Clinical Policy: Use of Thrombolytics for the Management of Acute Ischemic Stroke in the Emergency Department

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ABSTRACT

This clinical policy from the American College of Emergency Physicians (ACEP) is the revision of a clinical policy approved in 2015 addressing a critical question regarding the use of thrombolytics for the management of acute ischemic stroke. A writing committee conducted a systematic review of the literature to derive evidence-based recommendations to answer the following clinical question: In adult stroke patients who are a candidate for mechanical thrombectomy, is the use of intravenous thrombolysis prior to mechanical thrombectomy (Bridge therapy) beneficial and safe versus mechanical thrombectomy alone? Evidence was graded, and recommendations were made based on the strength of the available data.

INTRODUCTION

Approximately 30% of all acute ischemic strokes have a large vessel occlusion (LVO), which contributes to 64% of all moderate-to-severe disability from stroke at 3 months and over 95% of stroke deaths at 6 months.[1,2] Over the past decade, acute treatment for LVO has expanded beyond thrombolytics with evidence supporting the use of endovascular therapy (EVT) such as mechanical thrombectomy.[3-5]

For patients who are eligible for both interventions, this has led to recent debate on the use of intravenous thrombolysis (IVT) prior to EVT in patients with an LVO. On one hand, the use of IVT may contribute to early reperfusion from an LVO and resolve residual distal thrombi after EVT.[6,7] However, IVT alone has low recanalization rates in patients with an LVO, especially with proximal lesions, and may fragment and cause distal embolization, making EVT less effective.[8,9] Intravenous thrombolysis may also increase the risk of symptomatic intracranial hemorrhage (sICH) and delay EVT, although the outcomes of such delays in patients receiving both interventions is unclear.[10,11]

Another challenge in determining the optimal treatment paradigm is the availability of EVT. Although approximately 90% of patients in the United States have access to a stroke center within 60 minutes, most lack timely access to an EVT-capable center, with only around 20% residing within a 15-minute and 50% within a 60-minute radius of a stroke center equipped for EVT.[12-14] This may lead to varying treatment strategies for patients with an LVO: individuals who initially present to a facility without EVT capabilities and require transfer and those who directly present to an EVT-capable facility.

Studies that compared EVT alone (direct endovascular therapy or direct mechanical thrombectomy) with IVT + EVT (bridging therapy) used the modified Rankin score (mRS) to assess functional outcomes. The mRS ranges from 0 (no neurologic symptoms) to 6 (death). Good functional outcome or functional independence is often defined as mRS of 0 to 2, which represents patients with slight disability but who can look after their own affairs without assistance. Excellent functional outcome is usually defined as mRS of 0 to 1, which represents no significant disability and the ability to carry out all duties and activities.[15] Although the mRS is the most common tool used for evaluating disability in stroke research, there are known limitations with inter-rater reliability.[16]

Recently, an international survey showed that 63% of stroke physicians consisting of neurologists, interventionalists, and neurosurgeons would still give IVT prior to EVT.[17] However, published consensus from experts has been conflicting on whether to support IVT prior to EVT due to differing interpretations of the data.[18,19] This systematic review will evaluate outcomes for patients who present with an acute stroke from an LVO and received EVT with or without IVT.

METHODOLOGY

This American College of Emergency Physicians (ACEP) clinical policy was developed by emergency physicians with input from medical librarians and a patient safety advocate; is based on a systematic review and critical descriptive analysis of the medical literature; and is reported in accordance with Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines.[20]

Search and Study Selection

This clinical policy is based on a systematic review with critical analysis of the medical literature meeting the inclusion criteria. Searches of PubMed, SCOPUS, Embase, Web of Science, and the Cochrane Database of Systematic Reviews were performed by a second librarian. Search terms and strategies were peer reviewed by a second librarian. All searches were limited to human studies published in English. Specific key words/phrases, years used in the searches, dates of searches, and study selection are identified under each critical question. In addition, relevant articles from the bibliographies of included studies and more recent articles identified by committee members and reviewers were included.

Using Covidence (Covidence, Melbourne, Australia), 2 subcommittee members independently reviewed the identified abstracts to assess for possible inclusion. Of those

identified for potential inclusion, each full-length text was reviewed for eligibility. Those identified as eligible were subsequently abstracted and forwarded to the committee's methodology group (emergency physicians with specific research methodological expertise) for methodological grading using a Class of Evidence framework (Appendix E1, available at http://www.annemergmed.com).

Assessment of Risk of Bias and Determination of Classes of Evidence

Each study identified as eligible by the subcommittee was independently graded by 2 methodologists. Design 1 represents the strongest possible study design to answer the critical question, which relates to whether the focus was therapeutic, diagnostic, prognostic, or meta-analysis. Subsequent design types (ie, design 2 and design 3) represent respectively weaker study designs. Articles are then graded on dimensions related to the study's methodological features and execution, including but not limited to randomization processes, masking, allocation concealment, methods of data collection, outcome measures and their assessment, selection, and misclassification biases, sample size, generalizability, data management, analyses, congruence of results and conclusions, and potential for conflicts of interest.

Using a predetermined process that combines the study's design, methodological quality, and applicability to the critical question, 2 methodologists independently assigned a preliminary Class of Evidence grade for each article. Articles with concordant grades from both methodologists received that grade as their final grade. Any discordance in the preliminary grades was adjudicated through discussion, which involved at least one additional methodologist, resulting in a final Class of Evidence assignment (ie, Class I, Class II, Class III, or Class X) (Appendix E2, available at http://www.annemergmed.com). Studies identified with significant methodologic limitations and/or ultimately determined to not be applicable to the critical question, received a Class of Evidence grade "X" and were not used in formulating recommendations for this policy. However, content in these articles may have been used to formulate the background and to inform expert consensus in the absence of evidence. Classes of Evidence grading may be found in the Evidentiary Table included at the end of this policy.

Translation of Classes of Evidence to Recommendation Levels

Based on the strength of evidence for each critical question, the subcommittee drafted the recommendations and supporting text, synthesizing the evidence using the following guidelines:

Level A recommendations. Generally accepted principles for patient care that reflect a high degree of scientific certainty (eg, based on evidence from one or more Class of Evidence I or multiple Class of Evidence II studies that demonstrate consistent effects or estimates).

Level B recommendations. Recommendations for patient care that may identify a particular strategy or range of strategies that reflect moderate scientific certainty (eg, based on evidence from one or more Class of Evidence II studies or multiple Class of Evidence III studies that demonstrate consistent effects or estimates).

Level C recommendations. Recommendations for patient care that are based on evidence from Class of Evidence III studies or, in the absence of adequate published literature, based on expert consensus. In instances where consensus recommendations are made, "consensus" is placed in parentheses at the end of the recommendation.

There are certain circumstances in which the recommendations stemming from a body of evidence should not be rated as highly as the individual studies on which they are based. Factors such as consistency of results, uncertainty of effect magnitude, and publication bias, among others, might lead to a downgrading of recommendations. When possible, clinically oriented statistics (eg, likelihood ratios [LRs], number needed to treat) are presented to help the reader better understand how the results may be applied to the individual patient. This can assist the clinician in applying the recommendations to most patients but allow adjustment when applying to patients with extremes of risk (Appendix E3, available at http://www.annemergmed.com).

Evaluation and Review of Recommendations

Once drafted, the policy was distributed for internal review (by members of the entire committee), followed by external expert review and an open comment period for all ACEP membership. Comments were received during a 60-day open comment period, with notices of the comment period sent electronically to ACEP members, published in *EM Today*, posted on the ACEP website, and sent to other pertinent physician organizations. The responses were used to further refine and enhance this clinical policy, although responses do not imply endorsement. Clinical policies are scheduled for revision every 3 years; however, interim reviews are conducted when technology, methodology, or the practice environment changes significantly.

Application of the Policy

This policy is not intended to be a complete manual on the use of thrombolytics for the management of acute ischemic stroke but rather a focused examination of critical questions that have particular relevance to the current practice of emergency medicine. Potential benefits and harms of implementing recommendations are briefly summarized within each critical question.

It is the goal of the Clinical Policies Committee to provide evidence-based recommendations when the scientific literature provides sufficient quality information to inform recommendations for a critical question. In accordance with ACEP Resolution 56(21), ACEP clinical policies do not use race-based calculators in the formulation of the recommendations. When the medical literature does not contain adequate empirical data to inform a critical question, the members of the Clinical Policies Committee believe that it is equally important to alert emergency physicians to this fact.

This clinical policy is not intended to represent a legal standard of care for emergency physicians. Recommendations offered in this policy are not intended to represent the only diagnostic or management options available to the emergency physician. ACEP recognizes the importance of the individual physician's judgment and patient preferences. This guideline provides clinical strategies for which medical literature exists to inform the critical questions addressed in this policy. ACEP funded this clinical policy.

Scope of Application. This guideline is intended for physicians working in emergency departments (EDs).

Inclusion Criteria. This guideline is intended for adult patients aged 18 years and older presenting to the ED with acute ischemic stroke.

Exclusion Criteria. This guideline is not intended to be used for pediatric or pregnant patients.

CRITICAL QUESTION

In adult stroke patients who are a candidate for mechanical thrombectomy, is the use of IVT prior to mechanical thrombectomy (Bridge therapy) beneficial and safe versus mechanical thrombectomy alone?

Patient management recommendations

Level A recommendations. None specified.

Level B recommendations. In stroke patients who are candidates for both mechanical thrombectomy and IVT*, IVT should be offered and may be given prior to mechanical thrombectomy.

*IVT is given within 4.5 hours from symptom onset

Level C recommendations. When feasible, shared decisionmaking between the patient (and/or their surrogate) and a member of the health care team should include a discussion of potential benefits and harms prior to the decision whether to administer intravenous thrombolytics (Consensus recommendation).

Potential Benefit of Implementing the Recommendations:

- Improved functional outcomes
- Decreased mortality

Potential Harm of Implementing the Recommendations:

- Delays in EVT
- Increased cost with the use of thrombolytics

Key words/phrases for literature searches: Acute Ischemic Stroke, Acute Stroke, Alteplase, Anticoagulation Bridge, Brain Ischemia, Bridge Therapy, Bridging Anticoagulation, Catheter-directed Thrombectomy, Cerebrovascular Accident, Directed, Thrombectomy, Elaxim, Emergency Department, Emergency Health Service, Emergency Medical Services, Emergency Medicine, Emergency Treatment, Emergency Ward, EMS, Endovascular Therapy, Endovascular Thrombectomy, EVT, Fibrinolytic, Fibrinolytic Agents, Guided Thrombectomy, Intravenous, Intravenous Drug Administration, Ischemic Stroke, IV, Mechanical Thrombectomy, Metalyse, Percutaneous Thrombectomy, rTPA, Stroke, Tenecteplase, Thrombectomy, Thrombolytic Therapy, Thrombolytic Treatment, Thrombolytic, Tissue Plasminogen Activator, TNKase, tPA, and variations and combinations of key words/phrases. Searches included January 2015 to search the date of April 10, 2023 (Appendix E4, available at http://www.annemergmed.com).

Study Selection: Five hundred and fifty-seven articles were identified in the searches. Three hundred and thirty-four articles were selected from the search results as candidates for further review. After grading for methodological rigor, 3 Class I studies, 7 Class II studies, and 8 Class III studies were included for this critical question (Appendix E5, available at http://www.annemergmed.com). Appendix E6 (available at http://www.annemergmed.com) lists the 69 articles graded for methodological rigor but ultimately found to be fatally flawed.

Randomized Controlled Trials

Six randomized controlled trials (RCTs) were included: 1 Class I study, 4 Class II studies, and 1 Class III study. [21-26] All included RCTs were open-labeled with masked assessment of outcomes and included only adult patients who presented within 4.5 hours of symptom onset without contraindications for thrombolytics. Alteplase at 0.9 mg/kg was used in all studies except in studies where it was noted that either a different alteplase dose was given or tenecteplase was used.

All the RCTs were designed primarily to evaluate if EVT alone was noninferior to IVT + EVT, except for one trial (LeCouffe[22]) that evaluated superiority of EVT alone, followed by noninferiority of EVT alone. As opposed to superiority studies, which are designed to demonstrate better effectiveness of one intervention over another, noninferiority studies are powered to evaluate whether one intervention is potentially "less good" than another intervention within a predefined range.[27] Noninferiority trials are appropriate if one intervention has added costs, risks, or limited availability that might render superiority less important.[28] Because intention-to-treat analysis is more likely to create Type 1 error by falsely concluding noninferiority compared with per-protocol analysis, dual reporting of both analyses is preferable for noninferiority trials.[29,30] To achieve noninferiority, the lower limit of the confidence interval (CI) should exceed the prespecified noninferiority margin. Each of the noninferiority RCT trials in this clinical policy used different primary end points as well as various noninferiority margins. Both per-protocol and intention-to-treat analyses were performed and remained consistent within each study and are summarized in Table 1.

In a Class I study, the DIRECT-MT trial enrolled 654 patients from 41 academic tertiary care centers in China with an internal carotid artery (ICA) or first segment middle cerebral artery (M1)/second segment middle cerebral artery (M2) LVO.[21] The primary outcome was a median 90-day mRS. Both EVT alone and IVT + EVT had similar 90-day mRS (3 versus 3). The adjusted odds ratio (OR) for the mRS was 1.08 (95% CI 0.82 to 1.43). These results demonstrate noninferiority as the lower limit margin was set at 0.80. There was no statistical difference in sICH or death at 90 days observed between the 2 groups.

The DEVT trial was a Class II study that enrolled 234 patients with an ICA or M1 LVO from 33 stroke centers in China.[24] The primary outcome was the proportion of patients achieving mRS 0 to 2 at 90 days. Results from the per-protocol analysis showed an mRS 0 to 2 in 53.2% of the EVT alone group versus 46% of the IVT + EVT group. The absolute difference of 7.1% (97.5% CI −5.9 to ∞) allowed them to conclude noninferiority based on their prespecified margin of 10%. The DEVT trial was stopped early after enrolling only 235 out of the planned 970 patients because of a statistical finding of likely futility. Both groups had similar rates of sICH and death at 90 days, with no statistical differences observed.

In a Class II study, the SKIP trial enrolled 204 patients from 23 stroke centers in Japan with an ICA or M1 LVO.[25] Whereas 0.9 mg/kg of alteplase was used in other trials, this trial used 0.6 mg/kg of alteplase. The primary outcome was mRS 0 to 2. Results from the per-protocol analysis showed a favorable neurologic outcome in 60.8% of the EVT alone group versus 58.8% of the IVT + EVT group and an OR of 1.06 (1-sided 97.5% CI 0.60 to ∞), which did not meet the prespecified lower margin of 0.74. The investigators were unable to conclude noninferiority.

Table 1. A synthesis of the ACEP Clinical Policy Level of Evidence, direction of support for BT, original investigator's NI margin, and Per-Protocol and Intention-to-Treat analysis.

RCT	Level of Evidence	Study Size	NI Margin	Per Protocol	Intention To Treat	Support BT?
DIRECT MT[21]	I	654	0.8	1.08 (95% CI 0.82-1.43)[1]	1.07 (95% CI 0.81-1.40)*	No
DEVT[24]	II	234	−10%	7.1% (97.5% CI −5.9 to ∞)[2]	7.7% (97.5% CI −5.1% to ∞)†	No
SKIP[25]	II	204	0.74	1.06 (97.5% CI 0.60-∞)[3]	1.09 (97.5% CI 0.63-∞)‡	Yes
MR CLEAN NO IV[22]	II	539	0.8	0.84 (95% CI 0.61-1.16)[1]	0.84 (95% CI 0.62-1.15)*	Yes
SWIFT DIRECT[23]	II	408	−12%	−4.6% (95% CI −14.8 to 5.8%)[4]	−7.3% (95% CI −16.6 to 2.1)§	Yes
DIRECT SAFE[26]	III	295	−0.1	−0.062 (95% CI −0.173 to 0.049)[4]	−0.051 (95% CI −0.160 to 0.059)‖	Yes

BT, Bridging therapy; *CI,* confidence interval; *NI,* noninferiority; *RCT,* randomized control trial.
*Adjusted common odds ratio.
†Unadjusted difference.
‡Odds ratio.
§Adjusted risk difference.
‖Unadjusted risk difference.

Mortality at 90 days and sICH were not observed to be statistically different between the 2 groups.

The MR CLEAN NO IV trial was a Class II study that included 539 patients from 20 hospitals in the Netherlands, Belgium, and France.[22] Patients had an acute ischemic stroke due to a proximal occlusion of the anterior circulation. The primary outcome was median mRS at 90 days, first evaluating for superiority of EVT alone over IVT + EVT. If superiority was not established, then an evaluation of noninferiority of EVT alone compared with IVT + EVT was performed. The noninferiority margin was set at 0.8 for the adjusted common OR. Median mRS favored IVT + EVT over EVT alone (2 versus 3). Results from the adjusted common OR were 0.84 (95% CI 0.62 to 1.15), which demonstrated neither superiority nor noninferiority for EVT alone. No statistical difference was observed between the 2 groups for sICH or death within 90 days.

The SWIFT DIRECT was a Class II trial that enrolled 408 patients with anterior strokes from 48 EVT-capable centers in Europe and Canada.[23] The primary outcome was mRS 0 to 2 at 90 days. Results from the per-protocol analysis showed favorable neurologic outcomes in 57% of the EVT alone group versus 64% of the IVT + EVT group. Absolute risk difference was −4.6% (95% CI −14.8 to 5.8%), with the lower limit of 1-sided 95% CI of −13.2%. The lower limit exceeded the prespecified 12%, and noninferiority of EVT alone could not be concluded in the overall study population or in any of the prespecified subgroups. There was no statistical difference in sICH or mortality by 90 days between both groups.

In a Class III study, the DIRECT-SAFE trial enrolled 295 patients from 25 acute-care hospitals in Australia, New Zealand, China, and Vietnam.[26] Patients needed to have an LVO in either the ICA, M1, or M2 segments of the middle cerebral artery (MCA) or basilar artery and were randomized with or without alteplase in Asian countries (83%) and tenecteplase in non-Asian countries (17%). The primary outcome was mRS 0 to 2 at 90 days. Results from the per-protocol analysis showed a favorable neurologic outcome in 54% of the EVT alone group versus 62% of the IVT + EVT group. The risk difference was −0.062 (95% CI −0.173 to 0.049). The lower end of the 95% CI exceeded −0.1 prespecified threshold and therefore noninferiority of EVT alone was not demonstrated. Safety outcomes were not statistically different, with 1% sICH in both groups and a similar number of deaths at 90 days.

Of the 6 RCTs, 4 did not show noninferiority of EVT alone compared with IVT + EVT, thus supporting the use of IVT in this patient population.[22,23,25,26] In all RCT studies, sICH and death were not statistically significant between the 2 groups, although the studies were not all powered for safety.[21-26]

Systematic Reviews/Meta-Analyses

Six systematic reviews/meta-analyses (SRMA) were included in this guideline. Three SRMAs included RCTs only, which were included in this review.[10,31,32] Two other SRMAs included both RCTs and observational studies, including studies that were eliminated during the critical appraisal (grading) process.[33,34] Lastly, one SRMA compared patients presenting to a primary stroke center with LVO who received IVT prior to receiving EVT at a comprehensive stroke cener with patients who presenting to a primary stroke center with LVO who did not receive IVT prior to receiving EVT at a comprehensive stroke center.[35]

In a Class I meta-analysis, Kaesmacher et al[31] included 6 randomized clinical trials (DEVT, SKIP, DIRECT-MT, DIRECT-SAFE, SWIFT DIRECT, and MR CLEAN NO IV) totaling 2,023 patients comparing EVT alone with IVT + EVT for patients with anterior circulation LVO only.[21-26] The primary outcome was time from symptom onset to expected administration of IVT plus thrombectomy versus thrombectomy alone with a minimal clinically important difference for the rate of mRS 0 to 2 of 1.3% at 90 days. There was a statistically significant interaction between time from symptoms onset to expected administration of IVT and the association of allocated treatment with functional outcomes (adjusted OR per 1-hour delay, 0.84; 95% CI 0.72 to 0.97). The benefit of IVT + EVT decreased with longer times from symptom onset to IVT administration and the benefit was not statistically significant after 2 hours 20 minutes.

In a Class II meta-analysis, Lin et al[32] reviewed 4 RCTs (DEVT, SKIP, DIRECT-MT, and MR CLEAN NO IV) for a total of 1,633 patients. Based on the literature, they assessed 5 different noninferiority margins for functional independence (mRS 0 to 2) at 90 days.[21,22,24,25] There was no observed statistical heterogeneity among trials (I^2=0%). Although the risk difference was 1% (95% CI −4% to 5%) favoring EVT alone, the lower margin of the 95% CI suggests EVT alone is noninferior to IVT + EVT except when using the most stringent of margins at −1.3%. The outcome measure of mRS 0 to 1 showed a similar risk difference of 1% (95% CI −3% to 5%), showing noninferiority except when using the margin of −1.3%. Symptomatic intracranial hemorrhage and mortality were not shown to be different between study groups.

In another Class II meta-analysis, Wang et al[10] reviewed 6 RCTs (DEVT, SKIP, DIRECT-MT, DIRECT-SAFE,

SWIFT DIRECT, and MR CLEAN NO IV) for a total of 2,334 patients.[21-26] This international workgroup consisted of various stakeholders, including stroke experts, pharmacists, academics, and caregivers of stroke patients. The workgroup established minimally important differences through survey of their guideline panel and discussion for the following outcomes: 1% for recovery with minimal disability (mRS 0 to 2), 0.8% for mortality, and 1% for sICH. Pooled estimate of effect showed lack of observed statistical heterogeneity (I^2=0%). They concluded with low certainty of evidence that EVT alone had a smaller decrease in patients with minimal disability (risk ratio [RR] 0.97, 95% CI 0.89 to 1.05; risk difference −1.5%; 95% CI −5.4% to 2.5%) and a small increase in mortality (RR 1.07, 95% CI 0.88 to 1.29; risk difference 1.2%, 95% CI −2.0% to 4.9%), but moderate certainty of evidence that EVT alone had a small decrease in sICH (RR 0.75, 95% CI 0.52 to 1.07; risk difference −1.0%, 95% CI −1.8% to 0.27%).

In a Class I meta-analysis, Zheng et al[33] reviewed a total of 55 studies that included 9 RCTs and 46 observational/retrospective studies for a total of approximately 20,000 patients.[21,22,24,25,36-40] A comprehensive meta-analysis was performed using both RCTs and observational/retrospective studies to investigate various outcomes. Functional independence was defined as mRS of 0 to 2, and excellent outcomes were defined as mRS of 0 to 1. For RCTs, the IVT + EVT group reduced the risk of mortality versus EVT alone (OR 0.65, 95% CI 0.49 to 0.88, I^2=52%) but not functional independence (OR 1.17, 95% CI 0.99 to 1.38, I^2=0%). On the other hand, the observational studies showed that IVT + EVT had better outcomes for functional independence (OR 1.36, 95% CI 1.21 to 1.52, I^2=48%), excellent outcomes (OR 1.49, 95% CI 1.26 to 1.75, I^2=4%), and mortality (OR 0.73, 95% CI 0.56 to 0.94, I^2=67%). Neither the RCTs nor observational studies showed an increased risk in sICH.

In a Class II meta-analysis, Ghaith et al[34] reviewed 49 studies (4 RCTs and 44 observational studies) with a total of 36,123 patients.[21,22,24,25] In the analysis combining both RCTs and observational studies, they demonstrated that IVT + EVT had better mortality (RR 0.75, CI 95% 0.68 to 0.82, I^2=36%), successful recanalization (RR 1.06, 95% CI 1.03 to 1.09, I^2=50%), and 90-day functional independence (RR 1.21, 95% CI 1.13 to 1.29, I^2=52%), but no improvement in National Institutes of Health Stroke Scale (NIHSS). Subgroups were stratified accounting to study design showing similar benefits with IVT + EVT for observational studies but not for RCTs. No difference was seen between the 2 groups related to sICH.

Lastly, in a Class III study, Katsanos et al[35] included 6 observational studies totaling 1,723 patients. Patients who received IVT at a primary stroke center before transferring for EVT ("drip and ship" or DNS, 53% of the group) were compared with those receiving EVT alone at a Comprehensive Stroke Center (CSC). In their analysis adjusted for potential confounders, "DNS patients" had higher odds of mRS 0 to 1 (adjusted OR 1.32, 95% CI 1.00 to 1.74, I^2=0%) and lower probability for all-cause mortality at 3-months (adjusted OR 0.50, 95% CI 0.27 to 0.93, I^2=69%) compared with patients receiving EVT alone at a CSC. No differences were found between the 2 groups in probability of 3-month disability, mRS 0 to 2, or sICH.

The majority of SRMA favored IVT + EVT. Two of the SRMA showed either improved mortality or improved functional outcomes with IVT + EVT; however, these results varied based on whether the analysis used RCTs and/or observational studies.[33,34] Of the 3 studies that looked at the RCTs alone, one SRMA showed noninferiority of EVT alone compared with IVT + EVT in various cutoffs except for the most strict cutoff for functional outcomes, whereas another SRMA suggested a possible small increase in mortality, a small decrease in recovery with minimal disability, but moderate certainty of decreased sICH with EVT alone.[10,32] The other SRMA that used RCTs alone suggests that IVT + EVT is superior to EVT alone but is time-dependent.[31] Lastly, in patients who are transferred, evidence suggests patients who received IVT + EVT have better functional outcomes and mortality compared with EVT alone.[35]

Observational and Retrospective Evidence

Multiple nonrandomized Class III studies have also explored the role of thrombolysis with thrombectomy. Abilleira et al[41] analyzed Spanish stroke registry data from Catalonia to compare EVT alone with IVT + EVT. After adjusting for higher proportion of patients with heart failure, atrial fibrillation, oral anticoagulation, and previous stroke among patients receiving EVT alone, no differences in 90-day mortality, symptomatic bleeding at 24 to 36 hours, or mRS 0 to 2 were noted between the 2 treatment groups.

Balodis et al[42] reported a single-center prospective observational analysis of IVT + EVT versus EVT alone for anterior cerebral artery LVO in a single Latvian university hospital. Although exclusions did not include a time-of-onset for symptoms, all thrombectomy occurred within 8 hours of symptom onset, and all patients presenting within 4.5 hours received IVT unless contraindications were

identified or physician's preference was not to provide IVT. A 90-day mRS 0 to 2 was observed in 44% of the IVT + EVT group versus 42% in the EVT alone group. No significant differences were observed in 90-day mortality or sICH.

Broocks et al[43] retrospectively analyzed a cohort of acute ischemic stroke patients treated at one of two high-volume tertiary stroke centers in Germany and the United States for ICA or MCA LVO. The Alberta Stroke Program Early CT Score (ASPECTS) was determined on pretreatment noncontrast head CT by one neuro-radiologist.[44] Most had ASPECTS >5 (86%). Overall, those receiving IVT + EVT had better NIHSS at 24 hours (11 versus 13) and mRS at 90 days (3 versus 4). More patients in the IVT + EVT cohort had an mRS of 0 to 2 at 90 days (43% versus 32%). Among the 14% with ASPECTS <6, no difference was seen for mRS of 0 to 2. ASPECTS was the only variable demonstrating a significant interaction with IVT.

Casetta et al[45] reviewed the Italian Registry of Endovascular Stroke Treatments prospective observational data from 13 hospitals, which included 1,148 patients with either an ICA or MI/M2 LVO who were eligible for IVT. Endovascular thrombectomy was performed within 6 hours of symptom onset, and decisions about IVT were left to the discretion of the treating neurology team. Although the median time from symptom onset to hospital arrival was similar between the 2 groups (95 minutes for IVT + EVT versus 96 minutes for EVT alone patients), the symptom onset to groin puncture was significantly prolonged in the IVT + EVT subset (230 minutes versus 210 minutes in EVT). Multivariate analysis for stroke patients surviving with mRS of 0 to 3 demonstrated a significant benefit favoring IVT + EVT (adjusted OR 1.42; 95% CI 1.04 to 1.95) and a significantly lower risk of death or unfavorable outcome in that same group (adjusted OR 0.62; 95% CI 0.45 to 0.84). No differences were found regarding sICH.

Di Maria et al[46] retrospectively evaluated acute ischemic stroke patients involving the proximal or distal MCA or ICA within 6 hours of symptoms. A stroke neurologist decided whether or not to treat with IVT. IVT + EVT patients were matched with patients treated with EVT alone using a propensity score. An mRS of 0 to 2 was more likely with IVT + EVT (OR 1.31; 95% CI 1.02 to 1.68). All-cause mortality and sICH did not differ between groups. Only ASPECTS ≥7 demonstrate the benefit of IVT + EVT compared with EVT alone (OR 1.48, 95% CI 1.10 to 2.0).

Zha et al[47] reported a post hoc analysis of a prospective study across 16 Chinese stroke centers. The prespecified outcome was an mRS of 0 to 2 at 90 days. In a multivariable analysis, IVT + EVT more frequently demonstrated a higher mRS of 0 to 1 at 90 days (adjusted OR 2.731; 95% CI 1.238 to 6.023), but not the primary outcome of mRS of 0 to 2. The 90-day mortality rate was significantly lower in the IVT + EVT cohort (13.9% versus 27.7%).

Of the 6 studies, 4 showed an improvement in functional outcomes with IVT + EVT compared with EVT alone.[43,45-47] In several studies, the use of ASPECTS further defined which patients benefited from IVT prior to EVT.[43,46] In 2 studies, mortality was decreased with IVT + EVT, but no difference in the others.[45,47] Lastly, there was no increase in sICH with IVT + EVT compared with EVT alone in any of the studies.

Summary

The majority of published research favored the use of IVT + EVT over EVT alone. This includes RCTs where the majority of trials failed to show noninferiority with EVT alone despite using wide noninferiority thresholds. However, there are a number of limitations to these trials, including different outcome measures and different noninferiority thresholds. Among systematic reviews, inclusion of observational studies increased observed statistical heterogeneity.

From a safety standpoint, although some studies showed a decrease in mortality with IVT + EVT, most studies showed no difference. Lastly, although there have been concerns about the increased risk of sICH with the addition of IVT before EVT, no study included in our review showed an increased risk of sICH. However, safety data from these studies may have also been under-reported.[48,49] It is important that with any intervention, shared decisionmaking is made when feasible with the patient and/or family.

Future Research

Existing research predominantly employed alteplase as the primary thrombolytic agent. Subsequent investigations should explore alternative thrombolytics, such as tenecteplase.[50] Future studies should also look at timing of thrombolytics prior to EVT with patient outcomes. In addition, the role of ASPECTS score and other tools in identifying individuals unlikely to benefit from the addition of IVT prior to EVT should be explored prospectively.[44] Furthermore, future studies ought to consider larger sample sizes, using more stringent noninferiority margins or ideally conducting superiority studies, as well as evaluating the cost-effectiveness of different treatment strategies.[51]

Because the majority of the literature has focused on anterior strokes, future studies should also evaluate the role

of IVT before EVT in posterior circulation strokes. Finally, more studies evaluating the role of thrombolytics in patients with an LVO who are candidates for EVT but need to be transferred are needed. This includes patients who are considered for out-of-hospital diversion to EVT-capable centers and the use of mobile stroke units to triage potential patients for EVT.

Relevant industry relationships: There were no relevant industry relationships disclosed by the subcommittee members for this topic.

Relevant industry relationships are those relationships with companies associated with products or services that significantly influence the specific aspect of disease addressed in the critical question.

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APPENDIX

Appendix E1. Literature classification schema.*

Design/Class	Therapy†	Diagnosis‡	Prognosis§
1	Randomized, controlled trial or meta-analysis of randomized trials	Prospective cohort using a criterion standard or meta-analysis of prospective studies	Population prospective cohort or meta-analysis of prospective studies
2	Nonrandomized trial	Retrospective observational	Retrospective cohort Case control
3	Case series	Case series	Case series

*Some designs (eg, surveys) will not fit this schema and should be assessed individually.
†Objective is to measure therapeutic efficacy comparing interventions.
‡Objective is to determine the sensitivity and specificity of diagnostic tests.
§Objective is to predict outcome, including mortality and morbidity.

Appendix E2. Approach to downgrading strength of evidence.

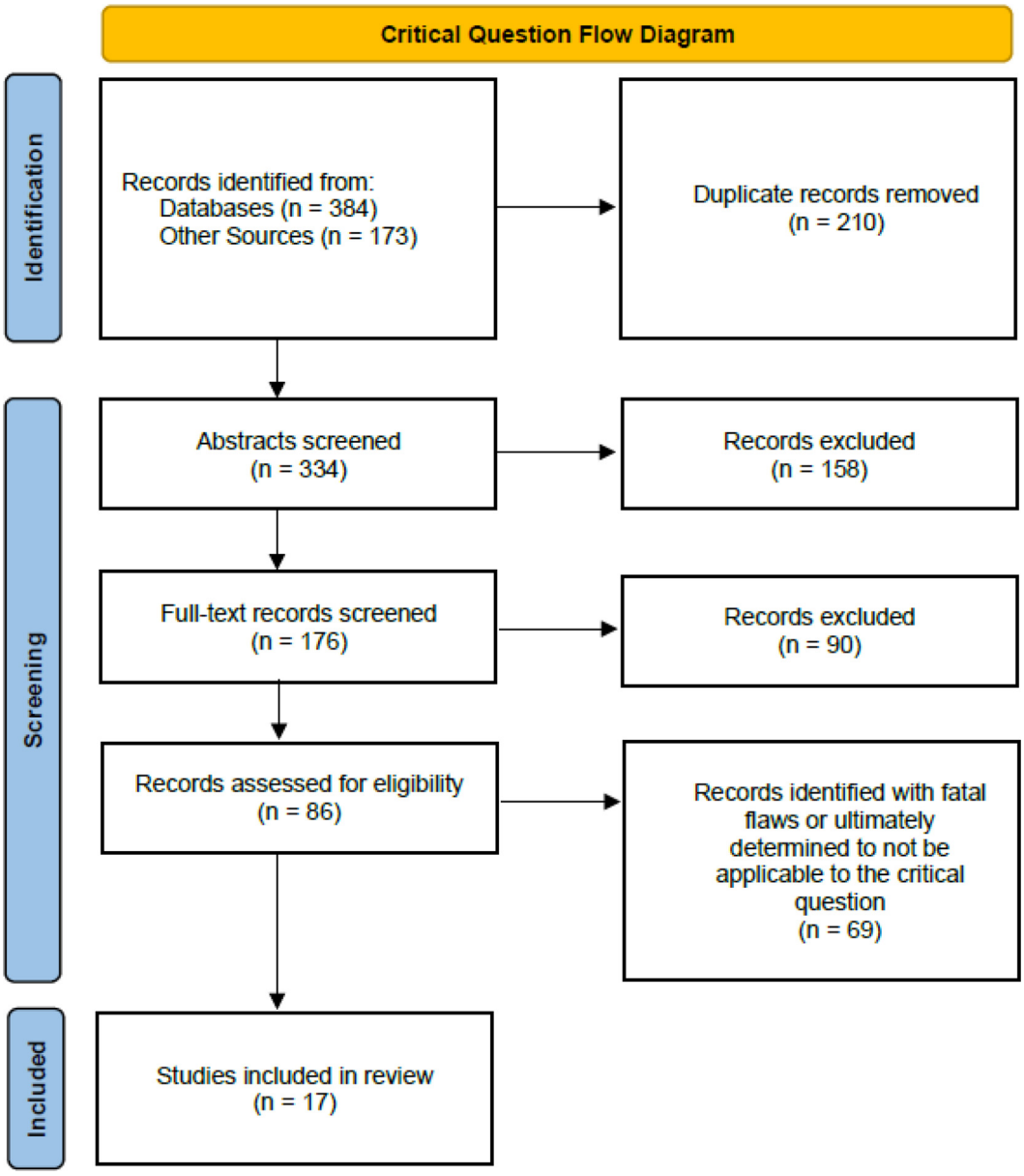
	Design/Class		
Downgrading	**1**	**2**	**3**
None	I	II	III
1 level	II	III	X
2 levels	III	X	X
Fatally flawed	X	X	X

Appendix E3. Likelihood ratios and number needed to treat.*

LR (+)	LR (–)	
1.0	1.0	Does not change pretest probability
1-5	0.5-1	Minimally changes pretest probability
10	0.1	May be diagnostic if the result is concordant with pretest probability
20	0.05	Usually diagnostic
100	0.01	Almost always diagnostic, even in the setting of low or high pretest probability

LR, likelihood ratio.
*Number needed to treat (NNT): number of patients who need to be treated to achieve 1 additional good outcome; NNT=1/absolute risk reduction×100, where absolute risk reduction is the risk difference between 2 event rates (ie, experimental and control groups).

Appendix E4. PRISMA flow diagrams.[20]



Appendix E5. Literature Searches.

Search Date	Database	Search Strings	Filters
4/10/2023	PubMed	((Mechanical Thrombectomy[tiab]) OR (Bridge Therapy[tiab]) OR (Percutaneous Thrombectomy[tiab]) OR (Endovascular Therapy[tiab]) OR (EVT[tiab]) OR (Endovascular Thrombectomy[tiab]) OR (Guided Thrombectomy[tiab]) OR (Catheter-directed Thrombectomy[tiab]) OR ("Thrombectomy"[mh]) OR ("Bridge Therapy"[Mesh])) AND ((Tissue Plasminogen Activator[tiab]) OR (Alteplase[tiab]) OR (tPA[tiab]) OR (rTPA) OR (Tenecteplase[tiab]) OR (Thrombolytic*[tiab]) OR (Fibrinolytic*[tiab]) OR ("Tissue Plasminogen Activator"[mh]) OR ("Tenecteplase"[mh]) OR ("Fibrinolytic Agents"[mh]) OR ("Fibrinolytic Agents" [Pharmacological Action]) OR ("Thrombolytic Therapy"[mh])) AND ((Intravenous[tiab]) OR (IV[tiab]) OR("Administration, Intravenous"[mh])) AND((Acute Stroke[tiab]) OR (Acute Ischemic Stroke[tiab]) OR (Brain Ischemia[tiab]) OR ("Stroke"[mh]) OR ("Ischemic Stroke"[mh]) OR ("Brain Ischemia"[mh])) AND ((Emergency Medicine[tiab]) OR (Emergency Treatment[tiab]) OR (Emergency Department[tiab]) OR (Emergency Medical Service*[tiab]) OR (EMS[tiab]) OR ("Emergency Medicine"[mh]) OR ("Emergency Service, Hospital"[mh]) OR ("Emergency Treatment"[mh]) OR ("Emergency Medical Services"[mh]))	2015-Current
4/10/2023	Scopus	TITLE-ABS-KEY(“Mechanical Thrombectomy” OR “Bridge Therapy” OR "Anticoagulation Bridge" OR “Percutaneous Thrombectomy” OR “Endovascular Therapy” OR “EVT” OR “Endovascular Thrombectomy” OR “Guided Thrombectomy” OR “Directed Thrombectomy” OR “Catheter-directed Thrombectomy”) AND TITLE-ABS-KEY(“Tissue Plasminogen Activator” OR “Alteplase” OR “tPA” OR “rTPA” OR “Tenecteplase” OR “Metalyse” OR “TNKase” OR “Elaxim” OR “Thrombolytic*” OR “Fibrinolytic*”) AND TITLE-ABS-KEY(“Intravenous” OR “IV”) AND TITLE-ABS-KEY("Stroke" OR “Acute Stroke” OR “Acute Ischemic Stroke” OR “Brain Ischemia”) AND TITLE-ABS-KEY(“Emergency Medicine” OR “Emergency Treatment” OR “Emergency Department” OR “Emergency Medical Service*”)	2015-Current
4/10/2023	Embase	(‘Mechanical Thrombectomy’:de,ti,ab,kw OR ‘Bridge Therapy’:ti,ab,kw OR ‘Bridging Anticoagulation’:de OR ‘Percutaneous Thrombectomy’:de,ti,ab,kw OR ‘Endovascular Therapy’:ti,ab,kw OR ‘EVT’:ti,ab,kw OR ‘Endovascular Thrombectomy’:ti,ab,kw OR ‘Guided Thrombectomy’:ti,ab,kw OR ‘Directed Thrombectomy’:ti,ab,kw OR ‘Catheter-directed Thrombectomy’:ti,ab,kw) AND (‘Tissue Plasminogen Activator’:de,ti,ab,kw OR ‘Alteplase’:de,ti,ab,kw OR ‘tPA’:ti,ab,kw OR ‘rTPA’:ti,ab,kw OR “Tenecteplase’:de,ti,ab,kw OR ‘Metalyse’:ti,ab,kw OR ‘TNKase’:ti,ab,kw OR ‘Elaxim’:ti,ab,kw OR ‘Thrombolytic*’:ti,ab,kw OR ‘Thrombolytic Therapy’:de,ti,ab,kw OR ‘Thrombolytic treatment’:de,ti,ab,kw OR ‘Fibrinolytic’:de,ti,ab,kw) AND (‘Intravenous’:ti,ab,kw OR ‘Intravenous Drug Administration’:de,ti,ab,kw OR ‘IV’:ti,ab,kw) AND (’Stroke’:ti,ab,kw OR ’Cerebrovascular Accident’:de OR ‘Acute Stroke’:ti,ab,kw OR ‘Acute Ischemic Stroke’:de,ti,ab,kw OR ‘Brain Ischemia’:de,ti,ab,kw) AND (‘Emergency Medicine’:de,ti,ab,kw OR ‘Emergency Treatment’:de,ti,ab,kw OR ‘Emergency Department’:ti,ab,kw OR ‘Emergency Ward’:de,ti,ab,kw OR ‘Emergency Medical Service*’:ti,ab,kw OR ‘Emergency Health Service’:de,ti,ab,kw)	2015-Current
8/24/2022	Web of Science	TS=(“Mechanical Thrombectomy” OR “Bridge Therapy” OR "Anticoagulation Bridge" OR “Percutaneous Thrombectomy” OR “Endovascular Therapy” OR “EVT” OR “Endovascular Thrombectomy” OR “Guided Thrombectomy” OR “Directed Thrombectomy” OR “Directed Thrombectomy” OR “Catheter-directed Thrombectomy”) AND TS=(“Tissue Plasminogen Activator” OR “Alteplase” OR “tPA” OR “rTPA” OR “Tenecteplase” OR “Metalyse” OR “TNKase” OR “Elaxim” OR “Thrombolytic*” OR “Fibrinolytic*”) AND TS=(“Intravenous” OR “IV”) AND TS=("Stroke" OR “Acute Stroke” OR “Acute Ischemic Stroke” OR “Brain Ischemia”) AND TS=(“Emergency Medicine” OR “Emergency Treatment” OR “Emergency Department” OR “Emergency Medical Services”)	2011-Current

Appendix E5. Continued.

Search Date	Database	Search Strings	Filters
8/24/2022	Cochrane Library	("Mechanical Thrombectomy":ti,ab,kw OR "Bridge Therapy":ti,ab,kw OR "Bridging Anticoagulation":ti,ab,kw OR "Percutaneous Thrombectomy":ti,ab,kw OR "Endovascular Therapy":ti,ab,kw OR "EVT":ti,ab,kw OR "Endovascular Thrombectomy":ti,ab,kw OR "Guided Thrombectomy":ti,ab,kw OR "Directed Thrombectomy":ti,ab,kw OR "Catheter-directed Thrombectomy":ti,ab,kw) AND ("Tissue Plasminogen Activator":ti,ab,kw OR "Alteplase":ti,ab,kw OR "tPA":ti,ab,kw OR "rTPA":ti,ab,kw OR "Tenecteplase":ti,ab,kw OR "Metalyse":ti,ab,kw OR "TNKase":ti,ab,kw OR "Elaxim":ti,ab,kw OR "Thrombolytic*":ti,ab,kw OR "Thrombolytic Therapy":ti,ab,kw OR "Thrombolytic treatment":ti,ab,kw OR "Fibrinolytic":ti,ab,kw) AND ("Intravenous":ti,ab,kw OR "Intravenous Drug Administration":ti,ab,kw OR "IV":ti,ab,kw) AND ("Stroke":ti,ab,kw OR "Acute Stroke":ti,ab,kw OR "Acute Ischemic Stroke":ti,ab,kw OR "Brain Ischemia":ti,ab,kw) AND ("Emergency Medicine":ti,ab,kw OR "Emergency Treatment":ti,ab,kw OR "Emergency Department":ti,ab,kw OR "Emergency Ward":ti,ab,kw OR "Emergency Medical Service*":ti,ab,kw OR "Emergency Health Service":ti,ab,kw)	2011-Current

Evidentiary Table.

Graded RCTs					
Author and Year Published	**Class of Evidence**	**Setting and Study Design**	**Methods and Outcome Measures**	**Results**	**Limitations and Comments**
Yang et al (2020)[21]	I	Multicenter (Chinese tertiary care centers); prospective randomized open label, noninferiority trial w/blinded outcome assessments	Adults ≥18 y, AIS of ICA or first segment MCA (M1)/second segment MCA (M2) or both by computed tomography angiography that could be treated <4.5 h after symptom onset and NIHSS ≥2; 2 arms: EVT alone vs IVT+EVT in patients with AIS with LVO; primary outcome: 90 d mRS for noninferiority (logistic regression – ordinal) margin of 0.8 through telephone/in-person interview (intention-to-treat analysis)	N=656; 327 EVT alone; 329 IVT+EVT; EVT alone noninferior aOR 1.07 (95% CI 0.81 to 1.40, *P*=.04), but was associated with lower percentage with successful reperfusion before thrombectomy (2.4% vs 7%) and overall successful reperfusion (79.4% vs 84.5%) and 90 d mortality 17.7% in EVT only vs 18.8% in IVT+EVT	Open label, not generalizable outside China, excluded those with missing outcomes, no adjustment for multiple comparisons, and this is a noninferiority trial, whereas the Clinical Policies Committee question is for superiority

Evidentiary Table (continued).

Graded RCTs					
Author and Year Published	**Class of Evidence**	**Setting and Study Design**	**Methods and Outcome Measures**	**Results**	**Limitations and Comments**
LeCouffe et al (2021)[22]	II	Multicenter, randomized, open label, clinical trial from 20 hospitals in Europe	Adult patients with AIS randomly assigned to either endovascular treatment or IVT followed by endovascular treatment; outcomes: mRS at 90 d; sICH; mortality	N=539; median mRS of 3 for thrombectomy alone group vs mRS of 2 for bridge thrombolysis plus thrombectomy, OR 0.84 (95% CI 0.62 to 1.15, *P*=.28); mortality: 21% for thrombectomy alone group vs 16% for bridge thrombolysis plus thrombectomy, OR 1.39 (95% CI 0.84 to 2.30); sICH: 6% for thrombectomy alone group vs 5% for bridge thrombolysis plus thrombectomy group, OR 1.30 (95% CI 0.60 to 2.81)	Open label, unblinded to treatment, although blinded outcome assessment
Fischer et al (2022)[23]	II	Multicenter, academic centers in Europe and Canada; noninferiority, randomized clinical trial	Adults with acute AIS+LVO, onset <4.5 h; thrombectomy alone vs thrombectomy + intravenous alteplase; efficacy outcome: mRS of 0 to 2 at 90 d; safety outcome: ICH	N=408: thrombectomy alone (N=201) vs thrombectomy + intravenous alteplase (N=207); mRS of 0 to 2: thrombectomy alone 57% vs thrombectomy + intravenous alteplase 65%; adjusted risk difference −7.3, one-sided (95% CI −16.6 to 2.1); ICH: thrombectomy alone 2% vs thrombectomy + intravenous alteplase 3%, risk difference −1.0% (95% CI −4.8 to 2.7)	Open label design could result in differential treatment bias; prespecified noninferiority margin=12%

Evidentiary Table (continued).

Graded RCTs					
Author and Year Published	**Class of Evidence**	**Setting and Study Design**	**Methods and Outcome Measures**	**Results**	**Limitations and Comments**
Zi et al (2021)[24]	II	Multicenter (China) noninferiority study, 4-block randomized 1:1	Adults ≥18 y, AIS of proximal circulation occlusion strokes that could be treated <4.5 h after symptom onset; 2 arms: EVT alone vs IVT+EVT in patients with AIS; outcomes: proportion of patients with mRS of 0 to 2 at 90 d (assessors were blinded neurologists) vs telephone call or video call with noninferiority margin of -10%; safety outcomes were sICH within 48 h and 90 d mortality	N=234, 116 EVT, 118 in IVT+EVT Primary Outcome: median mRS EVT alone was 2, 1 to 4, and IVT+EVT was 3, 1 to 4, and unadjusted difference was 0, −1 to 0, aOR is 1.13 (95% CI 0.71 to 1.79) and no difference in secondary outcomes Safety Outcomes: 90 d mortality was 17.2% in EVT only vs 17.8% in IVT+EVT −0.5, −10.3 to 9.2%) and sICH difference was 6.1% vs 6.8%, difference −0.8%, (95% CI −7.1 to 5.6); asymptomatic hemorrhage was 15.7% vs 25.6%, 10% difference, 95% CI −20.3 to 0.3%, clot migration occurred in 113 (17.7%) vs 28 of 117 (23.9%) in IVT+EVT group with no differences in serious adverse events	Infused whole dose of tPA despite achieving reperfusion earlier, which might pose a bleeding risk; within-site correlations analysis was post hoc and successful reperfusion before EVT; study was powered for noninferiority, rather than whether IVT+EVT was "beneficial" (Clinical Policies Committee question)

Evidentiary Table (continued).

Graded RCTs					
Author and Year Published	**Class of Evidence**	**Setting and Study Design**	**Methods and Outcome Measures**	**Results**	**Limitations and Comments**
Suzuki et al (2021)[25]	II	Multicenter, randomized, open label, noninferiority clinical trial from 23 centers in Japan	Adult patients randomly assigned to MT alone or IVT+MT; outcomes: mRS 0 to 2 at 90 d; mortality; sICH	N=204; mRS of 0 to 2; 59% in MT group vs 57% in bridge thrombolysis plus thrombectomy, *P*=.18; among 7 secondary efficacy endpoints and 4 safety endpoints, 10 were not different, including mortality (8% vs 9%, *P*=1.0) and sICH (6% vs 8%, *P*=.78)	Open label, unblinded
Mitchell et al (2022)[26]	III	Multicenter, randomized, open label, noninferiority clinical trial from 25 acute-care hospitals in Australia, New Zealand, China, and Vietnam	Adult patients with AIS eligible for thrombolysis, allocated 1:1 to either direct thrombectomy or IVT plus thrombectomy; outcomes: mRS of 0 to 2 at 90 d; mRS of 0 to 1 at 90 d; sICH; mortality	N=295; 148 assigned to direct thrombectomy and 147 assigned to bridge therapy; mRS of 0 to 2: 55% for thrombectomy group vs 61% for bridge thrombolysis plus thrombectomy, OR 0.75 (95% CI 0.45 to 1.24, *P*=.19) for noninferiority, *P*=.26 for superiority; sICH: 1% vs 2%, OR 1.70 (95% CI 0.22 to 13.04, *P=0.61*); mortality: 15% vs 16%, OR 0.92 (95% CI 0.46 to 1.84, *P*=.82)	Open label, unblinded to treatment although blinded outcome assessment; trial terminated early; some imbalances in baseline characteristics

Evidentiary Table (continued).

Graded Systematic Reviews/Meta-Analysis					
Author and Year Published	**Class of Evidence**	**Setting and Study Design**	**Methods and Outcome Measures**	**Results**	**Limitations and Comments**
Kaesmacher et al (2024)[31]	I	Individual participant data meta-analysis from 6 randomized clinical trials 190 sites across 15 countries	Systematic review and meta-analysis to estimate the association of treatment with IVT plus thrombectomy vs thrombectomy alone and better outcomes was modified by the time from stroke symptom onset to treatment; primary outcome: disability at 90 d using the mRS	6 randomized clinical trials; N=2,313, 1,160 IVT + thrombectomy, 1,153 thrombectomy alone; median time from symptom onset to IVT administration was 2 h 28 min (interquartile range [IQR] 1 h 46 min to 3 h 17 min); statistically significant interaction between time from symptom onset to administration of IVT and functional outcome (aOR per 1-h delay 0.84 (95% CI 0.72 to 0.97), *P*=.02 for interaction); after 2 h 20 min, the benefit associated with IVT + thrombectomy was not significant, and the point estimate crossed the null association at 3 h 14 min	Trials performed at thrombectomy-capable stroke centers; only patients with anterior circulation large vessel occlusion were included; nearly all patients in the IVT + thrombectomy group were treated with alteplase; thus, results may not be generalizable to those treated with tenecteplase
Lin et al (2022)[32]	II	Meta-analysis of randomized clinical trials	Trials comparing thrombectomy along vs IVT plus thrombectomy among adults with AIS-LVO; Primary outcome: functional independence (mRS of 0 to 2) at 90 d	N=4 trials with 1,633 participants; 817 assigned to thrombectomy alone vs 816 to bridge thrombolysis plus thrombectomy; pooled difference with risk difference of 1% for good functional outcomes (95% CI −4% to 5%); pooled difference in sICH was also 1%, 95% CI −1% to 3%	Included studies with different noninferiority margins

Evidentiary Table (continued).

Graded Systematic Reviews/Meta-Analysis					
Author and Year Published	**Class of Evidence**	**Setting and Study Design**	**Methods and Outcome Measures**	**Results**	**Limitations and Comments**
Wang et al (2022)[10]	II	Meta-analysis of randomized clinical trials	Trials of adult patients with AIS comparing thrombectomy alone vs IVT plus thrombectomy; outcomes: mRS of 0 to 2; sICH; mortality	N=6 trials with 2,334 participants; mRS of 0 to 2: pooled RR 0.97 (95% CI 0.89 to 1.05); sICH: pooled RR 0.75 (95% CI 0.52 to 1.07); mortality: 1.07 (95% CI 0.88 to 1.29)	Only used fixed effects modeling; limited subgroup/sensitivity analyses
Zheng et al (2023)[33]	I	Meta-analysis	RCTs of MT alone vs MT+IVT for patients with AIS as a result of anterior circulation large vessel occlusion; outcomes: 3 mo mRS of 0 to 2; sICH at 24 h or 36 h; mortality at discharge or 3 mo; 3 mo mRS of 0 to 1	mRS of 0 to 2: 6 studies. aOR 1.17 (95% CI 0.99 to 1.38); sICH: 6 studies; aOR: 1.07 (95% CI 0.79 to 1.46); mortality: 6 studies; aOR 0.65 (95% CI 0.49 to 0.88) favoring IVT+EVT mRS 0 to 1: 4 studies; aOR: 1.11 (95% CI 0.90 to 1.38)	Heterogeneity is less of a factor in the adjusted analysis. Data reported here are from RCTs, although the published manuscript also includes data from observational studies

Evidentiary Table (continued).

Graded Systematic Reviews/Meta-Analysis					
Author and Year Published	**Class of Evidence**	**Setting and Study Design**	**Methods and Outcome Measures**	**Results**	**Limitations and Comments**
Ghaith et al (2022)[34]	II	Meta-analysis	Included studies on patients with AIS-LVO, exposed/experimental group received IVT+MT and comparison group only MT; outcomes: favorable neurologic function based on mRS; mortality, successful recanalization, complications; comparative studies designs including both experimental and quasi-experimental or observational designs	N=49 studies; pooled RR for favorable neurologic outcome, 45% for bridge thrombolysis plus thrombectomy group vs 39% for thrombectomy alone, RR 1.21 (95% CI 1.13 to 1.29, *P*<.0001); subgroup analyses by study design showed favorable outcomes for bridge thrombolysis among observational studies (RR 1.25, 95% CI 1.17 to 1.34) but not for experimental studies (RR 0.99, 95% CI 0.89 to 1.09); sICH: RR 0.88 (95% CI 0.70 to 1.10, *P*=.27)	Subgroup analysis by study design demonstrated significant differences in reported efficacy and heterogeneity among studies, although random effects modeling used to mitigate

Evidentiary Table (continued).

Graded Systematic Reviews/Meta-Analysis					
Author and Year Published	**Class of Evidence**	**Setting and Study Design**	**Methods and Outcome Measures**	**Results**	**Limitations and Comments**
Katsanos et al (2023)[35]	III	Meta-analysis	Observational studies of patients with LVO receiving IVT at a primary stroke center before transfer for EVT vs transfer for EVT alone; outcomes: 3 mo mRS of 0 to 1; 3 mo mRS of 0 to 2; sICH within 48 h; 3 mo all-cause mortality	mRS of 0 or 1: 5 studies, 1,518 participants; aOR 1.32 (95% CI 1.00 to 1.74) favoring IVT+EVT mRS of 0 to 2: 5 studies, 1,518 participants; aOR 1.22 (95% CI 0.95 to 1.58); symptomatic ICH: 5 studies, 1,535 participants; aOR 0.72 (95% CI 0.42 to 1.25); mortality: 5 studies; 1,549 participants; aOR: 0.50 (95% CI 0.27 to 0.93) favoring IVT+EVT	Included primarily lower quality studies which studies patients who received thrombectomy rather than patients who were eligible for thrombectomy

Evidentiary Table (continued).

Observational and Retrospective Evidence					
Author and Year Published	**Class of Evidence**	**Setting and Study Design**	**Methods and Outcome Measures**	**Results**	**Limitations and Comments**
Abilleira et al (2017)[41]	III	Regional registry retrospective cohort from Catalonia, Spain	Patients with anterior circulation stroke caused by large vessel occlusion; EVT vs bridging thrombolysis prior to EVT; outcomes: mRS of 0 to 2 at 3 mo; death; symptomatic bleeding 24 h to 36 h	N=1,166; 599 received EVT only and 567 IVT followed by EVT; OR for mRS of 0 to 2 at 90 d: 0.97 (95% CI 0.74 to 1.27); OR for death: 1.07 (95% CI 0.74 to 1.54); OR for symptomatic bleeding: 0.56 (95% CI 0.25 to 1.27)	Discrepancies in important baseline features is accounted for by using propensity score to stratify subjects into blocks; outcome assessments are unblinded; study population included only patients who received thrombectomy rather than those who were eligible for thrombectomy
Balodis et al (2019)[42]	III	Prospective single-center study from Latvia	Patients with acute stroke and eligible for endovascular treatment; EVT vs bridging thrombolysis prior to EVT; outcomes: mRS of 0 to 2 at discharge and 90 d; symptomatic and asymptomatic intracranial hemorrhage; mortality	N=146; 84 received bridging thrombolysis followed by thrombectomy, 62 received thrombectomy alone; mRS of 0 to 2: 44% in bridging group vs 42% in thrombectomy only group, OR 0.48 (95% CI 0.22 to 1.07), *P*=.14; mortality: 17% in bridging group vs 21% in thrombectomy only group, *P*=.57; symptomatic hemorrhage: 12% in bridging group vs 10% in thrombectomy only group, *P*=.79	Single center; nonrandomized; limited adjustment, including for treatment by indication; unclear outcome assessment blinding

Evidentiary Table (continued).

Observational and Retrospective Evidence					
Author and Year Published	**Class of Evidence**	**Setting and Study Design**	**Methods and Outcome Measures**	**Results**	**Limitations and Comments**
Broocks et al (2022)[43]	III	Multicenter, academic center in Germany and the United States; retrospective cohort	Adults with AIS+LVO who received EVT, with or without IVT, 2013 to 2021; outcome: functional independence (mRS of 0 to 2) at 90 d	N=720, IVT (N=366) vs no IVT (N=354); proportions with favorable outcome: IVT (43%) vs none (32%); aOR 1.57 (95% CI 1.16 to 2.14) for functional independence, favoring IVT	Multivariable regression analysis with propensity weighting but residual confounding due to treatment indication may bias estimates
Casetta et al (2019)[45]	III	Regional registry, multicenter prospective enrollment from an Italian registry; 13 centers	All patients who underwent endovascular treatment, either thrombectomy only vs intravenous thrombolytics plus thrombectomy for anterior circulation stroke; outcomes: mRS at 90 d; sICH	N=1,148, 635 with intravenous thrombolytics plus thrombectomy, 513 with thrombectomy only; IPTW mRS of 0 to 2: OR 1.3 (95% CI 0.98 to 1.75); IPTW sICH: OR 2.1 (95% CI 0.93 to 1.62)	Propensity score methods, including use of IPTW; residual confounding still possible; unclear blinding outcome assessment

Evidentiary Table (continued).

Observational and Retrospective Evidence					
Author and Year Published	**Class of Evidence**	**Setting and Study Design**	**Methods and Outcome Measures**	**Results**	**Limitations and Comments**
Di Maria et al (2018)[46]	III	Retrospective registry cohort from 3 stroke centers located in France	Adult patients with AIS within 6 h of onset with imagining evidence of anterior circulation occlusion; outcomes: mRS of 0 to 2 at 90 d; sICH	N=1,507; of the 1,507, 65% received intravenous thrombolytics; 407 propensity score matched patients and use of multiple imputation to account for missing data; propensity-matched mRS of 0 to 2: 49% in the thrombolytics plus thrombectomy group vs 45% in the thrombectomy only group, OR 1.21 (95% CI 0.90 to 1.63), *P*=.21; sICH: 9% for the thrombolytic plus thrombectomy vs 7% for the thrombectomy only group, OR 1.21 (95% CI 0.70 to 2.09, *P*=.5)	Propensity score methods, including matching and adjustment; residual confounding still possible; no apparent blinding for outcome assessment

Evidentiary Table (continued).

Observational and Retrospective Evidence					
Author and Year Published	**Class of Evidence**	**Setting and Study Design**	**Methods and Outcome Measures**	**Results**	**Limitations and Comments**
Zha et al (2021)[47]	III	Post hoc analysis of a multicenter, prospective cohort study from China	Adult, AIS with baseline mRS<2 who received thrombectomy within 8 h or bridge thrombolysis (within 4.5 h) plus thrombectomy; outcomes: mRS of 0 to 2 at 90 d and successful recanalization; sICH; mortality	N=245; propensity score matching with use of multiple imputation for missing values, resulting in 65 pairs; propensity score matched mRS of 0 to 2: 49% in bridging thrombolysis group vs 42% in thrombectomy only group, *P*=.46; propensity score matched mRS of 0 to 1: 43% in bridging thrombolysis group vs 25% in thrombectomy only group, *P*=.023; propensity score matched sICH: 11% in bridging thrombolysis group vs 9% in thrombectomy alone group, *P*=1.0; propensity score matched mortality: 15% in bridging thrombolysis group vs 25% in thrombectomy alone group, *P*=.31	Non-randomized limited power\ limited detail regarding use of propensity score methods and thus concern related to remaining imbalances between groups

AIS, acute ischemic stroke; *aOR*, adjusted odds ratio; *CI*, confidence interval; *EVT*, endovascular thrombectomy; *ICH*, intercranial hemorrhage; *IPTW*, inverse probability of treatment weighting; *IQR*, interquartile range; *IVT*, intravenous thrombolysis; *LVO*, large vessel occlusion; *MT*, mechanical thrombectomy; *OR*, odds ratio; *RR*, risk ratio; *sICH*, symptomatic intracranial hemorrhage.

APPENDIX E6. Articles Graded for Methodological Rigor But Ultimately Found To Be Fatally Flawed.

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