79	NR
PS matched	0.31	0.22	NR



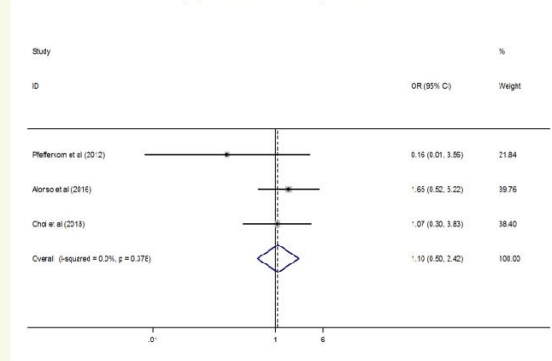
Supplemental figure 1. Pooled results from unadjusted analysis of comparisons between bridging thrombolysis(BT) and direct mechanical thrombectomy (d-MT) in terms of 4 outcome measures.

(A)Functional independence at 90 Days; **(B)** Successful recanalization; **(C)** mortality at 90 days; **(D)** symptomatic intracranial hemorrhage. BT indicates bridging thrombolysis; d-MT, direct mechanical thrombectomy.

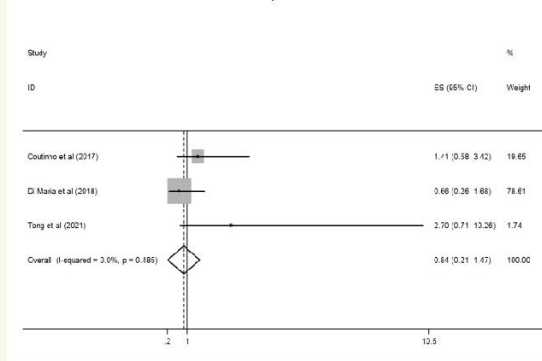
A Large or malignant middle cerebral artery infarction



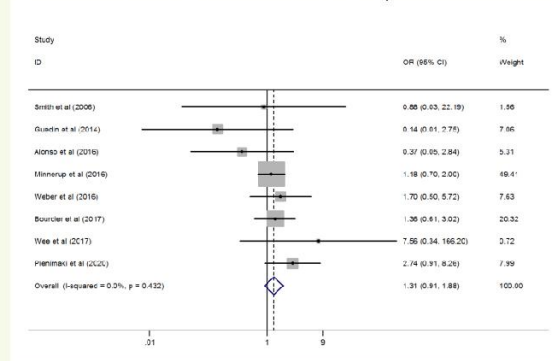
B Any procedural complications



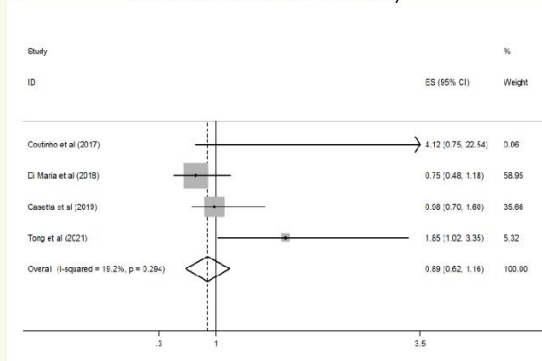
C Vasospasm



D Emboli into an uninvolved territory

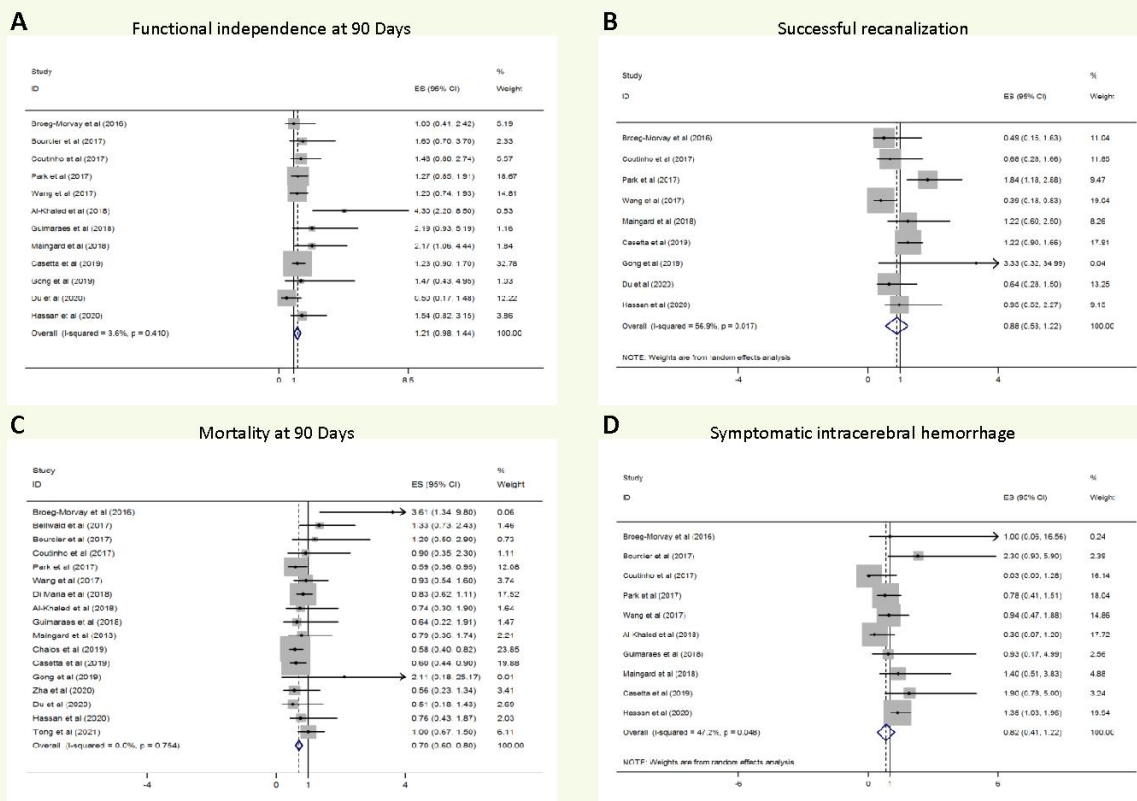


E Emboli into an uninvolved territory

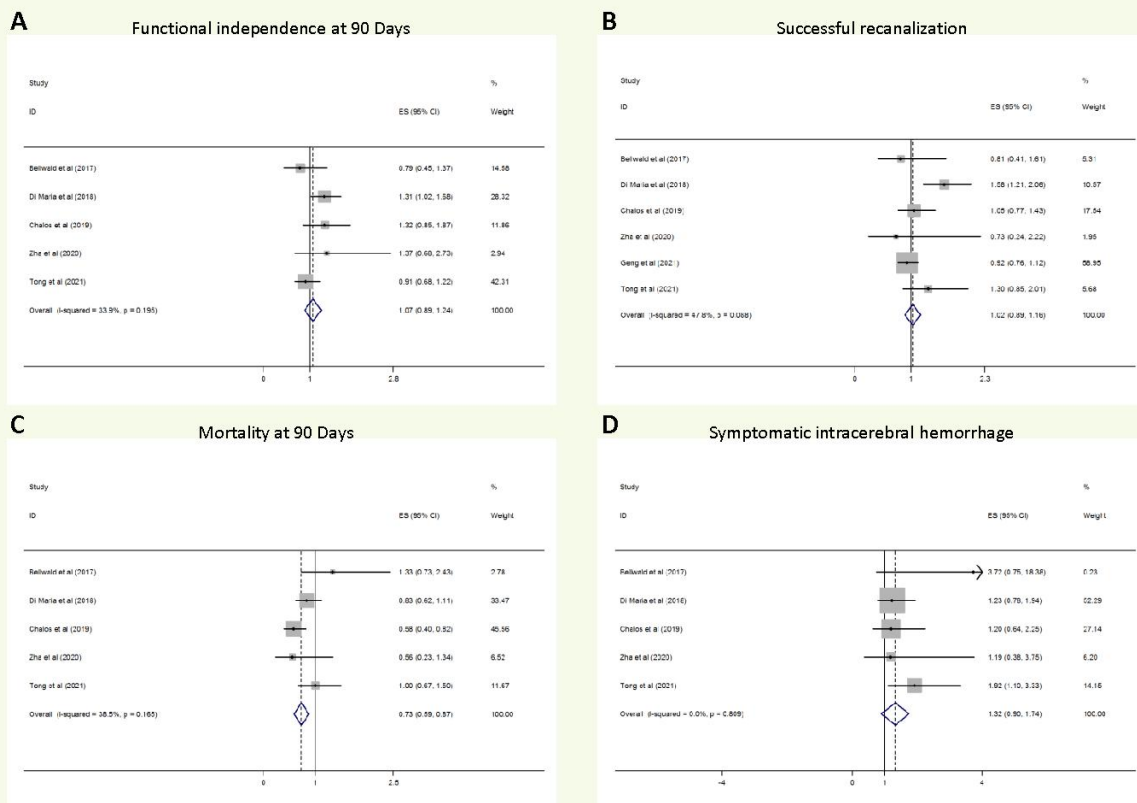


Supplemental figure 2. Pooled results of comparisons between bridging thrombolysis(BT) and direct mechanical thrombectomy (d-MT) in terms of other clinical outcomes.

(A)Unadjusted analysis of large or malignant middle cerebral artery infarction; **(B)** Unadjusted analysis of any procedural complications; **(C)** Adjusted analysis of vasospasm; **(D)** Unadjusted analysis of emboli into an uninvolved territory; **(E)** Adjusted analysis of emboli into an uninvolved territory.

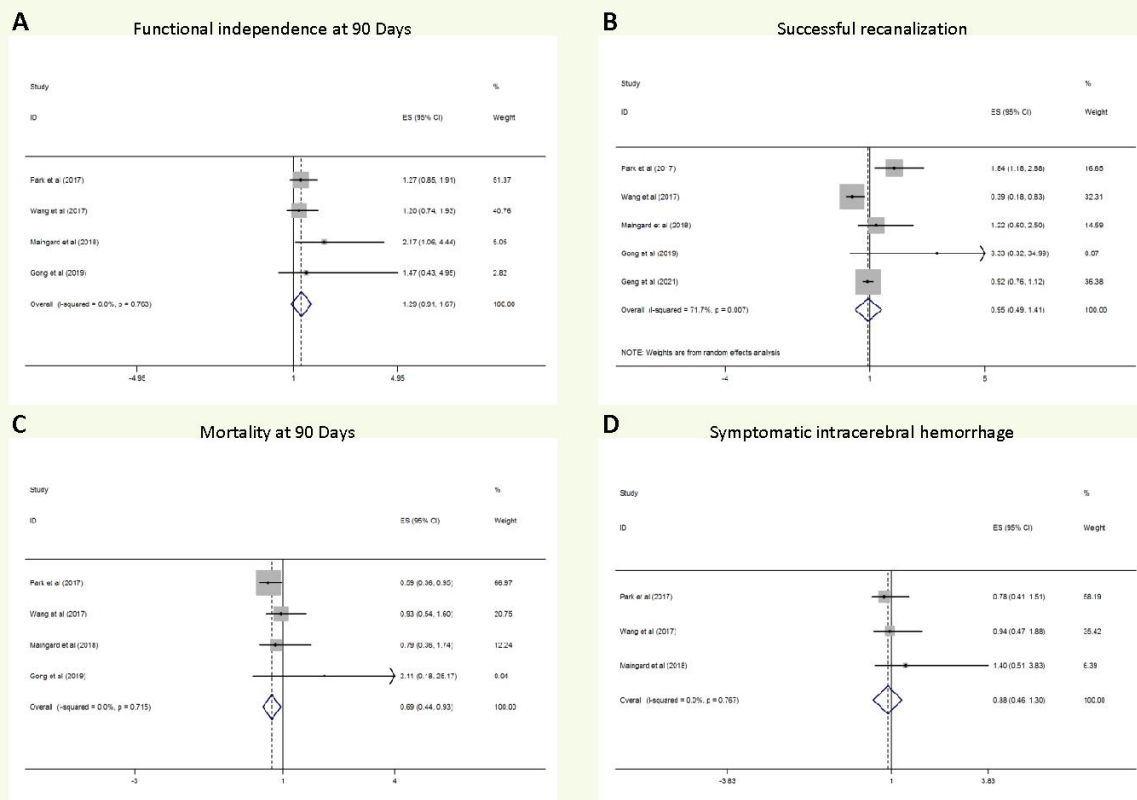


Supplemental figure 3. Pooled results from subgroup analysis of prospective study(PO) subgroup comparing bridging thrombolysis(BT) with direct mechanical thrombectomy (d-MT) in terms of 4 outcome measures. (A)Functional independence at 90 Days; (B) Successful recanalization; (C) mortality at 90 days; (D) symptomatic intracranial hemorrhage. PO indicates prospective study.



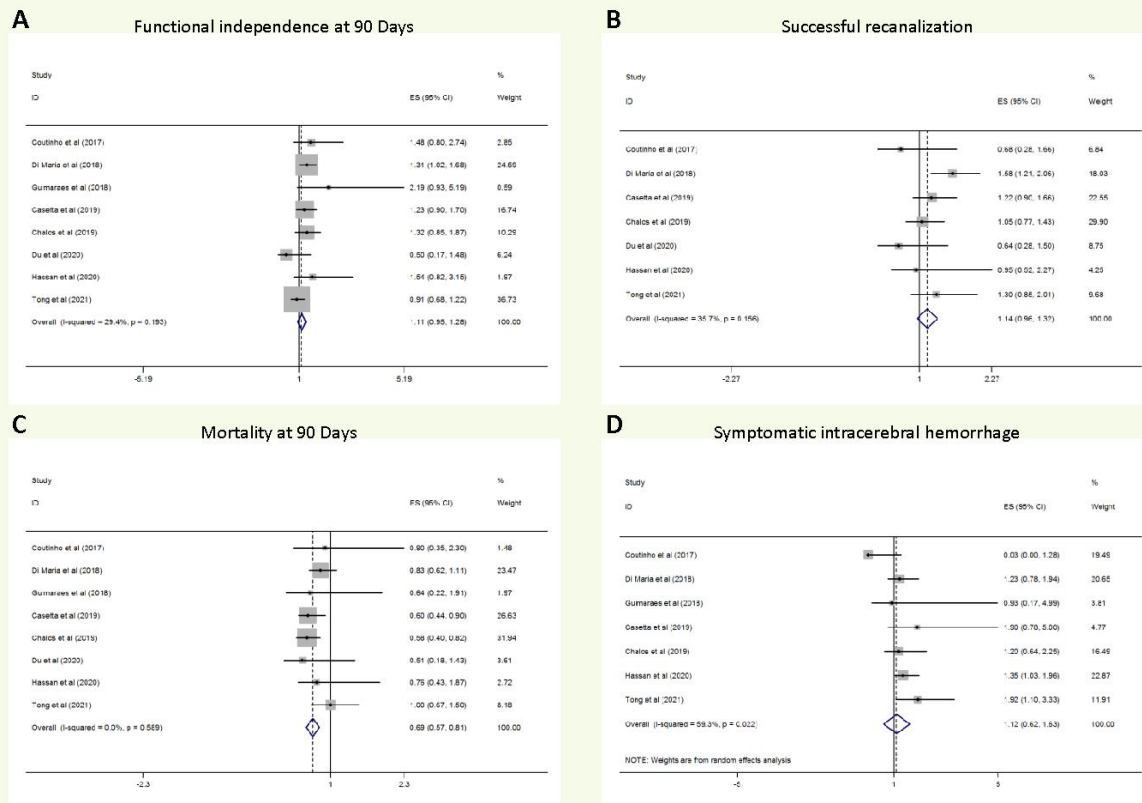
Supplemental figure 4. Pooled results from subgroup analysis of retrospective study (RO) subgroup comparing bridging thrombolysis (BT) with direct mechanical thrombectomy (d-MT) in terms of 4 outcome measures.

(A) Functional independence at 90 Days; **(B)** Successful recanalization; **(C)** mortality at 90 days; **(D)** symptomatic intracranial hemorrhage. RO indicates retrospective study.

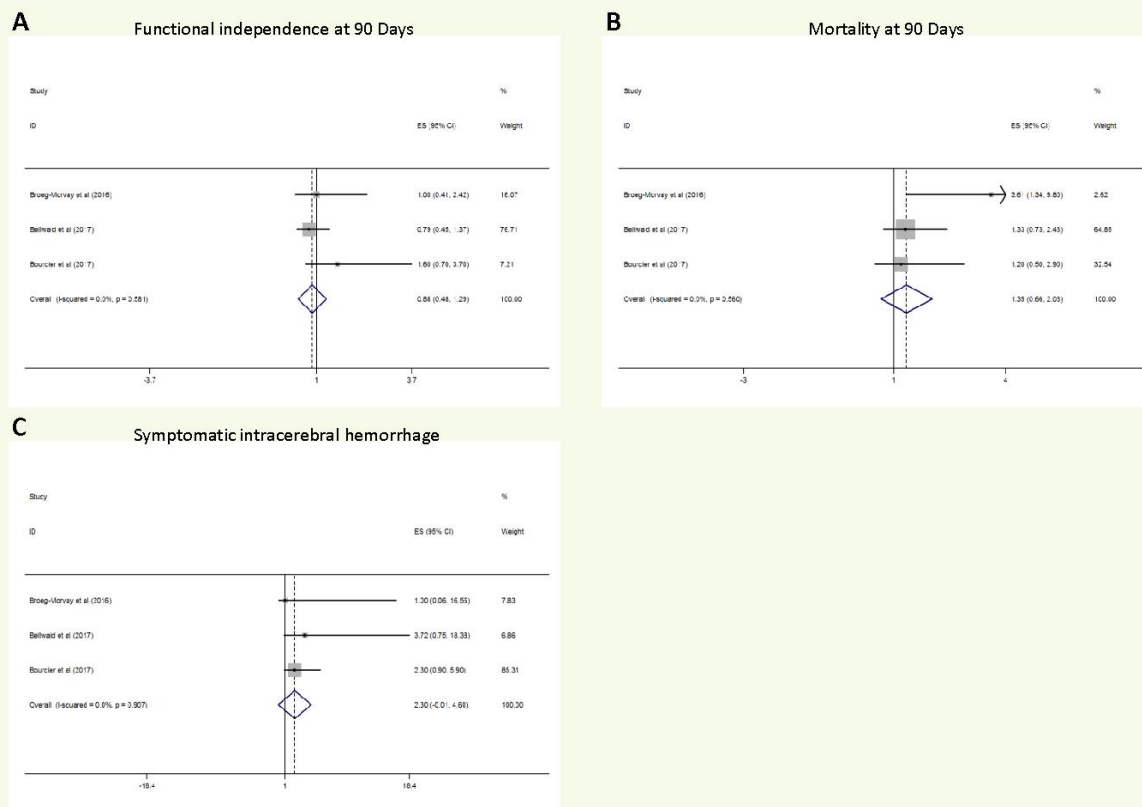


Supplemental figure 5. Pooled results from subgroup analysis of I > C subgroup comparing bridging thrombolysis(BT) with direct mechanical thrombectomy (d-MT) in terms of 4 outcome measures.

(A)Functional independence at 90 Days; **(B)** Successful recanalization; **(C)** mortality at 90 days; **(D)** symptomatic intracranial hemorrhage. I > C indicates the onset to groin time of intervention group is more than that of control group.



Supplemental figure 6. Pooled results from subgroup analysis I = C subgroup comparing bridging thrombolysis(BT) with direct mechanical thrombectomy (d-MT) in terms of 4 outcome measures. (A)Functional independence at 90 Days; (B) Successful recanalization; (C) mortality at 90 days; (D) symptomatic intracranial hemorrhage.



Supplemental figure 7. Pooled results from subgroup analysis I < C subgroup comparing bridging thrombolysis(BT) with direct mechanical thrombectomy (d-MT) in terms of 4 outcome measures.

(A)Functional independence at 90 Days; **(B)** mortality at 90 days; **(C)** symptomatic intracranial hemorrhage.