Appendix 1: Summary of search strategy

Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Search Strategy:

1 exp Stroke/ (151427)

2 (Cerebrovascular event or Stroke or apoplex or CVA or cerebrovascular accident or brain vascular accident or brain isch* or brain infarc* or cerebral infarc$ or cerebral isch$ or cerebral vessel occlusion or large vessel occlusion or intracranial isch* or intracranial infarction or intracranial vessel occlusion or brain vessel occlusion).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (390015)

3 1 or 2 (393519)

4 exp Thrombectomy/ (9289)

5 (Thrombectomy or thrombectomie$ or mechanical or endovascular or embolectomy or intracranial intervention or Stent-retriever or stentretriever or preset or solitaire or trevo or catch).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (532741)

6 4 or 5 (532741)

7 3 and 6 (22234)

8 exp Tissue Plasminogen Activator/ (19562)

9 ((plasminogen adj2 (activator or recombinant)) or (bridging* or thrombolysis or rtPA or tpA or rt PA or alteplase or Tenecteplase or reteplase or Metalyse or tnkase or tenecteplase or ecokinase or rapilysin or retavase or actilyse or activase or alteplase or lysatec rt pa or lysatec rt-pa or lysatec rtpa or atlepase or cathflo activase or bridging-therapy)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary

concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (130860)

10 8 or 9 (130860)

11 7 and 10 (5276)

12 (direct or combined or with or alone or combination or preceding or preinterventional or prior or before or previous or concomitant or stand-alone or together or following or followed or eligible or contraindication or ineligible or preproced$ or preinterv$ or prethrom$ or pre-proced$ or pre-inter$ or pre-throm$).mp. (20428682)

13 11 and 12 (4887)

14 randomized controlled trial.pt. (550704)

15 controlled clinical trial.pt. (94547)

16 randomized.ab. (541037)

17 placebo.ab. (223248)

18 drug therapy.fs. (2404278)

19 randomly.ab. (370115)

20 trial.ab. (576336)

21 groups.ab. (2273783)

22 or/14-21 (5179308)

23 exp animals/ not humans.sh. (4917301)

24 22 not 23 (4505655)

25 11 and 24 (2245)

26 random:.tw. or placebo:.mp. or double-blind:.tw. (1378661)

27 ((treatment or control) adj3 group*).ab. (665358)

28 (allocat* adj5 group*).ab. (29061)

29 ((clinical or control*) adj3 trial).ti,ab,kw. (324097)

30 or/26-29 (1918347)

31 30 not 23 (1654690)

32 11 and 31 (1138)

33 25 or 32 (2337)

34 limit 33 to ed=20210419-20211122 (232)

Database: Embase <1974 to 2021 November 19>

Search Strategy:

1 exp cerebrovascular accident/ (247559)

2 (Cerebrovascular event or Stroke or apoplex or CVA or cerebrovascular accident or brain vascular accident or brain isch* or brain infarc* or cerebral infarc$ or cerebral isch$ or cerebral vessel occlusion or large vessel occlusion or intracranial isch* or intracranial infarction or intracranial vessel occlusion or brain vessel occlusion).mp. (655054)

3 1 or 2 (655054)

4 exp thrombectomy/ (31288)

5 (Thrombectomy or thrombectomie$ or mechanical or endovascular or embolectomy or intracranial intervention or Stent-retriever or stentretriever or preset or solitaire or trevo or catch).mp. (641195)

6 4 or 5 (643465)

7 3 and 6 (43522)

8 tissue plasminogen activator/ (30971)

9 (bridging$ or thrombolysis or rtPA or tpA or rt PA or alteplase or bridging-therapy or plasminogen activator or recombinant-plasminogen or plasminogen-activator).mp. (183948)

10 8 or 9 (183948)

11 7 and 10 (11978)

12 (direct or combined or with or alone or combination or preceding or preinterventional or prior or before or previous or concomitant or stand-alone or together or following or followed or eligible or contraindication or ineligible or preproced$ or preinterv$ or prethrom$ or pre-proced$ or pre-inter$ or pre-throm$).mp. (25262604)

13 11 and 12 (11097)

14 limit 13 to yr="2017 -Current" (6400)

15 randomized controlled trial/ (683426)

16 Controlled clinical study/ (464339)

17 random$.ti,ab. (1723999)

18 randomization/ (92125)

19 intermethod comparison/ (277105)

20 placebo.ti,ab. (332140)

21 (compare or compared or comparison).ti. (550422)

22 ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab. (2397242)

23 (open adj label).ti,ab. (92320)

24 ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab. (250276)

25 double blind procedure/ (189607)

26 parallel group$1.ti,ab. (28397)

27 (crossover or cross over).ti,ab. (113472)

28 ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab. (366751)

29 (assigned or allocated).ti,ab. (432042)

30 (controlled adj7 (study or design or trial)).ti,ab. (392334)

31 (volunteer or volunteers).ti,ab. (262212)

32 human experiment/ (558858)

33 trial.ti. (343162)

34 or/15-33 (5572251)

35 (random$ adj sampl$ adj7 ("cross section$" or questionnaire$1 or survey$ or database$1)).ti,ab. not (comparative study/ or controlled study/ or randomi?ed controlled.ti,ab. or randomly assigned.ti,ab.) (8759)

36 Cross-sectional study/ not (randomized controlled trial/ or controlled clinical study/ or controlled study/ or randomi?ed controlled.ti,ab. or control group$1.ti,ab.) (288322)

37 (((case adj control$) and random$) not randomi?ed controlled).ti,ab. (19134)

38 (Systematic review not (trial or study)).ti. (191316)

39 (nonrandom$ not random$).ti,ab. (17382)

40 "Random field$".ti,ab. (2603)

41 (random cluster adj3 sampl$).ti,ab. (1392)

42 (review.ab. and review.pt.) not trial.ti. (940188)

43 "we searched".ab. and (review.ti. or review.pt.) (39021)

44 "update review".ab. (118)

45 (databases adj4 searched).ab. (46422)

46 (rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/ (1128444)

47 Animal experiment/ not (human experiment/ or human/) (2368551)

48 or/35-47 (3826805)

49 34 not 48 (4942605)

50 11 and 49 (3566)

51 random:.tw. or placebo:.mp. or double-blind:.tw. (1988253)

52 ((treatment or control) adj3 group*).ab. (963695)

53 (allocat* adj5 group*).ab. (37958)

54 ((clinical or control*) adj3 trial).ti,ab,kw. (458102)

55 or/51-54 (2778117)

56 11 and 55 (2486)

57 56 not 48 (2136)

58 50 or 57 (3886)

59 limit 58 to dc=20210416-20211122 (466)

Cochrane Library (Wiley)

Date Run: 22/11/2021

ID Search Hits

#1 MeSH descriptor: [Stroke] explode all trees10731

#2 "Cerebrovascular event" or Stroke or apoplex or CVA or "cerebrovascular accident" or "brain vascular accident" or "brain isch*" or "brain infarc*" or "cerebral infarc$" or "cerebral isch$" or "cerebral vessel occlusion" or "large vessel occlusion" or "intracranial isch*" or "intracranial infarction" or "intracranial vessel occlusion" or "brain vessel occlusion" 77142

#3 #1 or #2 77428

#4 MeSH descriptor: [Thrombectomy] explode all trees 327

#5 Thrombectomy or thrombectomie$ or mechanical or endovascular or embolectomy or "intracranial intervention" or Stent-retriever or stentretriever or preset or solitaire or trevo or catch 34519

#6 #4 or #5 34519

#7 #3 and #6 4017

#8 MeSH descriptor: [Tissue Plasminogen Activator] explode all trees 1729

#9 bridging$ or thrombolysis or rtPA or tpA or rt PA or alteplase or bridging-therapy or "plasminogen activator" or recombinant-plasminogen or plasminogen-activator 12868

#10 plasminogen near/2 (activator or recombinant) 4833

#11 bridging* or thrombolysis or rtPA or tpA or rt PA or alteplase or Tenecteplase or reteplase or Metalyse or tnkase or tenecteplase or ecokinase or rapilysin or retavase or actilyse or activase or alteplase or lysatec rt pa or lysatec rt-pa or lysatec rtpa or atlepase or cathflo activase or bridging-therapy 10919

#12 #9 or #10 or #11 13058

#13 #7 and #12 in Trials 1029

#14 #13 with Cochrane Library publication date Between Apr 2021 and Nov 2021 97

Web of Science (Clarivate)

10 #8 and #9 194

9 LD=(2021-04-16/2021-11-22) 2,345,234

8 #7 AND #6 2,563

7 TS= clinical trial* OR TS=controlled trial* OR TS=random* OR TS=placebo* OR TS=(single blind*) OR TS=(double blind*) 2,812,250

6 #5 AND #2 AND #1 6,724

5 #4 OR #3 224,286

4 TS=(bridging* or thrombolysis or rtPA or tpA or rt PA or alteplase or Tenecteplase or reteplase or Metalyse or tnkase or tenecteplase or ecokinase or rapilysin or retavase or actilyse or activase or alteplase or lysatec rt pa or lysatec rt-pa or lysatec rtpa or atlepase or cathflo activase or bridging-therapy) 178,080

3 TS=(plasminogen NEAR/2 (activator or recombinant)) 63,775

2 TS=(Thrombectomy OR thrombectomie* OR mechanical OR endovascular OR embolectomy OR intracranial intervention OR Stent-retriever OR stentretriever OR preset OR solitaire OR trevo OR catch) 1,549,779
1 TS=(Cerebrovascular event OR Stroke OR apoplex OR CVA OR cerebrovascular accident OR brain vascular accident OR brain isch* OR brain infarc* OR cerebral infarc* OR cerebral isch* OR cerebral vessel occlusion OR large vessel occlusion OR intracranial isch* OR intracranial infarction OR intracranial vessel occlusion OR brain vessel occlusion) 504,353

PubMed

(((((publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb] OR pubstatusaheadofprint)) AND (stroke or cerebrovascular accident)) AND (Thrombectomy)) AND ((bridging* or thrombolysis or rtPA or tpA or rt PA or alteplase or Tenecteplase or reteplase or Metalyse or tnkase or tenecteplase or ecokinase or rapilysin or retavase or actilyse or activase or alteplase or lysatec rt pa or lysatec rt-pa or lysatec rtpa or atlepase or cathflo activase or bridging-therapy) OR (Tissue Plasminogen Activator))) AND (((random* or placebo or double-blind) OR (randomized clinical trial)) OR (controlled trial))

Appendix 2: Characteristics of included studies

Study		DIRECT-MT[1]	SKIP[2]	DEVT[3]	MR CLEAN-NO IV[4]	SWIFT DIRECT[5]	DIRECT SAFE[6]
Study Period		February 23,2018 - July 2,2019	January 1,2017 - July 31,2019	May 20,2018 - May 2,2020	January 2018 - October 2020	NA	April, 2018 - June, 2021
Country		China	Japan	China	Europe	North America and Europe	Australia, New Zealand, China and Vietnam
N	**EVT**	327	101	116	273	201	146
	EVT with alteplase	329	103	118	266	207	147
Age, median (IQR), y	**EVT**	69(61-76)	74(67-80)	70(60-77)	72(62-80)	73(64-81)	70（61-78）
	EVT with alteplase	69(61-76)	76(67-80)	70(60-78)	69(61-77)	72(65-81)	69（60-79）
Sex (Male%)	**EVT**	189 (57.8)	56(55)	66(56.9)	161(59)	96(48)	78（53.4）
	EVT with alteplase	181 (55.0)	72(70)	66(55.9)	144(54.1)	103(50)	88（59.9）
Alteplase Dose (mg/kg)		0.9	0.6	0.9	0.9	0.9	0.9
Inclusion criteria	**Occluded site**	ICA, MCA-M1 or M2 occlusion on CTA	ICA or MCA-M1 occlusion on CTA or MRA	ICA or MCA-M1 occlusion on CTA or MRA	ICA, MCA-M1 or proximal M2 occlusion on CTA or MRA	ICA or MCA-M1 occlusion or both on CTA or MRA	CTA or MRA of the ICA, M1, M2 or basilar artery
	mRS score	mRS ≤2	mRS ≤2	mRS ＜2	mRS ≤2	mRS ≤2	mRS ＜4
	NIHSS score	≥2	≥6	No limit	≥2	≥5 and ＜30	No limit

		ASPECTS	No limit	DWI ≥ 5 or CT ≥ 6	No limit	No limit	≥4	No limit
Grading sICH			Heidelberg	SITS-MOST	Heidelberg	Heidelberg	Any parenchymal hematoma type 1, parenchymal hematoma type 2, remote intracranial hemorrhage, subarachnoid hemorrhage, or intraventricular hemorrhage associated with a ≥4 point worsening on the NIHSS at 24 hours ± 6 hours post randomization	ICH on CT scan, 24h window post stroke, NIHSS increase of 4 or more points
Onset to randomization time, median (IQR), min		**EVT**	167(125-206)	NA	170 (129-204)	94(60-137)	NA	NA
		EVT with alteplase	177(126-215)	NA	168 (144-216)	93(71-152)	NA	NA
Randomization to groin puncture time, median (IQR), min		**EVT**	31(20-45)	20 (20)*	NA	NA	NA	NA
		EVT with alteplase	36(22-50.5)	22 (16)*	NA	NA	NA	NA
NIHSS score, median (IQR), min		**EVT**	17(12-21)	19(13-23)	16(12-20)	16(10-20)	17(13-20)	15（11-20）
		EVT with alteplase	17(14-22)	17(12-22)	16(13-20)	16(10-20)	17(12-20)	15（10-20）
ASPECTS, median (IQR), min		**EVT**	9(7-10)	7(6-9)	8(7-9)	9(8-10)	8(7-9)	10（9-10）
		EVT with alteplase	9(7-10)	8(6-9)	8(7-9)	9(8-10)	8(7-9)	10（9-10）
Comorbidities	**Hypertension**	**EVT**	193/327	61/101	69/116	121/273	NA	NA
		EVT with alteplase	201/329	61/103	74/118	139/265	NA	NA

	Diabetes mellitus	**EVT**	59/327	16/101	25/116	40/273	NA	NA
		EVT with alteplase	65/329	17/103	20/118	50/266	NA	NA
	Dyslipidemia	**EVT**	NA	30/101	18/116	NA	NA	NA
		EVT with alteplase	NA	37/103	22/118	NA	NA	NA
	Atrial fibrillation	**EVT**	152/327	57/101	62/116	86/273	NA	NA
		EVT with alteplase	149/329	64/103	62/118	63/266	NA	NA
	Prior stroke	**EVT**	43/327	12/101	14/116	47/273	NA	NA
		EVT with alteplase	47/329	14/103	19/118	44/266	NA	NA
	Prior cardiovascular disease	**EVT**	NA	7/101	30/116	NA	NA	NA
		EVT with alteplase	NA	7/103	19/118	NA	NA	NA
	Smoking	**EVT**	NA	42/101	28/116	NA	NA	NA
		EVT with alteplase	NA	54/103	29/118	NA	NA	NA
Stroke mechanism	**Cardioembolic**	**EVT**	146/327	67/101	65/116	NA	NA	NA
		EVT with alteplase	144/329	72/103	69/118	NA	NA	NA
	Large artery atherosclerosis	**EVT**	NA	21/101	32/116	NA	NA	NA
		EVT with alteplase	NA	15/103	28/118	NA	NA	NA
	Intracranial atherosclerosis	**EVT**	26/327	NA	28/116	NA	NA	NA
		EVT with alteplase	19/329	NA	23/118	NA	NA	NA
	Unknown/other	**EVT**	155/327	13/101	19/116	NA	NA	NA
		EVT with alteplase	166/329	16/103	21/118	NA	NA	NA
Clot location	**ICA**	**EVT**	112/320	36/101	18/116	68/273	58/201	33/146
		EVT with alteplase	114/326	36/103	17/118	50/266	59/207	31/147
	M1	**EVT**	161/320	54/101	95/116	156/272	142/201	80/146
		EVT with alteplase	178/326	47/103	99/118	174/266	148/207	83/147
	M2	**EVT**	42/320	10/101	3/116	45/272	1/201	21/146
		EVT with alteplase	33/326	20/103	2/118	40/266	0/207	23/147
	Tandem occlusion	**EVT**	NA	9/101	NA	48/257	30/201	27/146
		EVT with alteplase	NA	13/103	NA	40/250	33/207	20/147

EVT = endovascular thrombectomy, ICA = internal carotid artery, MCA = middle cerebral artery, MRA = magnetic resonance angiography, CTA = computed tomographic angiography, mRS = modified Rankin Scale, NIHSS = National Institutes of Health Stroke Scale, ASPECTS = Alberta Stroke Program Early Computed Tomography Score, sICH = symptomatic intracranial hemorrhage, SITS-MOST = Safe Implementation of Thrombolysis in Stroke–Monitoring Study, NA = not available.
* mean (SD)

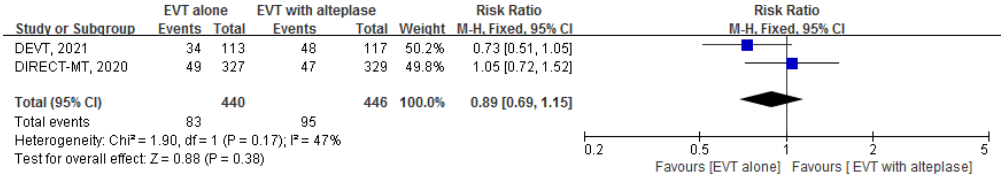
Appendix 3: Risk of bias assessment

Study	Sequence Generation	Allocation Sequence Concealment	Blinding					Missing Outcome Data	Free of selective outcome reporting
			Patients	Healthcare providers	Data collectors	Outcome assessors	data analysts		
DIRECT-MT[1]	Low	Low	High	High	High	Low	High	Low	Low
SKIP[2]	Low	Low	High	High	High	Low	High	Low	Low
DEVT[3]	Low	Low	High	High	High	Low	High	Low	Low
MR CLEAN-NO IV[4]	Low	Low	High	High	High	Low	High	Low	Low
SWIFT DIRECT[5]	Low	Low	High	High	High	Low	High	Low	Low
DIRECT SAFE[6]	Low	Low	High	High	High	Low	High	Low	Low

Appendix 4: Sensitivity analysis by excluding SKIP trial

Outcomes	Relative effects (95% CI)	
	Results from 6 RCTs	**Sensitivity analysis by excluding SKIP trial**
Minimal disability measured by modified Rankin Score 0-2	RR 0.97 (0.89-1.05)	RR 0.96 (0.88-1.04)
Mortality	RR 1.07 (0.88-1.29)	RR 1.07 (0.89-1.30)
Symptomatic intracranial hemorrhage	RR 0.75 (0.52-1.07)	RR 0.75 (0.51-1.09)

Appendix 5: Forest plots of procedure-related complications



Forest plot for endovascular thrombectomy (EVT) alone versus EVT with intravenous alteplase for procedure-related complications

Appendix 6: The definition of procedure-related complications and symptomatic hemorrhage

The definition of procedure-related complications

DIRECT-MT: Vessel dissection, contrast extravasation, embolization into a new territory and femoral access complications

DEVT: Clot migration, distal occlusion present at procedure end, contrast extravasation, arterial perforation and puncture access complications

The definition of symptomatic hemorrhage

Heidelberg[7]: Symptomatic intracerebral hemorrhage detected by brain imaging as a relevant change in neurological status; absence of another explanation for deterioration; an event leading to intubation, hemicraniectomy, or external ventricular draining placement; or other major medical or surgical intervention.

Safe Implementation of Thrombolysis in Stroke–Monitoring Study (SITS-MOST)[8]: Local or remote parenchymal hematoma type 2 on the imaging scan obtained 22 to 36 hours after treatment, plus neurological deterioration.

National Institute of Neurological Disorders and Stroke (NINDS)[9]: Symptomatic if hemorrhage had not been seen on a previous computed tomographic (CT) scan but either subsequent suspicion of hemorrhage or decline in neurological status existed.

References

1. Yang P, Zhang Y, Zhang L, et al. Endovascular Thrombectomy with or without Intravenous Alteplase in Acute Stroke. *The New England journal of medicine.* 2020;382(21):1981-1993.
2. Suzuki K, Matsumaru Y, Takeuchi M, et al. Effect of Mechanical Thrombectomy Without vs With Intravenous Thrombolysis on Functional Outcome Among Patients With Acute Ischemic Stroke: The SKIP Randomized Clinical Trial. *Jama.* 2021;325(3):244-253.
3. Zi W, Qiu Z, Li F, et al. Effect of Endovascular Treatment Alone vs Intravenous Alteplase Plus Endovascular Treatment on Functional Independence in Patients With Acute Ischemic Stroke: The DEVT Randomized Clinical Trial. *Jama.* 2021;325(3):234-243.
4. LeCouffe NE, Kappelhof M, Treurniet KM, et al. A Randomized Trial of Intravenous Alteplase before Endovascular Treatment for Stroke. *The New England journal of medicine.* 2021;385(20):1833-1844.
5. Fischer U. Solitaire™ With the Intention For Thrombectomy Plus Intravenous t-PA Versus DIRECT Solitaire™ Stent-retriever Thrombectomy in Acute Anterior Circulation Stroke. *European Stroke Conference.* 2021.
6. Mitchell P. DIRECT SAFE: A randomized controlled trial of DIRECT endovascular clot retrieval versus standard bridging thrombolysis with endovascular clot retrieval within 4.5 hours of stroke onset. *World Stroke Congress.* 2021.
7. von Kummer R, Broderick JP, Campbell BC, et al. The Heidelberg bleeding classification: classification of bleeding events after ischemic stroke and reperfusion therapy. Stroke 2015;46:2981-6.
8. Wahlgren N, Ahmed N, Eriksson N, et al. Multivariable analysis of outcome predictors and adjustment of main outcome results to baseline data profile in randomized controlled trials: Safe Implementation of Thrombolysis in Stroke-MOnitoring STudy (SITS-MOST). Stroke; a journal of cerebral circulation. 2008-Dec 2008;39(12):3316-22.
9. National Institute of Neurological D, Stroke rt PAS, Study G. Tissue plasminogen activator for acute ischemic stroke. The New England journal of medicine. 1995-12-14 1995;333(24):1581-7.