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Endovascular thrombectomy with or without intravenous alteplase for acute ischemic stroke due to large vessel occlusion: a systematic review and meta-analysis of randomized trials

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ABSTRACT

Background Among patients who had an ischaemic stroke presenting directly to a stroke centre where endovascular thrombectomy (EVT) is immediately available, there is uncertainty regarding the role of intravenous thrombolysis agents before or concurrently with EVT. To support a rapid guideline, we conducted a systematic review and meta-analysis to examine the impact of EVT alone versus EVT with intravenous alteplase in patients who had an acute ischaemic stroke due to large vessel occlusion.

Methods In November 2021, we searched MEDLINE, Embase, PubMed, Cochrane, Web of Science, clincialtrials.gov and the ISRCTN registry for randomised controlled trials (RCTs) comparing EVT alone versus EVT with alteplase for acute ischaemic stroke. We conducted meta-analyses using fixed effects models and assessed the certainty of evidence using the GRADE approach.

Results In total 6 RCTs including 2334 participants were eligible. Low certainty evidence suggests that, compared with EVT and alteplase, there is possibly a small decrease in the proportion of patients independent with EVT alone (risk ratio (RR) 0.97, 95% CI 0.89 to 1.05; risk difference (RD) −1.5%; 95% CI −5.4% to 2.5%), and possibly a small increase in mortality with EVT alone (RR 1.07, 95% CI 0.88 to 1.29; RD 1.2%, 95% CI −2.0% to 4.9%) . Moderate certainty evidence suggests that there is probably a small decrease in symptomatic intracranial haemorrhage (sICH) with EVT alone (RR 0.75, 95% CI 0.52 to 1.07; RD −1.0%; 95%CI −1.8% to 0.27%).

Conclusions Low certainty evidence suggests that there is possibly a small decrease in the proportion of patients that achieve functional independence and a small increase in mortality with EVT alone. Moderate certainty evidence suggests that there is probably a small decrease in sICH with EVT alone. The accompanying guideline provides contextualised guidance based on this body of evidence.

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WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ When possible, acute ischaemic stroke due to large vessel occlusion is managed with endovascular thrombectomy (EVT) and intravenous alteplase; however, whether combination therapy is superior to EVT alone is uncertain.

WHAT THIS STUDY ADDS

⇒ Low certainty evidence (rated down due to very serious imprecision) from six randomized trials suggests that treatment of acute stroke due to large vessel occlusion with EVT alone, versus EVT with alteplase, may slightly decrease the proportion of patients that achieve functional independence and slightly increase mortality. Moderate certainty evidence shows that EVT alone probably results in a small decrease in symptomatic intracranial haemorrhage.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE AND/OR POLICY

⇒ Further trials are required to establish whether combination therapy is superior to EVT alone for acute stroke due to large vessel occlusion, and EVT alone is probably associated with a lower risk of harms. Clinical practice guidelines should consider these findings to optimise evidence-based care of acute stroke.

INTRODUCTION

Over 2.7 million people die of ischaemic stroke each year, and many who recover are left with permanent disabilities.[1] Approximately 21% of acute ischaemic stroke are due to large vessel occlusion[2] for which the standard of care has historically been intravenous alteplase, a thrombolytic medication.[3] More recently, direct mechanical reperfusion with endovascular thrombectomy (EVT) has proven effective.[4] Both treatments are extremely time-sensitive, and delays of 15 min in treatment initiation are associated with worse outcomes.

Among patients who had an ischaemic stroke are eligible for and can be treated with both interventions immediately, there has been uncertainty regarding the role of intravenous alteplase.[5 6] Thrombolytic agents, such as alteplase, may contribute to early reperfusion of the ischaemic area and resolve residual distal thrombi after EVT.[7–11] For large, proximally located thrombi, however, the rate of early recanalisation is low in the first hour following alteplase administration, and fragmentation with distal embolisation of the target thrombus can result in worsening distal perfusion, potentially complicating EVT.[5 12]

In the last 18 months, six randomized trials have been completed that provide evidence to address this uncertainty.[13–18] We conducted a systematic review and meta-analysis to explore the benefits and harms of EVT with or without intravenous alteplase for acute ischaemic stroke due to large vessel occlusion. Our findings supported the development of a clinical practice guideline (Personal communication: Ye Z, Busse J, Hill M. Endovascular thrombectomy and intravenous alteplase in patients with acute ischemic stroke: a rapid clinical practice guideline. 2022).

METHODS

We followed the Preferred Reporting Items for Systematic Review and Meta-Analysis checklist[19] when writing our report. All subjective decisions (ie, study selection, data abstraction, risk-of-bias assessment) were made in duplicate by independent reviewers, and any disagreements were resolved by discussion or by referral to a third reviewer.

Guideline panel involvement

A guideline panel provided critical oversight of different steps of this review, including: (1) defining the study question; (2) prioritising outcome measures; and (3) informing if measures of precision associated with pooled effect estimates were imprecise. The panel included seven general stroke experts, three neurointerventionalists, six methodologists, four patient partners who had recovered from an acute ischaemic stroke and received thrombectomy with or without intravenous thrombolysis, one caregiver, two academic pharmacists, one emergency physician and one health economist. All patients received personal training and support to optimise contributions throughout the guideline development process. The members of the guideline panel led the interpretation of the results based on what they expected the typical values and preferences of patients to be, as well as the variation between patients.

Data sources and search strategy

We searched MEDLINE, Embase, PubMed, Cochrane Central Register of Controlled Trials, Web of Science, clincialtrials.gov and the International Standard Randomized Controlled Trial Number (ISRCTN) registry from inception to 22 November 2021. No language restrictions were applied, and a research information specialist (RJC) developed all database-specific search strategies (online supplemental appendix 1). We reviewed the reference lists of all included studies and relevant systematic reviews for additional eligible trials. In addition, we searched abstracts for the past 3 years of proceedings of the International Stroke Conference, European Stroke Conference, Asia-Pacific Stroke Meeting and the World Stroke Congress.

Study selection

We included randomized controlled trial (RCTs) that enrolled patients who had an acute ischaemic stroke due to large vessel occlusion and randomised them to receive EVT with intravenous alteplase versus EVT alone. Pairs of reviewers independently screened titles and abstracts and reviewed the full texts of potentially eligible studies.

Data extraction

Each eligible trial underwent duplicate data abstraction by pairs of reviewers working independently, who collected study characteristics, patient information including number enrolled, age, sex, comorbidities, stroke mechanism and clot location of participants, treatment details, and all patient-important outcomes: recovery with minimal disability (modified Rankin Scale (mRS) Score of 0–2), symptomatic intracranial haemorrhage (sICH), mortality and procedure-related complications.

Risk-of-bias assessment

Using a modified Cochrane risk-of-bias instrument, pairs of reviewers independently assessed each article for risk of bias considering sequence generation, allocation sequence concealment, blinding of participants, healthcare providers, data collectors, outcome assessor/adjudicator and missing outcome data (≥10% missing data were considered high risk of bias).[20] Response options for each item were 'definitely or probably yes' (assigned a low risk of bias) and 'definitely or probably no' (assigned a high risk of bias).[21]

Data analysis

We conducted fixed effects meta-analysis using the Mantel-Haenszel method to calculate risk ratios (RRs) and risk differences (RDs), and the associated 95% CI, for all patient-important outcomes reported by more than one study. For computing RDs and 95% CIs, we applied the RRs to the baseline risks from a high-quality observational study of 6350 ischaemic stroke from 42 centres that received EVT with or without intravenous alteplase.[22] We conducted a post-hoc sensitivity analysis excluding the SKIP trial[14] from our analyses on the basis that the dose of alteplase may affect results. Specifically, the SKIP trial administered alteplase at a dose of 0.6 mg/kg vs 0.9 mg/kg in other trials.

We performed all statistical analyses using Review Manager for Windows (RevMan, V.5.3). Comparisons were two-tailed using a p≤0.05 threshold.

Assessment of certainty of evidence

The authors and the guideline panel achieved consensus in categorising the certainty of evidence for all reported outcomes as high, moderate, low or very low using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.[23] With the GRADE approach, RCTs start as high certainty evidence,[23] but may be rated down for risk of bias,[24] imprecision,[25] indirectness,[26] inconsistency[27] or publication bias.[28] We also rated down significant effects for imprecision if they were informed by <300 patients for continuous outcomes or <300 events for dichotomised outcomes.[25] We did not rate down for risk of bias if the only criterion not met was blinding of study participants or personnel on the basis that a recent meta-epidemiological study found no evidence for an average difference in estimated treatment effect between trials with and without blinded patients, healthcare providers or outcome assessors.[29] We also did not rate down the same effect estimate two times for both inconsistency and imprecision.

Rating of imprecision was fully contextualised by the guideline panel,[30] and we followed GRADE guidance for communicating our findings.[31] We presented our evidence syntheses in a GRADE summary of findings tables as both relative and absolute effects to optimise interpretability. The minimally important difference (MID) was informed by a survey of guideline panel members' views of patient values and preferences, and their subsequent discussion. The thresholds for MID were 1% for recovery with minimal disability, 0.8% for mortality and 1% for sICH; the panel, however, acknowledged both their uncertainty around patient values and likely large variability between patients. We assessed inconsistency among studies by differences in point estimates and overlap of the CI, and the I^2 statistic. According to Cochrane Review Handbook, an I^2 of 0%–40% might not be important, 30%–60% may represent moderate heterogeneity, 50%–90% may represent substantial heterogeneity and 75%–100% indicates considerable heterogeneity.[32]

RESULTS

Of 11 121 citations, 4 published RCTs[13–16] including 1633 patients and 2 RCTs described at conference presentations[17 18] including 701 patients met eligibility criteria (figure 1). Characteristics of included clinical trials, which were all published in 2020 and 2021, are presented in online supplemental appendix 2. Sample size ranges from 200 to 700 and two doses of alteplase (0.6 mg/kg[14] and 0.9 mg/kg,[1315–18]) were administered to participants. All eligible trials adequately generated their randomisation

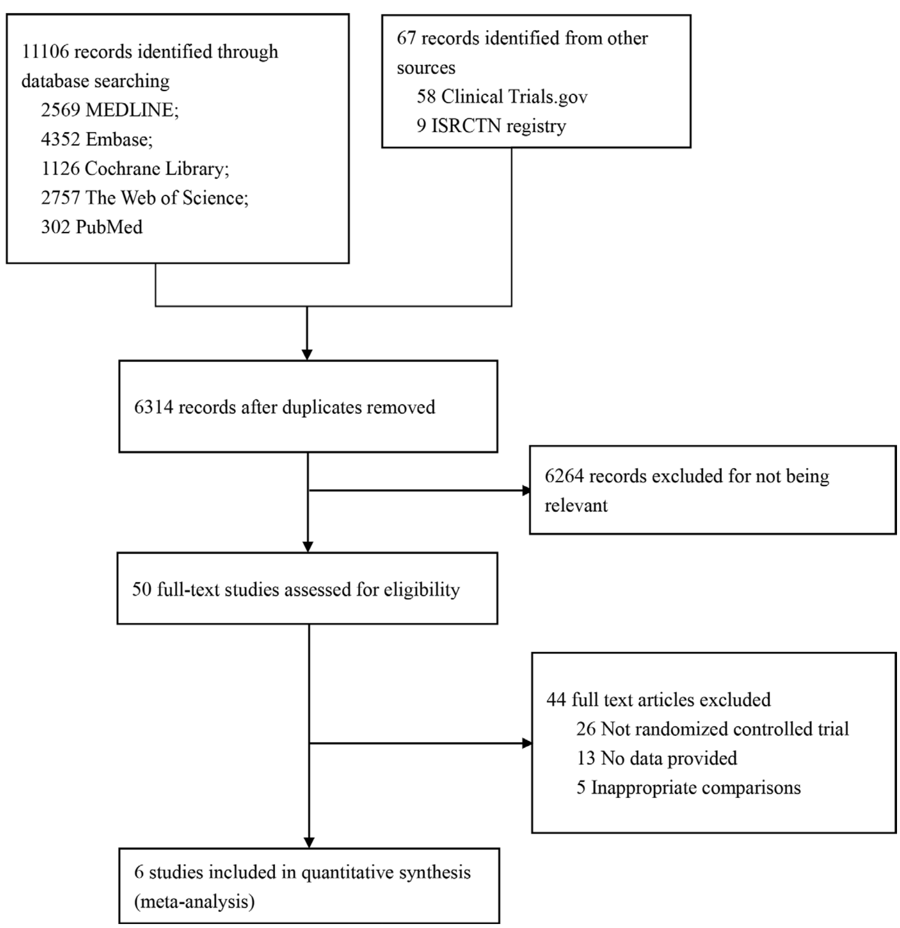

Figure 1 Flow chart for study selection.

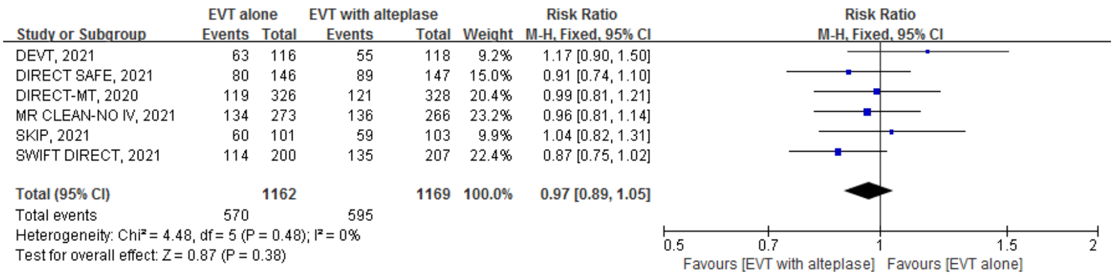

Figure 2 Forest plot for endovascular thrombectomy (EVT) alone versus EVT with intravenous alteplase for modified Rankin Scale (mRS) score 0–2.

sequence, appropriately concealed allocation, blinded outcome assessors and reported <10% missing outcome data. Due to the nature of the interventions, patients and healthcare providers were unblinded (online supplemental appendix 3).

Outcomes for EVT with intravenous alteplase versus EVT alone

Recovery with minimal disability (mRS Score 0–2)

Low certainty evidence from 6 RCTs[13–18] (2331 patients) suggests that, compared with EVT with alteplase, EVT alone possibly results in a small decrease in the proportion of patients that achieve functional independence (RR 0.97, 95% CI 0.89 to 1.05; RD −1.5%; 95% CI −5.4% to 2.5%) (figure 2, table 1).

Mortality

Low certainty evidence from 6 RCTs[13–18] (2333 patients) suggests that, compared with EVT with alteplase, EVT alone possibly results in a small increase in mortality (RR 1.07, 95% CI 0.88 to 1.29; RD 1.2%, 95% CI −2.0% to 4.9%) (figure 3, table 1).

Symptomatic intracranial haemorrhage (sICH)

Moderate certainty evidence from 6 RCTs[13–18] (2328 patients) suggests that, compared with EVT with alteplase, EVT alone probably results in a small decrease in sICH (RR 0.75, 95% CI 0.52 to 1.07; RD −1.0%; 95% CI −1.8% to 0.27%) (figure 4, table 1).

Sensitivity analysis excluding the SKIP trial[14] did not appreciably change recovery with minimal disability (mRS Score 0–2), mortality and sICH (online supplemental appendix 4).

Procedure-related complications

Overall, 2 studies[13 15] including 886 patients reported on procedure-related complications and the results showed

Table 1 GRADE summary of findings for EVT alone versus EVT with alteplase in patients who had an acute ischaemic stroke secondary to large vessel occlusion

Outcomes (timeframe)	Relative effects (95% CI); number of patients and trials.	Absolute effect estimates: Baseline risk of control group (EVT with alteplase)*	Absolute effect estimates: Difference (95% CI)	Certainty of evidence	Plain language summary
Minimal disability measured by modified Rankin Score 0–2 (90 days)	RR 0.97 (0.89 to 1.05) 2331 patients in six trials.[13–18]	49.1%	−1.5% (−5.4% to 2.5%)	Low (very serious imprecision)	There is possibly a small decrease in the proportion of patients that achieve functional independence with EVT alone
Mortality (90 days)	RR 1.07 (0.88 to 1.29) 2333 patients in six trials.[13–18]	16.8%	1.2% (−2.0% to 4.9%)	Low (very serious imprecision)	There is possibly a small increase in mortality with EVT alone
Symptomatic intracranial haemorrhage (90 days)	RR 0.75 (0.52 to 1.07) 2328 patients in six trials.[13–18]	3.8%	−1.0% (−1.8% to 0.27%)	Moderate (serious imprecision)	There is probably a small decrease in symptomatic intracranial haemorrhage with EVT alone

*The baseline risk for modified Rankin Score 0–2, mortality and symptomatic intracranial haemorrhage at 90 days was obtained from patients with anterior circulation large artery occlusion stroke receiving EVT with alteplase.[22]
EVT, endovascular thrombectomy; GRADE, Grading of Recommendations Assessment, Development and Evaluation; RR, risk ratio.

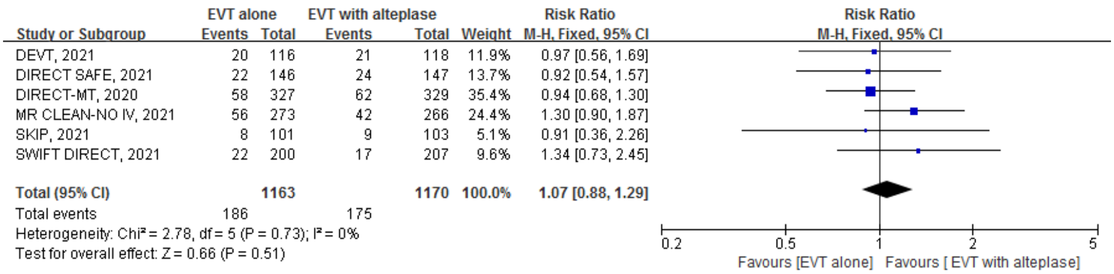

Figure 3 Forest plot for endovascular thrombectomy (EVT) alone versus EVT with intravenous alteplase for mortality.

no significant difference in procedure-related complications for EVT with or without alteplase (RR 0.89, 95% CI 0.69 to 1.15, p=0.38; online supplemental appendices 5 and 6).

Interpretation

For patients who had an ischaemic stroke with large vessel occlusion who present to comprehensive stroke centres and are eligible for both immediate thrombolysis and EVT, compared with EVT and intravenous alteplase, low certainty evidence suggests that there is possibly a small decrease in the proportion of patients that achieve functional independence and a small increase in mortality with EVT alone; CI are wide with very serious imprecision. Moderate certainty evidence suggests that there is probably a small decrease in sICH with EVT alone. Considering the small differences with very serious imprecision, this evidence supports only weak recommendations for future clinical care. The accompanying guideline[33] provides contextualised guidance based on this body of evidence.

Strengths of our systematic review include a comprehensive search for eligible RCTs in any language, and independent study selection, data abstraction and the risk-of-bias assessment by paired reviewers. We engaged a guideline panel of patients and clinical experts to fully contextualise our assessment of the evidence, and to establish MIDs for all outcomes. We used the GRADE approach to assess the certainty of evidence and converted all pooled relative effects to RDs to facilitate interpretation.

Compared with two recent published systematic reviews addressing EVT alone versus EVT with intravenous thrombolysis in acute ischaemic stroke from large vessel occlusion,[34 35] our review had the following distinctions. First, we used the GRADE approach to evaluate the certainty of evidence, which formally acknowledges imprecision in effect estimates. The results of our study suggested that EVT alone may decrease the proportion of patients that achieve functional independence and increase mortality, whereas previous systematic reviews concluded no difference between groups in functional independence and mortality. Second, we engaged a guideline panel, which involved patient partners, to contextualise the findings—including assessment of precision associated with pooled effect estimates. Third, prior reviews reported both patient-important and surrogate outcomes. In the systematic review of four trials, surrogate endpoints (successful reperfusion and any intracranial haemorrhage) showed significant improvement, the first favouring EVT plus alteplase and the second favouring EVT alone, and the authors did not address this issue.[34] In the systematic review of three trials, there were no significant differences in successful reperfusion.[35] Surrogate outcomes are less important when we have evidence to directly inform patient-important outcomes.[36] Our review recognised this and hence did not report these surrogate outcomes. Finally, on the definition of sICH used in these RCTs,[13–18] we chose the Heidelberg criteria for DIRECT-MT, DEVT and MR CLEAN-NO IV trials,[13 15 16] and the Safe Implementation of Thrombolysis in Stroke–Monitoring Study (SITS–MOST) criteria for the SKIP trial,[14] while for the SWIFT DIRECT and DIRECT SAFE[17 18] trials we used their own trial-specific definitions (online supplemental appendices 2 and 6); the previous systematic review of four trials[34] used Heidelberg criteria for DIRECT-MT and MR CLEAN-NO IV trials[13 16] and National Institute of Neurological Disorders and Stroke (NINDS) criteria for SKIP and DEVT trials[14 15] (online supplemental appendix

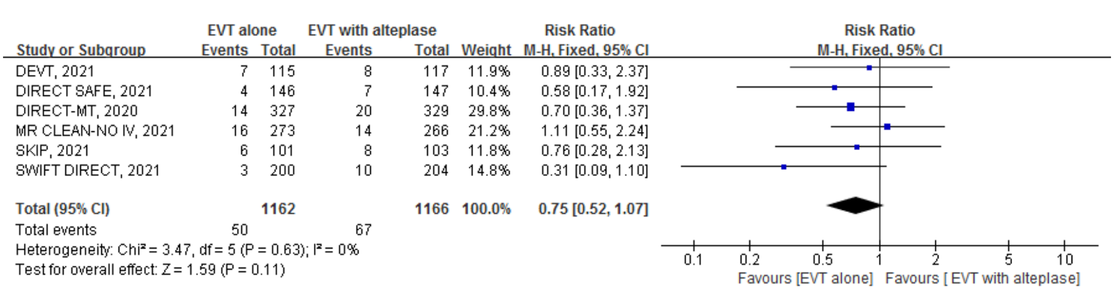

Figure 4 Forest plot for endovascular thrombectomy (EVT) alone versus EVT with intravenous alteplase for symptomatic intracranial haemorrhage.

6); the previous systematic review of three trials[35] used Heidelberg criteria for DIRECT-MT trials[13] and NINDS criteria for SKIP and DEVT trials.[14 15] Notwithstanding these differences in methods, our conclusion is essentially the same—there is little to no differences in outcomes with EVT alone compared with EVT plus alteplase.

On 3 February 2022, the European Stroke Organisation (ESO)–European Society for Minimally Invasive Neurological Therapy (ESMINT) published a guideline that made a strong recommendation in favour of intravenous thrombolysis plus mechanical thrombectomy over mechanical thrombectomy alone for patients who had an acute stroke presenting with anterior circulation large vessel occlusion and who are eligible for both treatments.[37] Their associated evidence synthesis concluded moderate certainty evidence (due to inconsistency) for no difference in functional recovery without impairment or sICH, and high certainty evidence for no difference in mortality but greater chance of successful reperfusion with EVT plus alteplase. They rated down for inconsistency for recovery and sICH even though all CI in these forest plots overlapped and the I^2 was 0% for both pooled effect estimates.

The difference in our appraisal of certainty of evidence is due to our approach of assessing imprecision. Specifically, we assessed values and preferences of patients presenting with acute stroke and found that most would consider a 1% absolute difference in functional recovery without impairment to be important. Accordingly, we judged the pooled effect for EVT alone versus combination therapy as imprecise as the 95% CI ranged from 5.4% more to 2.5% less recovering with no impairment; a range that includes both important benefits and harms associated with EVT alone and thus warranted rating down twice for imprecision according to the GRADE approach.[38] The ESO–ESMINT guideline, alternatively, applied a non-inferiority margin of 1.3% and concluded that non-inferiority was not met and did not rate down for imprecision. The same issue affected the assessment of mortality. We viewed the associated 95% CI, which included a 2% decrease and a 4.9% increase in mortality with EVT alone, as including both important benefits and harms and so rated down two times for imprecision. The ESO–ESMINT guideline, again, did not consider this imprecise. The ESO–ESMINT guideline's strong recommendation in favour of EVT plus alteplase appears to rest on significant effects on surrogate outcomes that favoured combination therapy; specifically, successful reperfusion and any intracranial haemorrhage. We did not include these outcomes in our review, and instead focused only on outcomes of direct important to patients: functional recovery, mortality and sICH.

Limitations

There are some limitations to our review. First, eligible trials used multiple criteria to define sICH. Based on feedback from our clinical experts, we chose the Heidelberg criteria for three trials,[13 15 16] SITS–MOST criteria for the SKIP trial.[14] The SWIFT DIRECT trial defined sICH as any parenchymal haematoma type 1, parenchymal haematoma type 2, remote intracranial haemorrhage, subarachnoid haemorrhage or intraventricular haemorrhage associated with a ≥4 point worsening on the National Institutes of Health Stroke Scale (NIHSS) at 24±6 hours post randomisation[17] and the DIRECT SAFE trial defined sICH as NIHSS increase of 4 or more points at 24 hours window post stroke with ICH on CT scan[18]; the lack of statistical heterogeneity in our pooled estimate of effect (I^2=0%) suggests our approach was valid. Second, although we found no difference in treatment effects between EVT with intravenous alteplase versus EVT alone, the associated estimates of precision included patient-important benefits and harms, which reduced our certainty of evidence to low or moderate. Third, our findings are only relevant to alteplase. Tenecteplase may be a more effective thrombolytic agent.[39 40] If so, additional trials will be needed to determine whether the combination of tenecteplase and EVT is superior to EVT alone. Fourth, we relied on conference publications for two (SWIFT DIRECT and DIRECT SAFE)[17 18] trials, and we contacted the lead investigators of each trial and confirmed the data presented at conferences.

CONCLUSIONS

Low certainty evidence suggests that there is possibly a small decrease in the proportion of patients that achieve functional independence and a small increase in mortality with EVT alone. Moderate certainty evidence suggests that there is probably a small decrease in sICH with EVT alone. The accompanying guideline provides contextualised guidance based on this body of evidence.

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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 trees 10731

#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)

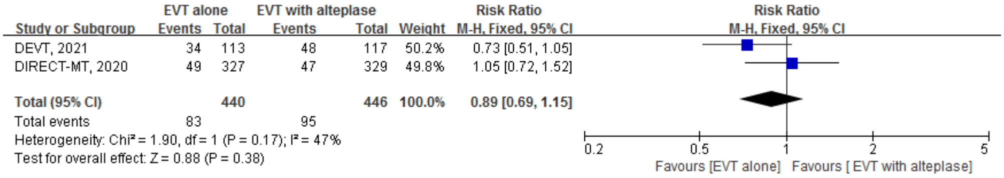
Appendix 3: Risk of bias assessment

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.

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