Clinical Policy: Critical Issues in the Management of Adult Patients Presenting to the Emergency Department with Acute Ischemic Stroke
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ABSTRACT

This clinical policy from the American College of Emergency Physicians addresses key issues in acute stroke management in adult patients presenting to the emergency department. A writing subcommittee conducted a systematic review of the literature to derive evidence-based recommendations to answer the following clinical questions: (1) In adult patients with a suspected acute ischemic stroke, can a clinical decision instrument be used to identify patients who have a large vessel occlusion on computed tomography angiography or magnetic resonance angiography? (2) In adult patients with a suspected acute ischemic stroke, does the addition of perfusion imaging to a computed tomography angiography or magnetic resonance angiography identify patients more likely to benefit from thrombectomy? (3) In adult patients with a suspected acute ischemic stroke qualifying for intravenous thrombolysis, is tenecteplase safe and effective when compared with alteplase? (4) In adult patients who present with acute vertigo with possible stroke, are there history or physical exam findings (eg, Head Impulse-Nystagmus-Test of Skew [HINTS] exam) that can risk stratify for acute ischemic stroke? Evidence was graded and recommendations were made based on the strength of the available data

INTRODUCTION

Approximately 800,000 people in the United States are diagnosed with a stroke each year at an estimated cost of approximately $46 billion. As a result, stroke remains one of the leading causes of death as well as the leading cause of disability.[1] In 1996, the Food and Drug Administration (FDA) approved intravenous (IV) tissue plasminogen activator as the first treatment for an acute ischemic stroke. Since then, endovascular thrombectomy (EVT) has also been approved for the treatment of acute strokes due to large vessel occlusions (LVO). Approximately 30% of all patients with an acute ischemic stroke have an LVO, while 12% of acute stroke patients are thought to be candidates for EVT.[2] While the evidence supports the use of EVT for LVOs located in the middle cerebral and internal carotid arteries, the benefits of EVT for LVOs in other locations remain uncertain.[3-5]

Due to the expertise and resources needed to perform EVT, there are only approximately 300 centers that are certified in the United States.[2] Because of the limited number of EVT-capable stroke centers, timely access is

limited: approximately 20% of the US population live within 15-minutes and only 50% of the US population live within 60-minutes to an EVT-capable stroke center.[6,7]

Diagnosing an acute stroke patient with an LVO that may be a candidate for EVT requires advanced imaging such as computed tomography angiography (CTA). However, identifying which suspected stroke patients that are likely to have an LVO can be challenging. This has implications for determining who should receive advanced imaging such as a CTA in the emergency department (ED) or potentially be diverted to an EVT-capable stroke center. Other advanced imaging, such as computed tomography perfusion (CTP), have also started to become available to help select patients with an LVO who also may benefit from an intervention such as EVT.

The use of alteplase was reviewed in the 2015 clinical policy for acute ischemic stroke. Since then, there has been interest in the use of tenecteplase for acute ischemic stroke.[8] Similar to its use in ST-elevation myocardial infarction (STEMI) patients, the protocol for giving tenecteplase makes it much easier to administer than alteplase.

Finally, patients who present with vertigo can be a diagnostic challenge trying to differentiate a peripheral from a central etiology. Although the rate of misdiagnosis of stroke in patients who are discharged home from the ED with a diagnosis of peripheral vertigo is less than 0.2%,[9] up to 37% of posterior circulation strokes are missed on initial presentation.[10] Because the mortality of a missed posterior circulation stroke can be significantly higher,[11] strategies are needed to prevent misdiagnosis.

This clinical policy will tackle 4 questions: 1) can a clinical decision instrument be used to identify patients who have an LVO on CTA or MRA; 2) does the addition of perfusion imaging to a CTA or MRA identify patients more likely to benefit from thrombectomy; 3) is tenecteplase safe and effective when compared with alteplase when given for acute ischemic strokes; and 4) are there history or physical exam findings that can risk stratify for acute ischemic stroke in patients who present with acute vertigo.

METHODOLOGY

This ACEP clinical policy 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 (PRISMA) guidelines.[12]

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 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), two 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 A).

Assessment of Risk of Bias and Determination of Classes of Evidence

Each study identified as eligible by the subcommittee was independently graded by two methodologists. Grading was done with respect to the specific critical questions; thus, the Class of Evidence for any one study may vary according to the question for which it is being considered. For example, an article that is graded an "X" due to "inapplicability" for one critical question may be considered relevant for another question and graded I – III. As such, it was possible for a single article to receive a different Class of Evidence grade when addressing a different critical question.

Design 1 represents the strongest possible study design to answer the critical question, which relates to whether the focus was therapeutic, diagnostic, or prognostic, or a 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, blinding, 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, two 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 (i.e., Class I, Class II, Class III, or Class X) (Appendix B). 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. Question-specific 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 (e.g., 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 (e.g., 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 C).

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 Web site, 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 evaluation and management of adult patients with acute 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. 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 EDs.

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

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

CRITICAL QUESTIONS

1. In adult patients with a suspected acute ischemic stroke, can a clinical decision instrument be used to identify patients who have an LVO on CTA or MRA?

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. None specified.

Level C recommendations. In adult patients with suspected stroke, either the Los Angeles Motor Scale (LAMS) or Rapid Arterial Occlusion Evaluation Scale (RACE) may be used to identify patients with increased likelihood for an LVO.

Potential Benefit of Implementing the Recommendations:

- Increase appropriate diversion of suspected LVO patients to EVT capable hospitals.
- Decrease time to arrival of suspected LVO to EVT capable hospitals.

Potential Harm of Implementing the Recommendations:

- Increase diversion of non-LVO patients to EVT capable hospitals.
- Miss patients with an LVO that may benefit from EVT.

Key words/phrases for literature searches: brain ischemia, cerebral arterial disease, cerebral arterial infarction, clinical decision aid, clinical decision instrument, clinical decision rules, clinical decision support systems, clinical decision tools, computed tomography angiography, computer-assisted decision making, decision support systems, decision support techniques, emergency medicine, hospital emergency service, large vessel occlusion, magnetic resonance angiography, middle cerebral artery infarction, stroke, and variations and

combinations of key words/phrases. Searches included all dates up to the search dates of November 17 and 25, 2020, December 3, 2020, January 28 and 29, 2021, and February 4 and 5, 2021.

Study Selection: Eight hundred seven articles were identified in the searches. Ninety-six were selected from the search results as candidates for further review. After grading for methodological rigor, zero Class I studies, 2 Class II studies, and 11 Class III studies were included for this critical question (Appendix D).

LVO stroke includes acute and symptomatic occlusions of the internal carotid artery or proximal segments of the anterior cerebral artery, middle cerebral artery, or in a handful of studies the posterior cerebral artery. Multiple clinical trials have demonstrated the superiority of EVT in comparison with standard medical care for LVO within the appropriate time frame when performed at experienced EVT-capable centers.[13,14] The 2019 American Heart Association acute ischemic stroke guideline updates provide Level IIb recommendations favoring "Effective pre-hospital procedures to identify patients who are ineligible for IV thrombolysis and have a strong probability of LVO stroke should be developed to facilitate rapid transport of patients potentially eligible for thrombectomy to the closest healthcare facilities that are able to perform mechanical thrombectomy".(Powers 2019)[3] Each hour delay from symptom onset before EVT is associated with a 5.5% decrease in independent outcomes.[15] Unfortunately, only some hospitals are capable of EVT, so pre-hospital systems and non-thrombectomy capable hospitals must sometimes transfer acute ischemic stroke patients with suspected LVOs, which increase the workload for busy receiving hospitals and can displace patients and their families far from home.

Multiple decision aids have been derived and validated to screen patients for LVO in pre-hospital and ED settings, including 3-item Stroke Scale (3I-SS), Cincinnati Prehospital Stroke Scale (CPSS), Field Assessment Stroke Triage for Emergency Destination (FAST-ED), Los Angeles Motor Scale (LAMS), Prehospital Acute Stroke Severity Scale (PASS), Rapid Arterial Occlusion Evaluation Scale (RACE), and Vision-Aphasia-Neglect (VAN), as well as modifications to the National Institute of Health Stroke Scale (NIHSS).[16-20] The components and scoring of a few of these LVO decision aids are provided in Table 1, and the diagnostic accuracy of these same instruments are summarized in Table 2. Diagnostic accuracy research for LVO decision aids seeks to simultaneously optimize sensitivity and specificity. Sensitivity represents the proportion of patients with LVO who are correctly identified as having an LVO, whereas specificity represents the proportion of patients without LVO who are correctly identified as not having an LVO. For example, 1 single-center registry study noted that an

NIHSS >6 provided the highest sensitivity (68%) and specificity (80%) for LVO with higher thresholds reducing sensitivity but increasing specificity, and lower cut points increasing sensitivity but reducing specificity.[21] The problem with either sensitivity or specificity in isolation is that they do not alter the pre-test probability of the presence or absence of LVO, so likelihood ratios are more clinically useful.[22,23]

Table 1. Components of LVO Prediction Instruments.

LVO Prediction Instrument	Instrument Components	Instrument Scoring
LAMS	Facial droop – Ask the person to smile	0 = facial droop absent 1 = facial droop present
	Arm drift – Hold arm extended forward for 10 seconds. Is there any drift or drop of the arm?	0 = absent 1 = drifts down 2 = falls rapidly
	Grip strength – Ask the person to grip your hand. Does one hand have less power than the other?	0 = normal 1 = weak grip 2 = no grip
RACE	Facial palsy	0 = absent 1 = mild 2 = moderate/severe
	Arm motor	0 = normal/mild 1 = moderate 2 = severe
	Leg motor	0 = normal/mild 1 = moderate 2 = severe
	Head/gaze deviation	0 = absent 1 = present
	Aphasia (if right hemiparesis) – ask the patient to "close your eyes and make a fist"	0 = performs both tasks 1 = performs one task 2 = performs neither task
	Agnosia (if left hemiparesis) – evaluate the patient's recognition of deficit by 1) showing paretic arm and asking "Whose arm is this?" and 2) asking patient "Can you lift both arms and clap?"	0 = patient recognizes arm and impairment 1 = unable to recognize arm or impairment 2 = unable to recognize arm and impairment
VAN	Visual disturbance	Positive VAN if patient reports double-vision, field cut, or loss of vision
	Aphasia	Any new difficulty forming words? If yes, positive VAN. Can the patient repeat a short sentence, recognize two objects, and follow simple commands? If unable to perform any of these tasks, positive VAN.
	Neglect	Does the patient present with an acute forced gaze or conjugate gaze palsy? Is the patient unable to track an object to one side? When the patient's eyes are closed are they unable to feel sensation to an arm or leg when one or both are stimulated? Positive VAN if "yes" to any of these.

Table 2. Diagnostic Accuracy for LVO Decision Aids with Level II or Level III Evidence.

Decision Aid	Included Studies	Number Patients	Sensitivity (95% CI), %	Specificity (95% CI), %	Positive LR (95% CI)	Negative LR (95% CI)
LAMS ≥4	**Class II**					
	Nguyen et al[29] (2020)	2007	38 (29-46)	93 (89-92)	5.4 (NR)	0.67 (NR)
	Class III					
	Duvekot et al[32] (2021)	1039	63 (55-72)	84 (82-87)	4.1 (3.3-4.9)	0.44 (0.34-0.54)
	Helwig et al[34] (2019)	116	78 (43-96)	71 (63-74)	2.6 (1.2-3.7)	0.32 (0.06-0.90)
RACE ≥5	**Class II**					
	Nguyen et al[29] (2020)	2007	56 (46-65)	90 (89-92)	5.6 (NR)	0.49 (NR)
	Class III					
	Duvekot et al[32] (2021)	1039	67 (58-75)	87 (85-89)	5.2 (4.1-6.1)	0.38 (0.30-0.49)
	Perez de le Ossa et al[38] (2014)	654	85 (NR)	68 (NR)	2.7 (NR)	0.22 (NR)
	Lima et al[36] (2016)	727	55 (NR)	87 (NR)	4.2 (NR)	0.52 (NR)
VAN	**Class III**					
	Vidale et al[41] (2018)*	62	100 (77-100)	90 (83-90)	10 (5-10)	0 (0-0.27)

NR = not reported and unable to recalculate.

* Systematic review with VAN assessed in one single-center study of 62 consecutive code stroke activations.

The theoretical value of these decision aids is to identify individuals with LVO in the pre-hospital setting or immediately upon ED arrival in order to expedite requisite imaging and neuro-interventional consultations, including transportation of higher risk suspected LVO patients to EVT-capable hospitals. Ideally, the hierarchy of clinical evidence for these decision aids would progress from accuracy alone to diagnostic randomized controlled trials (RCT) comparing different approaches to risk-stratifying suspected LVO patients during the initial minutes of their medical care.[24,25] Unfortunately, diagnostic RCT are rare so clinical guideline recommendations are often extrapolated from diagnostic accuracy research.[26] A multi-organizational systematic review of the American Heart Association's "2018 Guidelines for the Early Management of Patients with Acute Ischemic Stroke" concluded that "no scale predicted LVO with both high sensitivity and specificity" in pre-hospital settings.[19] Nonetheless, pre-hospital systems currently use some of these LVO decision-aids in protocols to transport suspected LVO patients to EVT-capable hospitals with some evidence that the use of these scales reduce time-to-intervention without overwhelming these EVT-capable hospitals.[27,28]

Two Class II studies were identified.[29,30] The first Class II study by Nguyen et al[29] was a prospective pre-hospital cohort study in the Netherlands over a 15-month period that included 2,812 acute stroke codes across 2 emergency medical services (EMS) agencies, 3 comprehensive stroke centers, and 4 primary stroke centers. Researchers retrospectively evaluated LAMS, RACE, PASS, gaze-face-arm-speech-time (G-FAST), FAST-ED, and the Cincinnati Stroke Triage Assessment Tool (C-STAT) stroke prediction instruments using applications completed on site or during transportation by EMS personnel. The researchers reported the accuracy for a symptomatic anterior LVO for each instrument, as well as the feasibility rates based upon the proportion for whom each instrument could be computed with the available data. LAMS ≥4 (sensitivity 38%, specificity 93%, positive LR 5.4, negative LR 0.67) and RACE ≥5 (sensitivity 56%, specificity 90%, positive LR 5.6, negative LR 0.49) were significantly more specific than the other LVO instruments.[29] The PASS scale was the most feasible to extrapolate from EMS documentation, while the RACE scale was least feasible with full stroke code reconstruction achieved in only 57% of the included records.[29] No patient-centered outcomes or process measures were reported, but hypothetically applying LAMS to this population would require 155 stroke patients to be screened to identify 1 LVO patient to transfer to a EVT-capable hospital who otherwise would have been

transferred to a non-EVT-capable hospital, while 53 patients with high LAMS scores but without LVO would have also been transferred to EVT-capable hospital.

The second Class II study by Zhao et al[30] was a prospective pre-hospital cohort transporting suspected stroke patients to 15 urban and 17 rural Australian hospitals over a 20-month period. The likelihood of LVO was evaluated by paramedics using the ambulance clinical triage for acute stroke treatment (ACT-FAST) severity-based triage algorithm, which demonstrated 76% sensitivity (95% CI 69% to 82%), 82% specificity (95% CI 79% to 84%), positive LR 4.2 (95% CI 3.3 to 5.1), and negative LR 0.30 (95% CI 0.2 to 0.39) for LVO and similar accuracy for predicting EVT. Theoretically, if ACT-FAST were incorporated into pre-hospital decision-making it would have reduced transport times to an EVT-capable hospital by 98 minutes for LVO patients, while increasing the number of suspected LVO patient arrivals at the EVT-capable hospital by between 3.5 to 9.5 patients per week.[30]

Eleven Class III studies were identified, which evaluated a variety of LVO decision aids, including LAMS, RACE, VAN, CPSS, C-STAT, G-FAST, PASS, Conveniently-Grasped Field Assessment Stroke Triage (CG-FAST), Face-Arm-Speech-Time plus severe arm or leg motor deficit (FAST-PLUS), field cut, aphasia, neglect, gaze preference, and dense hemiparesis (FANG-D), The 7-Item Japan Urgent Stroke Triage (JUST-7) score, and the NIHSS.[31-41] For brevity, this clinical policy will only highlight the diagnostic accuracy results for decision aids evaluated in >1 study and with the highest positive LR or lowest negative LR across studies. A systematic review of 19 instruments from 13 studies of 9,824 patients by Vidale et al reported sensitivities ranging from 60% to 100% and specificities from 31% to 90%. VAN (positive LR 10, negative LR 0) and LAMS ≥4 demonstrated superior accuracy to rule-in (positive LR 7.4) or rule-out (negative LR 0.21) LVO.[41] LAMS ≥4 was evaluated by 2 Class III studies[32,34] and RACE ≥5 by 3 Class III studies[32,36,38] with the accuracy results summarized in Table 2. Since only 1 study evaluated VAN, which evaluated 62 patients and received a grade of Class X by the methodologists, and was the only study on VAN included in the Class III systematic review by Vidale et al, VAN is not included in the recommendations.[41,42] Other than Lima et al, in which hospital personnel obtained each component of these decision aids, the elements for each decision aid were obtained by EMS personnel in pre-hospital settings. Based upon these Class III studies, LAMS and RACE are similarly accurate to identify individuals at higher risk for LVO (RACE positive LR range 2.7 to 5.6 compared with LAMS positive

LR range 2.6 to 5.4) or lower risk for LVO (RACE negative LR 0.22 to 0.52 compared with LAMS negative LR range 0.32 to 0.67).[32,34,36,38,41]

The definition of LVO varied between studies. For example, Duvekot et al[32] defined occlusions of the internal carotid artery, M1 or M2 segments of the middle cerebral artery, and A1 or A2 segments of the anterior cerebral artery as LVO. Helwig et al[34] defined LVO as occlusion of the internal carotid artery, M1 segment of middle cerebral artery, or the basilar artery. These subtle differences between studies in defining LVO are likely impactful for posterior circulation strokes since decision aids were often derived retrospectively from elements of the NIHSS, which was not designed to diagnose stroke or LVO and is a relatively inaccurate indicator of posterior circulation strokes in particular. None of the included studies evaluated between-rater reproducibility or EMS/physician acceptability of their use, which may impact integration and implementation into local healthcare protocols. Nonetheless, if the risk of LVO in a pre-hospital patient is 10%, then a LAMS ≥4 or RACE ≥5 would increase the probability of LVO in that individual from 22% to 38% for LAMS or from 23% to 38% for RACE. On the other hand, LAMS <4 or RACE <5 would decrease the probability of LVO to 3% from 7% for LAMS or to 2% from 5% for RACE. Individual healthcare systems currently using or considering incorporating LVO decision aids into stroke protocols should contemplate their objectives in selecting an instrument. In rural areas with prolonged travel times to EVT-capable hospitals, a higher positive LR is of more importance to avoid unnecessary transports. On the other hand, in urban areas with crowded EVT-capable hospitals decision aids with lower negative LR are more important to limit the unintended consequences of exacerbating ED crowding.[43]

Summary

Multiple pre-hospital decision aids exist with the intent to distinguish high-risk or low-risk suspected stroke patients for LVO. LAMS and RACE have the largest quantity and highest quality of research to support their incorporation into pre-hospital or non-EVT capable hospital stroke protocols, although the actual impact of their use on resource use, time-to-intervention, or EVT outcomes remains unevaluated.

Future Research

Based upon this clinical policy question and the research identified and included, multiple high priority areas exist for future investigators. ACT-FAST and VAN appear promising as LVO prediction instruments but await external validation and impact analysis. LAMS, RACE, VAN, and ACT-FAST also await inter-rater reproducibility assessment in real-world settings because neurological exam findings often fluctuate over short time intervals, and some elements of these instruments are subjective. In addition to measures of accuracy and reliability, future researchers should explicitly quantify the number of suspected stroke patients to be screened with each instrument in order to identify 1 patient likely to benefit from EVT. Since the definition of LVO varies across studies, comparative accuracy assessments for each instrument for the same subtypes of LVO are lacking. Between instrument impact analyses that quantify differences in pre-hospital scene times and time-to-EVT along with patient-centric outcomes of functional recovery are also lacking. Finally, the factors that promote or impede uptake of each instrument, including local culture, feasibility, adaptability, costs, fidelity, unintended consequences, and sustainability will be essential implementation components to evaluate in future research.

2. In adult patients with a suspected acute ischemic stroke, does the addition of perfusion imaging to a CTA or MRA identify patients more likely to benefit from thrombectomy?

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. None specified.

Level C recommendations. Obtain CT or MR perfusion imaging in patients with acute ischemic stroke due to LVO, especially if the time the patient was last known normal was between 6 to 24 hours prior to arrival to the emergency department.

Potential Benefit of Implementing the Recommendations:

- Otherwise ineligible patients who present later in their stroke course may become eligible for EVT, leading to improved patient outcomes.
- Patients most likely to benefit from endovascular thrombectomy can be distinguished from those without salvageable brain tissue in whom risks outweigh benefits.

Potential Harm of Implementing the Recommendations:

- More patients may receive advanced imaging, potentially leading to increased costs, more radiation exposure, and preventable patient care delays.

- More patients may be transferred to an EVT-capable center for advanced imaging alone, potentially leading to increased costs, preventable patient care delays, and increased hospital crowding at the receiving EVT-capable hospital.

Key words/phrases for literature searches: brain ischemia, cerebral arterial disease, cerebral arterial infarction, computed tomography Angiography, CT angiography, CTA, emergency medicine, hospital emergency service, magnetic resonance angiography, mechanical thrombolysis, middle cerebral artery infarction, MRA, MRI angiography, perfusion imaging, perfusion magnetic resonance imaging, perfusion scintigraphy, stroke, thrombectomy, and variations and combinations of key words/phrases. Searches included all dates up to the search dates of November 19, 24, and 25, 2020, and December 3, 2020.

Study Selection: Two hundred fifty-two articles were identified in the searches. Thirty-four articles were identified from the search results as candidates for further review. After grading for methodological rigor, zero Class I studies, zero Class II studies, and 3 Class III study was included for this critical question (Appendix D).

Historically, when evaluating patients with a potential stroke, emergency physicians used imaging to exclude intracranial hemorrhage that would make therapies such as thrombolytics unsafe.[44] In the past decade, the imaging paradigm has evolved towards the addition of advanced imaging such as CTA and CTP to identify patients who may benefit from EVT.[45] With perfusion imaging, the amount of brain tissue that appears to be infarcted, also known as the ischemic core, and the amount of brain tissue that is hypoperfused and at risk for infarction, or the penumbra, can be quantified. It is hypothesized that CTP may be able to select patients who are more likely to benefit from EVT.

A Class III study by Marks et al assessed the relationship of angiographic collateral score to the target mismatch profile and clinical outcomes.[46] The study included patients within 12 hours of stroke onset due to an LVO. Patients underwent magnetic resonance (MR) diffusion-weighted imaging and perfusion-weighted imaging. MR data was used to calculate an ischemic core as well as hypoperfused tissue in order to calculate a target mismatch profile. The target mismatch profile was defined as a ratio between hypoperfused tissue and ischemic core of $\geq$1.8, with an absolute difference of 15 mL. Additional criteria were an ischemic core $\leq$70 mL and volume of tissue with severe hypoperfusion $\leq$100 mL. Sixty patients with a target mismatch were included. Collateral score correlated with the amount of hypoperfused tissue. Good neurologic outcome at 90 days was related to reperfusion scores, regardless of collateral score. In patients with good reperfusion, the odds ratio (OR) of a good neurologic outcome at 90 days was 12.0 (95% CI 1.6 to 98) in patients with a poor collateral score and 4.7 (95%

CI 0.8 to 26) in patients with a good collateral score. The study suggests that endovascular therapy can benefit patients with a target mismatch profile on MR perfusion imaging, regardless of collateral score.

Campbell et al was another Class III study which randomized patients to IV alteplase plus EVT versus IV alteplase alone based on CTP findings.[45] It was a prospective, randomized, open-label study of patients with acute ischemic stroke within 4.5 hours who were treated with IV alteplase. Patients were selected if the stroke was caused by anterior circulation LVO and if CTP imaging showed an ischemic core <70 mL, a ratio of hypoperfused tissue to ischemic core >1.2, and an absolute difference of 10 mL. Perfusion imaging was analyzed via proprietary automated software (RAPID, iSchemaView). The trial enrolled 70 patients but was stopped early by the data and safety monitoring board due to superior efficacy. Patients who received EVT had improved functional outcomes based on an OR of 4.2 (95% CI 1.4 to 12) for a modified Rankin score (mRS) of 0 to 2 at 90 days. Two patients who received EVT developed parenchymal hematomas, and 1 developed a groin hematoma that required a blood transfusion.

Nogueira et al was a prospective, randomized, open-label Class III study sponsored by Stryker Neurovascular that enrolled patients with acute ischemic stroke due to anterior LVO, symptom onset within 6 to 24 hours, and a mismatch between the severity of their clinical deficit and infarct volume.[47] The definition had 3 groups. The first group consisted of patients 80 years or older, an NIHSS $\geq$10, and an infarct volume <21 mL. The second group consisted of patients less than 80 years old, an NIHSS $\geq$10, and an infarct volume <31 mL. The third group consisted of patients less than 80 years old, an NIHSS $\geq$20, and an infarct volume of 31 to <51 mL. Infarct volume was assessed via magnetic resonance imaging (MRI) or CTP imaging. Perfusion imaging was also analyzed via automatic software (RAPID, iSchemaView). Patients were randomized to standard medical care versus standard medical care plus thrombectomy. A total of 206 patients were enrolled, but the trial was stopped early due to efficacy. Infarct volume was slightly smaller in patients randomized to thrombectomy, 7.6 mL versus 8.9 mL. Time since symptom onset was slightly shorter in patients randomized to thrombectomy, 12.2 hours versus 13.3 hours. NIHSS was similar between both groups. A score of 0 to 2 of the mRS scale at 90 days was achieved in 49% of patients in the EVT group versus 13% in the control group, an adjusted difference of 33% (95% CI 21 to 44). Death at 90 days was similar, 19% versus 18%. Symptomatic intracranial hemorrhage (ICH) at 24 hours was seen in 6% versus 3%.

Summary

CTP imaging can be used to assess the volume of infarcted and hypoperfused brain tissue in patients with an acute ischemic stroke. Based upon this indirect evidence in which patients were randomized to perfusion-guided EVT with thrombolysis or thrombolysis alone rather than more direct evidence that randomized stroke patients to EVT with perfusion imaging or EVT without perfusion imaging, advanced imaging is associated with better EVT outcomes. The number needed to treat (NNT) to avoid EVT in patients who have recanalized with thrombolytic therapy is 9. If patients have a favorable perfusion imaging profile, they may benefit from EVT up to 24 hours after they were last known to be normal. Of note, while other guidelines suggest using non-contrast CT imaging, ie the ASPECTS score, to assess for EVT eligibility within a certain time frame, our review did not assess this question.[3]

Future Research

Future studies should seek to find the optimal ratio of ischemic core to penumbra at which patients can be chosen for EVT. Studies should also evaluate if patients with favorable perfusion imaging could benefit from EVT regardless of the time of last known normal. Studies should seek to evaluate the cost-effectiveness of perfusion imaging, including quantifying the number needed to scan with perfusion imaging in order to identify 1 patient likely to benefit from EVT. Additionally, studies could evaluate whether perfusion imaging could be used to guide the decision on whether to administer thrombolytic therapy, including in patients without LVO. Lastly, future studies should look at pathways improving the timing of perfusion imaging to prevent delays in identifying patients who are candidates for intervention. This includes which patients should get perfusion imaging upfront prior to confirmation of an LVO.

3. In adult patients with a suspected acute ischemic stroke qualifying for IV thrombolysis, is tenecteplase safe and effective when compared with alteplase?

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. Use either tenecteplase or alteplase in patients with acute ischemic stroke who qualify for thrombolysis.

Level C recommendations. None specified.

Potential Benefit of Implementing the Recommendations:

- Reduce errors in administration compared with alteplase.
- Improved short term neurological outcomes.
- Improve the ease of patients needing to be transferred to a stroke facility.
- Improved 3-month outcomes in patients with confirmed LVO.

Potential Harm of Implementing the Recommendations:

- Incorrect dosing may increase risk of complications.

Key words/phrases for literature searches: alteplase, brain ischemia, cerebral arterial disease, cerebral arterial infarction, emergency medicine, fibrinolytic agents, fibrinolytic therapy, hospital emergency service, intravenous thrombolysis, intravenous thrombolytics, IV thrombolysis, IV thrombolytics, large vessel occlusion, metalyse, rtPA, rt-PA, stroke, Tenecteplase, thrombolytic therapy, tissue plasminogen activator, TNKase, tPA, t-PA, and variations and combinations of key words/phrases. Searches included all dates up to the search dates of November 19, 24, and 25, 2020, and December 4 and 5, 2020.

Study Selection: Five hundred ninety-seven articles were identified in the searches. Twenty-four articles were identified from the search results as candidates for further review. After grading for methodological rigor, zero Class I studies, 5 Class II studies, and 13 Class III studies was included for this critical question (Appendix D).

Tenecteplase is a genetically engineered form of tissue plasminogen activator that is more fibrin-specific and has a longer half-life than alteplase. Due to its longer half-life, tenecteplase can be administered as a single bolus over 5 seconds.[48] In contrast, alteplase requires a bolus followed by a continuous infusion for 60 minutes, making tenecteplase easier to administer. One study reported a 64% dosing/administration error rate in stroke patients who received alteplase.[49] Because of the ease of administration, there is interest in using tenecteplase instead of alteplase for acute stroke thrombolysis. This question will explore the evidence of tenecteplase as an alternative to alteplase for both clinical and safety outcomes.

Randomized Controlled Trials

Eight studies were identified with 7 RCT and 3 subgroup analysis from a single RCT. In a Class II study, the EXTEND-IA TNK trial[50] randomized 202 acute stroke patients who had an occlusion of either the internal carotid artery, middle cerebral artery, or basilar artery within 4.5 hours of onset to either tenecteplase (0.25 mg/kg,

maximum dose 25 mg) or alteplase (0.9 mg/kg, maximum dose 90 mg). The primary outcome of reperfusion ≥50% of the involved ischemic territory or absence of retrievable thrombus at the time of angiography occurred in 22% with tenecteplase versus 10% with alteplase (adjusted incidence ratio 2.2, 95% CI 1.1 to 4.4). Median 90-day mRS was better in the tenecteplase group than the alteplase group (2 versus 3, common OR 1.7, 95% CI 1.0 to 2). Symptomatic ICH occurred in 1% of patients in both groups.

In another Class II study, The Norwegian Tenecteplase Stroke Trial (NOR-TEST)[51] enrolled 1,107 patients that presented within 4.5 hours of an acute ischemic stroke or from waking up with an acute ischemic stroke to receive either alteplase 0.9 mg/kg (maximum dose 90 mg) or tenecteplase 0.4 mg/kg (maximum dose 40 mg). Primary outcome was a 3-month mRS score of 0 to 1 and was achieved in 64% in the tenecteplase group and 63% in the alteplase group (OR 1.08; 95% CI 0.84 to 1.38). Secondary outcomes such as major clinical improvement (ie, NIHSS score of 0 or an improvement of at least 4 points at 24 hours), ICH, symptomatic ICH, and death were similar between 2 groups.

In a Class III study, the AcT trial randomized 1,577 patients to receive either alteplase (0.9 mg/kg) or tenecteplase (0.25 mg/kg).[52] Non-inferiority was achieved as the primary outcome with an mRS of 0 to 1 at 90 to 120 days (36.9% in the tenecteplase group compared with 34.8% in the alteplase group). Safety outcomes such as 24-hour symptomatic ICH and 90-day mortality were similar between both groups.[52]

In a Class III study, Parsons et al conducted a phase 2b trial (Australian-TNK) randomizing 75 patients who presented with a hemispheric stroke within 6 hours of onset that had an intracranial occlusion of the anterior, middle, or posterior cerebral artery on CTA and a perfusion lesion at least 20% greater than infarct-core lesion on CTP imaging.[53] Patients were randomized to receive alteplase 0.9 mg/kg (maximum dose of 90 mg), tenecteplase 0.1 mg/kg (maximum dose 10 mg), or tenecteplase 0.25 mg/kg (maximum dose 25 mg). Primary co-endpoints were the percentage of perfusion lesions that were perfused and the change in NIHSS after treatment at 24 hours. For the co-primary endpoints, the percentage of reperfusion at 24 hours was higher in the combined tenecteplase group than alteplase (79.3% versus 55.4%, difference 23.9%; 95% CI 8.1 to 39.7) as well as improvement in NIHSS score between baseline and at 24 hours (mean change 8.0 versus 3.0, difference 5.0; 95% CI 2.2 to 7.8). Tenecteplase at 0.25 mg/kg was superior for both co-primary endpoints compared with tenecteplase at 0.1 mg/kg (complete perfusion at 24 hours: 88.8% versus 69.3%, difference 19.5%, 95% CI 3.9 to 35.1; mean NIHSS

improvement 9.6 versus 6.3, difference 3.3, 95% CI 0.3 to 6.3). Symptomatic ICH was similar between all 3 groups.

In a Class III study, the Alteplase-Tenecteplase Trial Evaluation for Stroke Thrombolysis (ATTEST) trial[54] enrolled 104 patients who were randomized to receive either alteplase (0.9 mg/kg, maximum dose 90 mg) or tenecteplase (0.25 mg/kg, maximum dose 25 mg) within 4.5 hours of onset. Primary outcome of percentage of penumbra salvaged did not differ between the 2 groups (68% versus 68%). Safety outcomes including any ICH or symptomatic ICH did not differ between the 2 groups.

The TASTE-A trial, a Class III study, was a phase 2, open-label, prehospital trial utilizing a mobile stroke unit that enrolled 104 patients.[55] Patients received either tenecteplase at 0.25 mg/kg or alteplase at 0.9 mg/kg. Primary outcome of perfusion lesion upon arrival to the hospital was smaller in the tenecteplase group compared with the alteplase group (adjusted incidence ratio of 0.55; 95% CI 0.37 to 0.81). Secondary outcomes such as 90-day mRS, symptomatic ICH, any ICH, and death were similar between both groups. The NOR-TEST 2, part A trial, another Class III study, enrolled 204 patients in an open-label, phase 3 trial.[56] In this trial, patients were randomized to receive either tenecteplase at 0.4 mg/kg or alteplase at 0.9 mg/kg. This study was terminated early due to safety reasons. Primary outcomes of favorable functional outcome (ie, mRS 0 to 1 at 3 months) was lower with tenecteplase compared with alteplase (32% versus 51%; unadjusted OR 0.45; 95% CI 0.25 to 0.80). Complications such as any ICH, symptomatic ICH, and 30-day mortality were higher with tenecteplase. Of note, part B of NOR-TEST 2 is evaluating tenecteplase at 0.25 mg/kg and is still ongoing as of this writing.

Three Class III studies involved subgroup analysis from the NOR-TEST trial were also included. Patients who had moderate stroke (NIHSS 6 to 14) or severe stroke (NIHSS ≥15) had similar outcomes between alteplase or tenecteplase.[57] Similar outcomes were also seen in patients treated between 3 to 4.5 hours as well as patients ≥80 years old.[58,59]

Meta-analyses

Three Class II and 5 class III meta-analyses were included.[60-69] These meta-analyses utilized similar studies, differing in patient cohorts evaluated.[50,51,53,54,68,69] The outcomes evaluated were similar and included excellent functional outcomes (ie, mRS 0 to 1 at 3 months), good functional outcomes (ie, mRS 0 to 2 at 3

559 months), and early neurological improvement (ie, ≥8 point difference in NIHSS at 24 hours). Safety measures
560 were also similarly defined for dependency (ie, mRS 3 to 5) and mortality (ie, death at 3 months). Recanalization
561 and symptomatic ICH were defined based on individual study definitions that were included. Other outcome
562 measures for each study are described separately.

563 In a Class II study, Burgos et al[60] reviewed 5 trials that included 1,585 patients. Their primary endpoint
564 was non-inferiority of tenecteplase compared with alteplase with an mRS of 0 to 1 at 3 months. The risk
565 difference between tenecteplase compared with alteplase was 4% favoring tenecteplase (95% CI, –1% to 8%),
566 meeting the predefined assessed noninferiority margin. In another Class II study, Xu et al[61] included 4 trials that
567 had a total of 1,390 patients. In their analysis, all doses of tenecteplase were superior to alteplase in early
568 neurologic improvement (relative risk [RR] 1.52; 95% 1.03 to 2.25) with tenecteplase 0.25 mg/kg superior to
569 other tenecteplase doses (RR 2.1; 95% CI 1.43 to 3.09). Lastly, in another Class II study, Thelengana et al[62]
570 evaluated 4 trials that included 1,334 patients. In their analysis, tenecteplase was found to be superior to alteplase
571 in early major neurological improvement (RR 1.56; 95% CI 1.00 to 2.43). All other outcomes such as excellent
572 and good functional outcomes, recanalization at 24 or 48 hours, any ICH, symptomatic ICH, and mortality were
573 similar between tenecteplase and alteplase.

574 Three Class III meta-analyses evaluated similar trials.[63-65] In a Class III study consisting of 3 trials of 291
575 patients,[63] only tenecteplase 0.25 mg/kg showed superiority to alteplase in early neurological improvement (OR
576 1.9; 95% CI 0.8 to 4.4). All other clinical outcomes and safety measures did not show a statistical difference.
577 Similarly in a study of 5 trials of 1,585 patients,[64] tenecteplase was found to be superior to alteplase only in rates
578 of recanalization (OR 2.01; 95% CI 1.04 to 3.87) and early neurological improvement (OR 1.43; 95% CI 1.01 to
579 2.03). No difference in safety or other clinical outcomes were noted between the 2 drugs. Lastly, in a study
580 consisting of 6 trials with 5 comparing tenecteplase with alteplase,[65] tenecteplase had significantly improved early
581 major neurological improvement compared to alteplase (RR 1.59; 95% CI 1.08 to 2.34) and reduced parenchymal
582 hematoma (RR 0.26; 95% CI 0.10 to 0.71). No other differences in clinical or safety outcomes were observed.

583 In a Class III study, Bivard et al[66] combined the results of ATTEST and Australian-TNK trials. Overall,
584 there was no difference with early clinical improvement, excellent functional outcome, or poor functional
585 outcome (ie, mRS 5 to 6) in patients receiving either tenecteplase or alteplase. However, in a subgroup of patients

that had documented target mismatch by advanced imaging (33 tenecteplase, 35 alteplase), tenecteplase had greater early clinical improvement (median NIHSS score change 6 versus 1), higher excellent functional outcomes (OR 2.33; 95% CI 1.13 to 5.94), and less poor functional outcomes (mRS 5 to 6: OR 0.3; 95% CI 0.09 to 0.97).

Lastly, in a Class III meta-analysis looking at tenecteplase versus alteplase in patients with confirmed LVO,[67] 4 studies were identified that included 433 patients. Patients receiving tenecteplase had higher odds of good functional outcome (OR 2.06; 95% CI 1.15 to 3.69), successful recanalization (OR 3.05; 95% CI 1.73 to 5.40), and better functional improvement defined as a 1-point decrease across all mRS grades (common OR 1.84; 95% CI 1.18 to 2.87) at 3 months compared with alteplase. No difference in excellent functional outcome, early neurological improvement, ICH, symptomatic ICH, or mortality at 3 months were found.

Summary

Multiple RCTs show either an improvement in early neurological outcomes or no difference between tenecteplase versus alteplase except for 1 Class III trial, which utilized a tenecteplase dose of 0.4 mg/kg.[56] Similarly, multiple meta-analyses show an improvement in early neurological improvement with tenecteplase, especially at 0.25 mg/kg compared with alteplase, with all other outcome and safety measures showing no difference between the 2 drugs.[60-67] However, because the use of thrombolytics in acute stroke requires coordination of care with multiple stakeholders, the use of tenecteplase should be adopted ideally as part of an institutional protocol.

Future Research

Although the current literature suggests that tenecteplase is non-inferior to alteplase, more studies are needed to evaluate optimal dosing of tenecteplase. Also, research into other cohorts comparing alteplase with tenecteplase including patients with different types of stroke (eg, different types of LVO, before and after thrombectomy, extended thrombolytic window) should be evaluated.

4. In adult patients who present with acute vertigo with possible stroke, are there history or physical exam findings (eg, Head Impulse-Nystagmus-Test of Skew [HINTS] exam) that can risk stratify for acute ischemic stroke?

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. None specified.

Level C recommendations. In addition to a standard comprehensive history and physical exam, physicians may use specific findings such as ABCD2 score, oculomotor examination, presence of additional neurologic deficits, and HINTS to risk stratify patients with possible stroke.

Prior to employing a maneuver such as HINTS, physicians should have sufficient education to perform the technique (Consensus recommendation).

Potential Benefit of Implementing the Recommendations:

- Use of current risk stratification tools may lead to an increased risk of misdiagnosis.

Potential Harm of Implementing the Recommendations:

- Without adequate risk stratification tools, patients are more likely to be admitted.
- Without adequate risk stratification tools, patients are more likely to undergo expensive testing (eg, MRI) and prolonged lengths of stay.
- Not using tools such as HINTS may lead to excessive testing and admission.

Key words/phrases for literature searches: acute ischemic stroke, acute vertigo, bedside testing, brain ischemia, cerebral arterial disease, cerebral arterial infarction, Dix-Hallpike, dizziness, emergency medicine, Head-Impulse—Nystagmus—Test-of-Skew, HINTS, HINTS exam, HINTS test, hospital emergency service, large vessel occlusion, physical examination, physiologic nystagmus, point of care, point-of-care testing, stroke, vertigo, and variations and combinations of key words/phrases. Searches included all dates up to the search dates of November 20 and 25, 2020, and December 3 and 4, 2020.

Study Selection: Five hundred twenty-six articles were identified in the searches. Thirty-seven articles were identified from the search results as candidates for further review. After grading for methodological rigor, zero Class I studies, zero Class II studies, and 2 Class III study was included for this critical question (Appendix D).

Dizziness or vertigo is a common presentation to the ED, comprising over 3.9 million presentations per year and an annual cost of $3.9 billion.[70] Patients presenting with dizziness have an increased likelihood of imaging, longer ED lengths of stay, and higher admission rates compared with other ED patients.[71] However, only approximately 3.3% of cases ultimately have a cerebrovascular etiology.[70]

There have been numerous attempts to identify historical features, physical examination findings, and clinical decision tools to guide the assessment of patients in order to reduce unnecessary imaging and admissions. Two commonly described and studied clinical decision tools include the ABCD2 (age, blood pressure, clinical features, duration, and diabetes) score and the HINTS examination. The ABCD2 is considered low-risk when the score is less than 4, while the HINTS examination is considered low-risk if all 3 findings are not consistent with stroke (ie, suggestive of a peripheral etiology). However, most studies have been limited by performance outside the ED setting by non-emergency physicians. While we identified several studies in our review that involved formal training programs for maneuvers such as HINTS,[72-74] these studies were among a limited number of emergency physicians and received a grade of Class X due to methodological issues. As such, none of the studies included reviewed training requirements.

In a Class III study, Kerber et al[75] prospectively evaluated patients presenting to the ED with acute dizziness without an obvious cause using MRI as the industry standard for stroke. They assessed history, the ABCD2 score, the HINTS examination, and performed a general neurologic examination. All examinations were performed by either a neurologist, who was fellowship trained in neuro-otology, or an emergency medicine physician who was fellowship trained in vascular neurology. They enrolled 272 patients (10.7% stroke). Most parameters had limited utility for diagnosing stroke, with the most useful components being the ABCD2 score (OR 1.74; 95% CI 1.20 to 2.51), a central pattern of nystagmus (OR 3.56; 95% CI 1.55 to 8.16), and concomitant neurologic symptoms (eg, visual field deficit, dysmetria, sensory symptoms/deficits; OR 2.54; 95% CI 1.06 to 6.08). Additionally, the authors found that none of these findings in isolation were able to adequately stratify patients as low-risk, with the stroke frequency in the low-risk groups being >5% for all the components. The HINTS examination also did not demonstrate a statistically significant difference (OR 2.82; 95% CI 0.96 to 8.30), though the wide confidence intervals do not exclude that a meaningful difference may exist. This study was limited in that all examinations were performed by either a neurologist who was fellowship trained in neuro-otology or an emergency physician who was fellowship trained in vascular neurology, which may not reflect the average emergency physician.

In another Class III study, Ohle et al[76] performed a systematic review and meta-analysis of the diagnostic accuracy of the HINTS examination to rule out a central cause of vertigo. The meta-analysis included five studies

(N=617 participants; 34.8% stroke) and demonstrated that the HINTS examination was 96.7% sensitive (95% CI 93.1% to 98.5%) and 94.8% specific (95% CI 91% to 97.1%) when performed by neurologists. However, when the HINTS examination was performed by a cohort of emergency medicine physicians and neurologists, the sensitivity decreased to 83% (95% CI 63% to 95%) and specificity decreased to 44% (95% CI 36% to 51%).

Summary

There is limited data evaluating the role of historical or physical examination features, alone or in combination, to accurately risk stratify patients with acute vertigo from possible stroke included in this clinical policy. The included studies suggest that the history and physical examination findings, alone or as combined tools, should not be used in isolation as they are unable to adequately risk stratify patients with acute ischemic stroke even when performed by trained emergency medicine physicians.

Future Research

Future research would benefit from additional trials assessing the diagnostic accuracy of emergency physicians for identifying acute ischemic stroke using existing features and risk assessment tools. Studies should also be performed to identify the ideal training to enhance emergency physician accuracy with tools such as the HINTS examination. Research should also evaluate the impact of technology (eg, Frenzel goggles, ocular tracking software) to enhance the potential accuracy of the HINTS examination. Additional research could also involve the derivation of new diagnostic tools to assess for the presence of acute ischemic stroke among patients presenting with acute vertigo, as well as the derivation of new decision tools using a combination of existing tests to enhance risk stratification.

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 impact the specific aspect of disease addressed in the critical question.

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Appendix A. 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 B. Approach to downgrading strength of evidence.

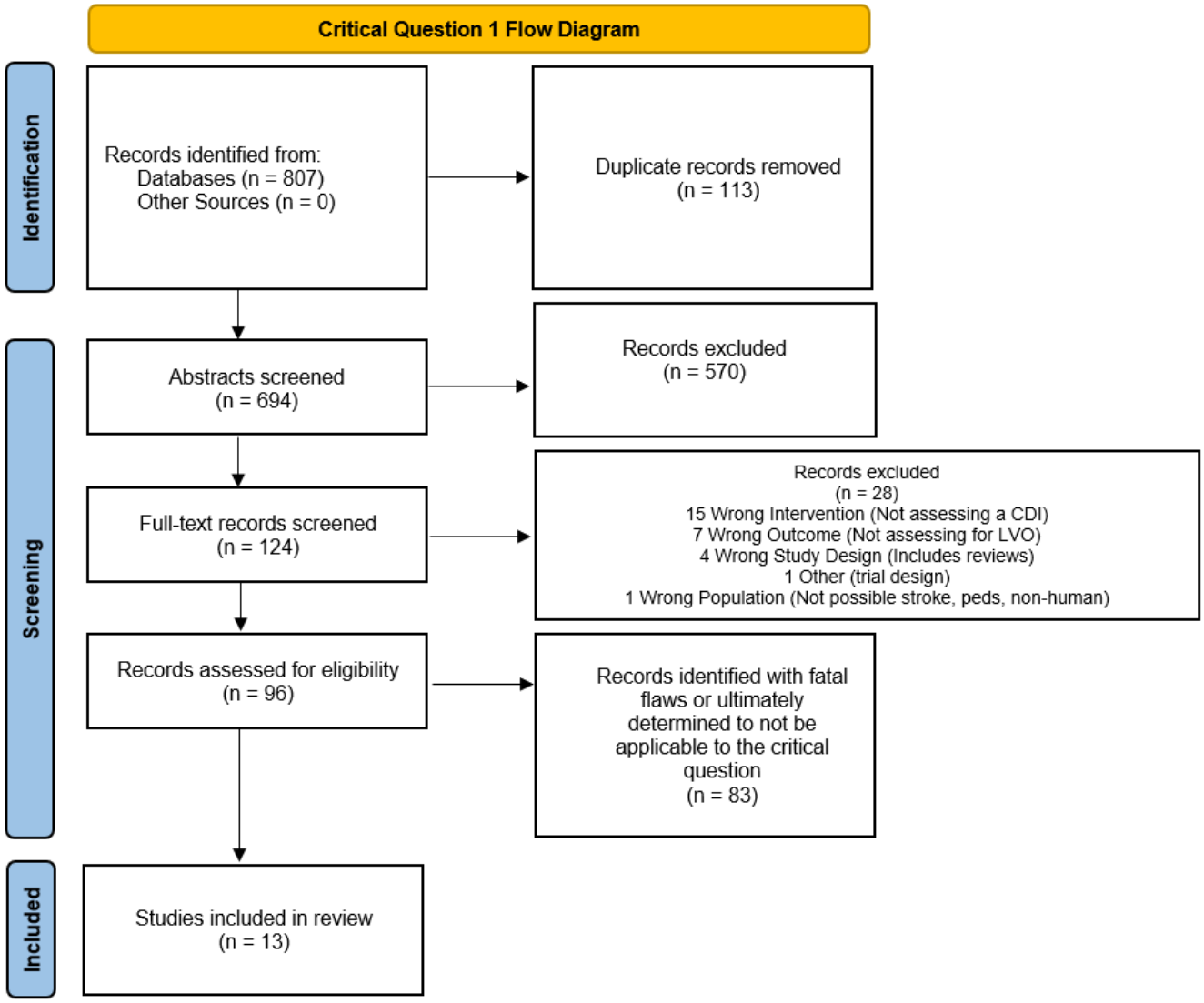
	Design/Class		
Downgrading	**1**	**2**	**3**
None	I	II	III
1 level	II	III	X
2 levels	III	X	X
Fatally flawed	X	X	X

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

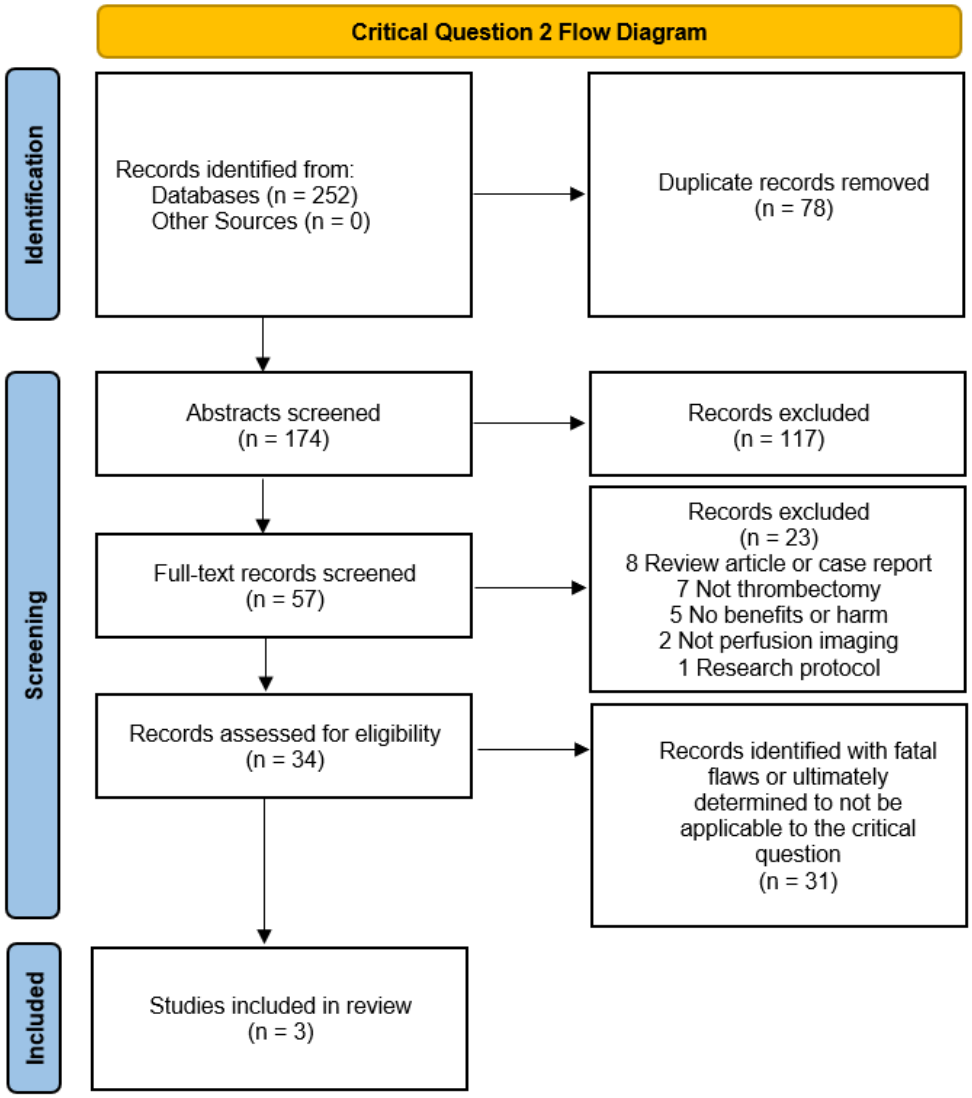
LR (+)	LR (–)	
1.0	1.0	Does not change pretest probability
1–5	0.5–1	Minimally changes pretest probability
10	0.1	May be diagnostic if the result is concordant with pretest probability
20	0.05	Usually diagnostic
100	0.01	Almost always diagnostic even in the setting of low or high pretest probability

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).

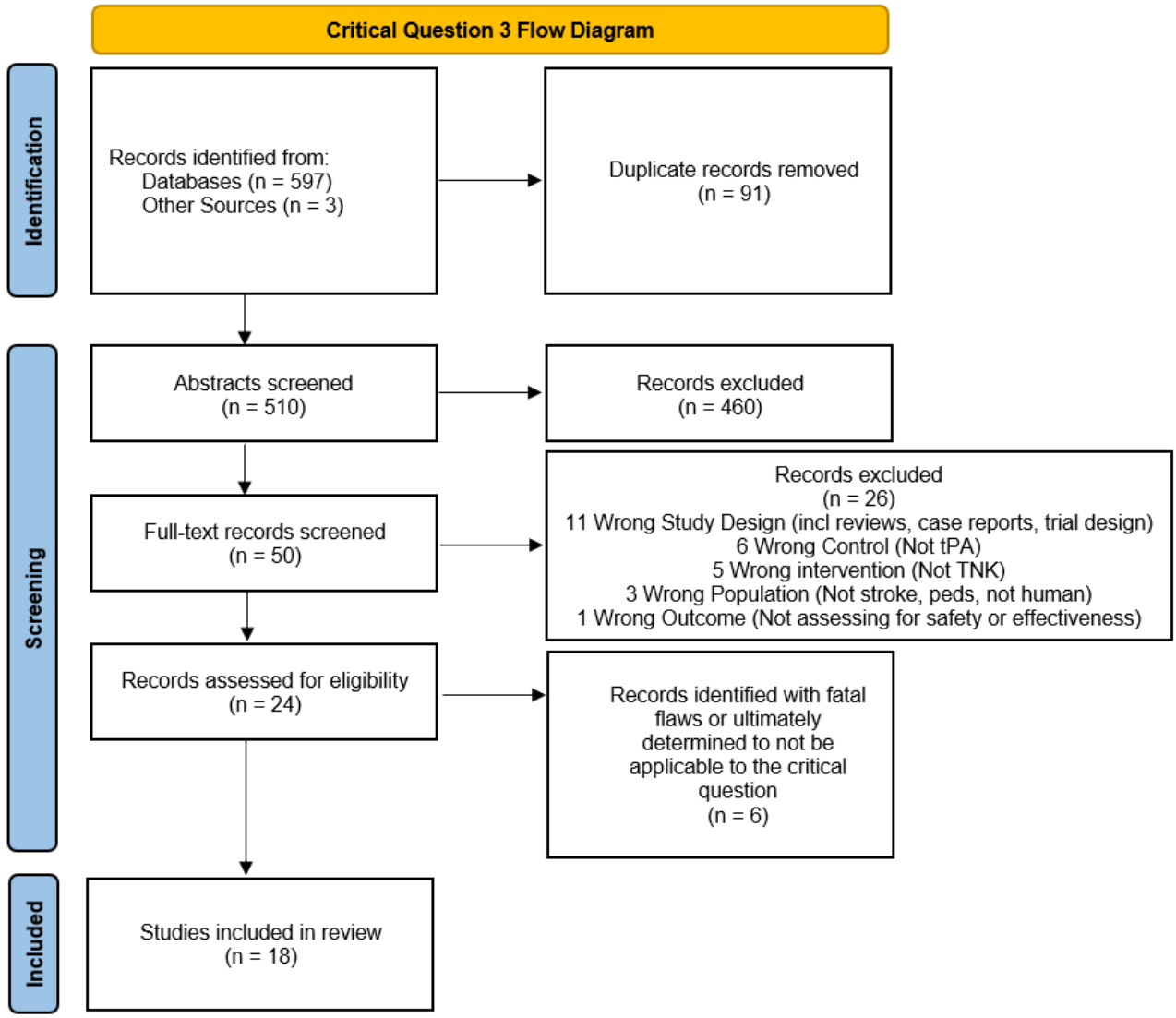
Appendix D. PRISMA[12] flow diagrams.



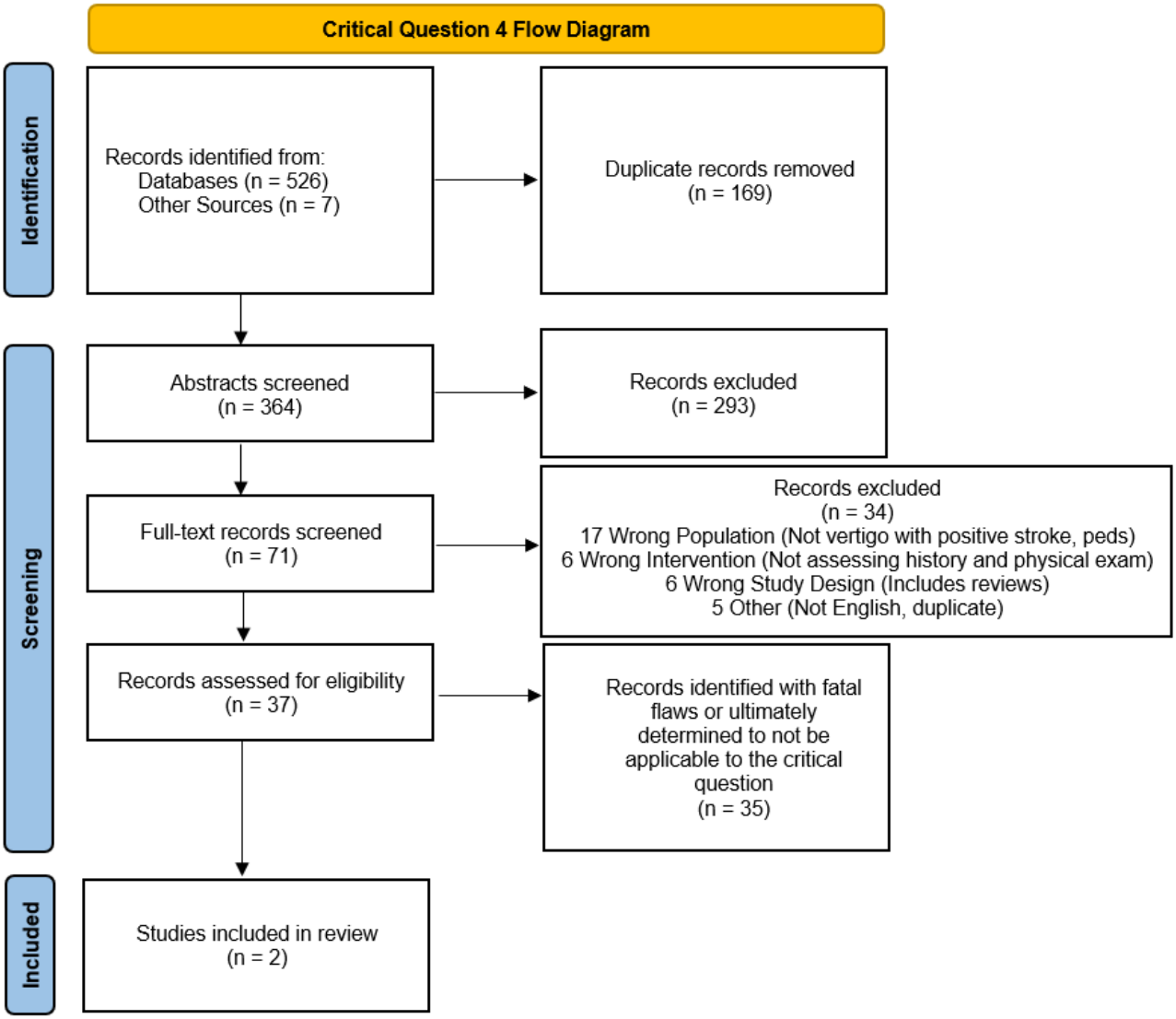
Appendix D. PRISMA flow diagrams. (Continued)



Appendix D. PRISMA flow diagrams. (Continued)



Appendix D. PRISMA flow diagrams. (Continued)



996 **Evidentiary Table.**

Author & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Nguyen et al[29] (2021)	II for Q1	Prospective cohort study; patients recruited from the Leiden and The Hague regions, Netherlands, encompassing 2 EMS systems, 3 comprehensive stroke centers, and 4 primary stroke centers, serving a total population of approximately 2 million	Externally validated field performance, of 7 prediction scales; an acute stroke code was initiated by EMS if there was a prehospital suspicion of acute stroke with a positive FAST or other focal neurologic symptoms; when symptom onset or last seen well was 6 hours or less, it was routine policy to transport these patients to the nearest hospital, and when symptom onset was 6 to 24 hours, it was policy to transport patients to a comprehensive stroke center; primary outcome was symptomatic large anterior vessel occlusion (sLAVO) clinically assessed by the treating stroke team taking the following radiologic criteria into account: occlusion of the intracranial carotid	N=2,007, 41% with stroke diagnosis, 7.9% with sLAVO; C-STAT ≥2: Sensitivity: 0.62 (95% CI 0.54 to 0.69) Specificity: 0.80 (95% 0.78 to 0.82) PPV: 0.21 (95% 0.18 to 0.24) NPV: 0.96 (95% 0.95 to 0.96) PASS ≥2: Sensitivity: 0.55 (95% 0.47 to 0.64) Specificity: 0.83 (95% 0.81 to 0.85) PPV: 0.21 (95% 0.18 to 0.25) NPV: 0.95 (95% 0.95 to 0.96) G-FAST ≥3 Sensitivity: 0.61 (95% 0.53 to 0.69) Specificity: 0.84 (95% 0.82 to 0.86) PPV: 0.24 (95% 0.21 to 0.27) NPV: 0.96 (95% 0.95 to 0.97)	Study strength: study included mimics and SAH cases providing more accurate performance characteristics; likely more severe scores got more imaging; no adjudication mentioned of unclear findings; seems that RACE was used, for transport, and NIHSS for clinical decisions, while the other scores were just calculated for later analysis; filling out these scores also might have swayed EMS transport and care decisions; excluded 805 acute stroke codes (28.6%), because no application was used (752 [26.7%]) or because no clinical data were available in the electronic patient record (53 [1.9%])

			artery, tandem intracranial carotid artery, MCA (M1 or M2 segment), or ACA (A1 or A2 segment)	FAST-ED ≥4 Sensitivity: 0.60 (95% 0.53 to 0.69) Specificity: 0.85 (95% 0.83 to 0.87) PPV: 0.25 (95% 0.22 to 0.29) NPV: 0.96 (95% 0.95 to 0.97) RACE ≥5 Sensitivity: 0.56 (95% 0.46 to 0.65) Specificity: 0.90 (95% 0.89 to 0.92) PPV: 0.32 (95% 0.27 to 0.38) NPV: 0.96 (95% 0.95 to 0.97) LAMS ≥4 Sensitivity: 0.38 (95% 0.29 to 0.46) Specificity: 0.93 (95% 0.91 to 0.94) PPV: 0.28 (95% 0.22 to 0.34) NPV: 0.95 (95% 0.94 to 0.96)	

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998 **Evidentiary Table. (continued)**

Author & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Zhao et al[30] (2021)	II for Q1	Prospective cohort study; patients recruited by Ambulance Victoria, the sole public provider of emergency services to a population of 5.33 million in the greater metropolitan Melbourne area; 15 metropolitan and 17 rural hospitals, incorporating a mixture of comprehensive, primary, telemedicine-enabled, and non-stroke designated centers	Evaluated the ambulance clinical triage for acute stroke treatment (ACT-FAST) severity-based triage algorithm to diagnose LVO; LVO defined as intra-cranial ICA, M1 and basilar artery occlusions, representing those generally regarded as eligible for EVT; and extended definitions not eligible for EVT	N=517; 54.4% were transported to a non-comprehensive stroke center, including 14.9% (77/517) patients transported to a rural or regional hospital; ACT-FAST positive in 32.5% (168/517) cases; hospital brain imaging data identified ICA/ M1/BA occlusion in 17.8% (92/517) ; sensitivity 82.6; specificity 77.9; PPV 44.7; NPV 95.4; AUC 0.802 (0.75 to 0.85); estimates also provided for extended definitions including comprehensive center needed (including LVO/ICH/tumor) etc	Scores determined triage, so there is work up bias for patients sent to higher level of care centers; investigators paid by pharma; attrition from those seen to those having assessments was not reported
Demeestere et al[31] (2017)	III for Q1	Retrospective cohort study; single academic institution in Australia and a comprehensive stroke center	Consecutive patients for whom the stroke team was activated by EMS and assessed by the stroke team on arrival from 2012 to 2016; retrospective assessment of the NIHSS and neuro-imagining; outcome=LVO	N=551: N=381 confirmed ischemic stroke, N=136 with LVO; National Institutes of Health Stroke Scale-8 (NIHSS-8) had area under AUROC of 0.82 for LVO; NIHSS-8 with a cut-off of 8 or more had a sensitivity=81% and specificity=75%	Limited by retrospective assessment, although NIHSS-8 was applied prospectively; single center in an established system that may limit generalizability; need for external validation

Evidentiary Table. (continued)

Author & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Duvekot et al[32] (2021)	III for Q1	Multi-center prospective observational cohort including eight hospitals and two ambulance services in southwest Netherlands	The primary objective was to validate and quantitatively compare the accuracy of 8 pre-hospital stroke scales for the diagnosis of LVO in persons with suspected stroke; inclusion criteria included at least one abnormality on the FAST test, age >18, normal glucose, and symptom onset <6 h prior; paramedics in the Netherlands are registered nurses with specialized education in emergency medicine, intensive care, or anesthesiology and prior to the study FAST was used routinely in suspected stroke. Prior to the study, paramedics received training on the study protocol and use of a mobile app to enter all components of each LVO decision instrument; 4 neuroradiologists and three interventional neuroradiologists determined presence or absence of LVO from CTA; LVO defined by occlusion of ICA, M1 or M2 segment of MCA, A1 or A2 segment of ACA	Among 1,039 included patients, median age 72, 12% diagnosed with LVO, and 25% with a stroke mimic; AUCs ranged from 0.72 for face-Arm-Speech-Time plus severe arm or leg motor deficit (FAST-PLUS) to 0.83 for RACE, but the clinician NIHSS was superior to all the pre-hospital stroke scales AUC 0.86 (95% CI 0.83 to 0.89); among all the pre-hospital stroke scales using the cutoff points originally described for each, RACE ≥5 demonstrated the highest combined sensitivity 67% (95% CI 58 to 75) and specificity 87% (95% CI 85 to 89); sensitivity analysis demonstrated no significant change in AUC when BA occlusions were included as LVO	EVT was only performed in 74% of patients with LVO, mostly because the LVO was undetected by the local radiologist

Evidentiary Table. (continued)

Author & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Gropen et al[33] (2019)	III for Q1	Single center prospective cohort: 1 academic hospital and 3 EMS organizations in Birmingham, Alabama	Objective was to develop and quantify the diagnostic accuracy and reliability of the EMSA; staff (24) training is 7.5-minute EMSA video, 18-minute stroke review video, 20-question exam; staff then guided on scene EMS using a scripted EMSA card; vascular neurologist reviewed communication center-EMS interactions and provided feedback; LVO determined by CTA/MRA if occlusion of ICA/M1/BA occlusion, determined by vascular neurologist blinded to pre-hospital data; excluded patients w/missing recorded EMSA or vascular imaging	891 EMS providers received EMSA training; September 2016 to February 2018, 463 eligible stroke patients analyzed; mean age 63 y and 56% non-Caucasian; LVO in 9.6% (45) of whom 46.7% (21) had MT; Number Needed to Screen of 22 to identify one suspected stroke patient who will undergo MT (21/463); EMSA ≥4, sensitivity 76%, specificity 62%, positive LR 2.0, negative LR 0.40 for LVO in initial 9 mo; NIHSS ≥6 sensitivity 89%, specificity 42%, positive LR 1.5 and negative LR 0.3 for LVO; NIHSS ≥10, sensitivity 69%, specificity 65%, positive LR 2.0, and negative LR 0.50 for LVO	Starts as design 1, but 24 providers performed the EMSA and no reliability assessment between the providers, no adjustment for correlation of outcome by provider, and variable diagnostic studies used to make criterion standard diagnosis, included transient ischemic attacks who could have LVO, single center

Evidentiary Table. (continued)

Author & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Helwig et al[34] (2019)	III for Q1	Prospective multicenter trial randomized by week to either treatment by EMS using the LAMS [OPM group] or a MSU in Germany	Primary outcome was the proportion of patients with an LVO or ICH that were accurately triaged to a comprehensive stroke center capable of endovascular therapy	The trial was terminated at interim analysis after 116 patients of the planned 232 patients had been enrolled, including 53 patients in the OPM group and 63 patients in the MSU group; triage decision was accurate for 37 of 53 patients (69.8%) in the OPM group and for 63 of 63 patients (100%) in the MSU group (difference, 30.2%; 95% CI 17.8% to 42.5%; *P*<.001)	Patients were not randomized individually; the trial was terminated early based upon the primary outcome, which may have led to missed differences in secondary outcomes; CTA from the MSU was used to diagnose LVO; therefore, confirmation bias of LVO in the MSU group leading to the 100% sensitivity
Hoglund et al[35] (2020)	III for Q1	Single center, urban, academic prospective cohort study	Adult patients with possible arterial ischemic stroke and LKWT <4.5 hours; treating ED provider assessed FANG-D score, and some patients had multiple assessments in order to assess interrater reliability; outcome=anterior circulation LVO (ICA, M1, or M2) per CTA interpreted by treating radiologist	Of 640 eligible patients, 23% were excluded due to missing FANG-D score or imaging; N=491 patients included in analysis with 608 assessments; 51/491 patients had anterior circulation large vessel occlusion (ACLVO) (64/608 assessments). FANG-D had sensitivity 91% (95% CI 81% to 96%) and specificity 35% (95% CI 31% to 39%) for anterior LVO; FANG-D Fleiss' kappa was 0.77 (95% CI 0.64 to 0.88) with hemiparesis demonstrating the highest agreement (Fleiss' kappa 0.78) and neglect the lowest agreement (Fleiss' kappa 0.63)	Analysis did not appropriately account for multiple assessments per patient, resulting in overly precise estimates of sensitivity and specificity; industry-funded study

Evidentiary Table. (continued)

Author & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Lima et al[36] (2016)	III for Q1	Prospective cohort study at 2 university-based hospitals in Brazil	Evaluated FAST-ED scale to predict large vessel occlusion strokes (LVOS) used to triage prehospital patients to endovascular capable centers; non-contrast computed tomography scans and CTA were obtained in all patients suspected of having ischemic stroke (stroke, transient ischemic attack, or stroke mimics) in the first 24 h of symptom onset; patients with unilateral acute complete symptomatic occlusion of the intracranial ICA, M1 and M2 segments of the MCA, and BA were selected and compared with patients without a proximal intracranial occlusion	N=727; LVO rate 33%; FAST-ED had comparable accuracy to predict LVO to the NIHSS and higher accuracy than RACE and CPSS (AUROC: FAST-ED=0.81 as reference; NIHSS=0.80, *P*=.28; RACE=0.77, *P*=.02; and CPSS=0.75, *P*=.002); A FAST-ED ≥4 had sensitivity of 0.60, specificity of 0.89, PPV of 0.72, and NPV of 0.82 versus RACE ≥5 of 0.55, 0.87, 0.68, and 0.79, and CPSS ≥2 of 0.56, 0.85, 0.65, and 0.78, respectively	Patients with symptomatic bilateral and anterior plus posterior circulation occlusions were excluded from the analysis; subjects with equivocal occlusion scores were excluded from the analysis; authorship disclosures with imaging and pharmaceutical companies related to the research; strength is all patients underwent imaging, including mimics; readers were blinded to results and adjudicated scores when required

1007 **Evidentiary Table. (continued)**

Author & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Mayasi et al[37] (2018)	III for Q1	Retrospective cohort, single academic center stroke registry in Worcester, Massachusetts	Objective was to quantify whether leukoaraiosis severity affects the diagnostic accuracy of pre-hospital stroke scales; LVO determined by CTA/MRA by a neuroradiologist w/ICA/ M1/M2/BA occlusions; leukoaraiosis was defined as MRI supratentorial white matter FLAIR hyperintensity lesions; degree of leukoaraiosis dichotomized according to the median Fazekas scale score 0 to 2 (absent to mild) or 3 to 6 (moderate to severe); multivariable logistic regression to determine whether individual scales identified LVO independent of leukoaraiosis	Between January 2013 and January 2014; 274 consecutive patients, mean age 69; NIHSS 5, 48% absent-to-mild Fazekas (65% in LVO versus 43% in no LVO); absent-mild Fazekas increase sensitivity of 3I-SS/VAN/RACE but decrease CPSS and FAST-ED unchanged; specificity VAN/CPSS/RACE/FAST-ED increase; specificity 3I-SS decreased; moderate-to-severe Fazekas increase sensitivity of 3I-SS and CPSSS, but decrease sensitivity of other tools; specificity decreased for every tool except 3I-SS; FAST-ED and RACE predict LVO independent of leukoaraiosis	Starts as design 2, since the scales are retrospectively calculated, no description of abstraction methods as to who did it or whether they were blinded to the radiology reads, single center, unique MRI predictor of LVO and only 46 had LVO

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Evidentiary Table. (continued)

Author & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Pérez de la Ossa et al[38] (2014)	III for Q1	Combination of retrospective derivation and prospective validation of the RACE score performed in Spain	Retrospective derivation of the RACE scale assessed various components of the NIHSS for their highest level of association in predicting LVO as diagnosed by transcranial doppler, MRI or CTA; prospective validation was performed in patients in whom a "code stroke" was activated either by EMS or at a community hospital	In the retrospective cohort of 654 patients the RACE scale was calculated based on NIHSS at admission and showed a similar predictive value compared with the NIHSS for detecting LVO (AUC 0.81 versus 0.80); correlation between RACE and NIHSS scores was 0.93 (P<.001); the best predictive value of RACE was established as ≥5; this cutoff value showed sensitivity 0.85, specificity 0.68, PPV 0.42, and NPV 0.94 for detecting LVO	It is not surprising that the RACE scale had good correlation with NIHSS given that it was derived from the NIHSS; in the validation study 40% of the patients who were "code stokes" were not enrolled; furthermore, among patients who were enrolled stroke severity was higher increasing concerns about the effects of spectrum bias on the diagnostic accuracy; neither sensitivity nor specificity were particularly high
Richards et al[39] (2018)	III for Q1	Secondary analysis of an AIS registry; single academic institution	Consecutive patients with a diagnosis of AIS from August 2012 to April 2014; retrospective assessment of the CPSS; outcome=LVO	N=138; N=59 with LVO; CPSS cut-off of 3 resulted in a sensitivity=41% and specificity=88%	Limited by retrospective assessment, although CPSS was applied prospectively; single center in an established system that may limit generalizability; need for external validation

Evidentiary Table. (continued)

Author & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Uchida et al[40] (2020)	III for Q1	Multicenter, academic; prospective cohort study	EMS patients with suspected stroke who had neuroimaging (CT or MRI) EMS providers completed the 21-item Japan Urgent Stroke Triage (JUST) score; JUST-7 included 7 of 21 elements; LVO determined by CTA, MRA or cerebral angiography with corresponding ischemic changes on neuroimaging or treating neurologist assessment; multivariable logistic regression model derived from derivation cohort	Historical derivation cohort: N=2,236 with 11% LVO prevalence; AUC for LVO was 0.89; prospective validation cohort: N=964 with 11% LVO prevalence; AUC for LVO was 0.81 (*P*=.004 for comparison with derivation cohort)	Proportion of patients excluded for lack of neuroimaging not reported and could result in verification bias; clinical prediction model did not perform as well in validation cohort and has not been validated externally

Evidentiary Table. (continued)

Author & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Vidale et al[41] (2018)	III for Q1	Systematic review and meta-analysis of prospective/ retrospective studies of pre-hospital LVO scores published between January 1990 to September 2017	Fixed-effect and random-effects models quantify pooled estimates of accuracy for different scores; individual study quality evaluated using Quality Assessment Diagnostic Accuracy Studies-2 (QUADAS-2)	19 LVO scoring systems from 13 studies: Cincinnati Prehospital Stroke Severity Scale (CPSSS), Recognition Of Stroke In the Emergency Room score (ROSIER), RACE, Acute Stroke Registry and Analysis of Lausanne (ASTRAL), modified NIHSS (mNIHSS), abbreviated NIHSS (aNIHSS), shortened NIHSS 5 items (sNIHSS 5), NIHSS-R, LAMS, PASS, 3I-SS, VAN, Lower extremity strength, Eyes/visual fields, Gaze deviation, Speech difficulty score (LEGS), , Large Vessel Occlusion Scale (LVOS), Maria Prehospital Stroke Scale (MPSS), FAST-ED, G-FAST, and sNIHSS-EMS; VAN positive had overall best accuracy with 100% sensitivity, 90% specificity, AUC 0.92; other instruments: sensitivity 60% to 95%; specificity 39% to 89%	Starts as design 2, but only 3 databases searched, they say that assessed quality of studies but QUADAS2 not described, no meta-analysis performed due to I^2 >50% (significant statistical heterogeneity), and the authors report risk of publication bias assessed by Funnel plot although this was not detailed in methods, and despite heterogeneity, lump together different instruments using different outcomes in summary receiver operating characteristic curve (ROC) curve with reporting of pooled positive LR and negative LR

Evidentiary Table. (continued)

Author & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Marks et al[46] (2014)	III for Q2	Secondary analysis of a prospective study, Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution 2 study (DEFUSE 2)	Prospective patient identification and inclusion from 2008 to 2011; outcome=reperfusion, infarct growth, and mRS at 90 d	N=60; collateral score correlated with NIHSS (*P*=.002)	Small sample; limited by secondary analysis of existing dataset, although collateral score was applied in blinded fashion; limited methodological detail
Campbell et al[45] (2015)	III for Q2	This was a randomized trial comparing endovascular therapy plus alteplase to alteplase alone among stroke patients with LVO and perfusion mismatch on CT perfusion scanning; the study was performed in New Zealand and Australia	Patients were enrolled if they had anterior circulation strokes within 4.5 h of symptom onset with LVO of the carotid or first or second segments of the middle cerebral artery; they also needed to have evidence of perfusion mismatch on CT perfusion imaging	From August 2012 through October 2014, a total of 70 patients underwent randomization (35 to the endovascular-therapy group and 35 to the alteplase-only group) at 10 study centers; 25% of clinically eligible patients with vessel occlusion were excluded on the basis of perfusion-imaging criteria; endovascular therapy led to greater early neurologic recovery at 3 d (*P*=.002) and improved functional outcome in an ordinal analysis of the score on the mRS at 90 d (generalized OR 2.0, 95% CI 1.2 to 3.8; *P*=.006)	This study did not compare the addition of perfusion imaging to without addition of perfusion imaging for risk stratification; the primary purpose of the study was comparing EVT to alteplase alone; all patients had to have evidence of perfusion mismatching; 25% of patients were excluded because of the absence of perfusion mismatch

Evidentiary Table. (continued)

Author & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Nogueira et al[47] (2018)	III for Q2	Multicenter randomized open-label trial with blinded outcomes; September 2014 to February 2017	AIS Patients due to anterior LVO symptom onset 6 to 24; NIHSS >10 and ischemic volume <21 ml if >80 y; <31 ml if <80 y; OR NIHSS >20, <80 y, and ischemic volume 31 to 51 ml; do patients with mismatch between clinical deficit and infarct by perfusion benefit from endovascular therapy versus standard therapy	206 patients. mRS 0 to 2 at 90 d 49% versus 13%; mortality 19% versus 18%; sICH 6% versus 3%	Starts as design 1, but there is no group that had the ICA or M1 occlusion on CTA but no mismatch that underwent MT (What happens if you just use the CTA findings? How many patients no longer qualify by calculating the infarct volume, and how many of those patients had they received MT would have been harmed or improved?) 43 outcomes were done via phone, not in-person, and industry sponsored, indirectly applicable. Trial stopped early due to interim analysis showing efficacy

Evidentiary Table. (continued)

Author & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Campbell et al[50] (2018)	II for Q3	Multicenter RCT	Adult patients with acute stroke, LKWT <4.5 hours, LVO, and candidates for thrombectomy arms: tenecteplase (0.25 mg/kg) versus alteplase (0.9 mg/kg primary outcome: reperfusion of >50% of ischemic territory or absence of retrievable thrombus; secondary outcomes: sICH, mRS at 90 d, death at 90 d	N=202 (tenecteplase 101); primary outcome: 22% for tenecteplase versus 10% for alteplase (adjusted OR 2.6, 95% CI 1.1 to 5.9); secondary outcomes: median mRS 2 for tenecteplase versus 3 for alteplase, common OR 1.7 (95% CI 1.0 to 2.8); sICH 1% in both groups	Open label; received industry funding
Logallo et al[51] (2017)	II for Q3	RCT, phase 3; multicenter, 13 institutions	Prospective enrollment of adult patients eligible for systemic thrombolysis after clinical diagnosis of AIS within 4.5 hours of symptom onset or who were eligible for bridging therapy prior to thrombectomy; allocated to either 0.4 mg/kg tenecteplase or 0.9 mg/kg alteplase; outcome=mRS of 0 to 1 at 3 mo	N=1,100; primary outcome achieved in 64% of those allocated to tenecteplase and 63% of those allocated to alteplase (*P*=.52); 3-month mortality same in both groups (5% for both groups); SAEs occurred in similar proportions (26% for both groups) (*P*=.74)	Multiple centers extended generalizability; open label, which may have introduced treatment bias

Evidentiary Table. (continued)

Author & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Menon et al[52] (2022)	III for Q3	Multicenter RCT, phase 3 trial; 22 primary and comprehensive stroke centers in Canada	Adult patients ≥18 y with an acute ischemic stroke within 4.5 hours of symptoms onset that qualified for thrombolytics; patients were randomized to receive 0.9 mg/kg alteplase or 0.25 mg/kg tenecteplase; primary outcome: mRS 0 to 1 at 90 to 120 d; secondary outcomes: sICH at 24 hours, mRS at 90 d	N=1,577 (tenecteplase 806); primary outcome: mRS 0 to 1 in 36.9% for tenecteplase and 34.8% for alteplase (unadjusted risk difference 2.1% [95% CI –2.6 to 6.9]); no difference in sICH at 24 hours (3.4% tenecteplase versus 3.2% alteplase) or death at 90 d (15.3% tenecteplase versus 15.4% alteplase)	Open label; non-inferiority trial
Parsons et al[53] (2012)	III for Q3	RCT; radiological and clinical outcome assessments were blinded to intervention	Objective was to compare standard dose of alteplase with 0.1 or 0.25 mg/kg tenecteplase, <6 h LKWT and use CT perfusion to select patients most likely to benefit with LVO and large perfusion lesion in absence of large infarct core (perfusion lesion >20% of infarct core, infarct core lesion had to be <1/3 of MCA territory or <½ of ACA or posterior cerebral artery); compared 0.1 or 0.25 mg/kg; primary outcome: proportion reperfused at 24 hours (on MRI) and extent of clinical improvement in 24 hours	The 3 treatment groups had 25 patients with a mean NIHSS of 14.4±2.6 and time to treatment was 2.9±0.8 and 2 tenecteplase groups; higher tenecteplase (0.25 mg/kg) was superior to lower dose and to alteplase for absence of serious disability at 90 d (72% versus 40%); dose-response identified with higher tenecteplase dose being superior to lower tenecteplase and alteplase for all imaging and clinical efficacy outcomes; reperfusion at 24 h (79% tenecteplase versus 55% alteplase, *P*=.004), improvement in NIHSS in 24 h (8 versus 3, tenecteplase versus alteplase, *P*<.001); no change in ICH or death	Starts as design 1, but a highly selected study population with perfusion mismatch, small sample sizes in groups of 25 each, 3 Australian centers, treating provider not blinded, endpoints modified during trial, and slight imbalance in diabetes and smoking status; phase 2b trial

1023 **Evidentiary Table. (continued)**

Author & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Huang et al[54] (2015)	III for Q3	RCT, phase 2; single academic center	Prospective enrollment of adult patients eligible for systemic thrombolysis after clinical diagnosis of AIS within 4.5 hours of symptom onset; allocated to either 0.25 mg/kg tenecteplase or 0.9 mg/kg alteplase; outcome=% penumbra salvaged at 24 to 48 hours	N=104; 71 contributed to primary endpoint, 35 from tenecteplase group and 36 from alteplase group; no difference in endpoint between groups, 68% for both (*P*=.8)	Single center limits generalizability; open label, which may have introduced treatment bias; per protocol analysis, not intention-to-treat; only 68% of the enrolled cohort contributed to the primary endpoint, which may have introduced selection bias
Bivard et al[55] (2022)	III for Q3	Prehospital RCT, phase 2 trial	Adult patients ≥18 y with an acute ischemic stroke within 4.5 hours of symptom onset that qualified for thrombolytics; patients were randomized to receive 0.9 mg/kg (maximum 90 mg) alteplase or 0.25 mg/kg (maximum 25 mg) tenecteplase; primary outcome: volume of perfusion lesion at receiving hospital. Secondary outcome: sICH at 36 h and death at 90 d	N=104 (tenecteplase 55); primary outcome: perfusion lesion volume smaller with tenecteplase vs alteplase (12 ml versus 35 ml, adjusted incidence ratio 0.55, 95% CI 0.37 to 0.81); death at 90 d: 9% for tenecteplase and 10% for alteplase; no difference in sICH	Open label; non-inferiority trial; utilized a prehospital MSU to evaluate and give thrombolytics

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Evidentiary Table. (continued)

Author & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Kvistad et al[56] (2022)	III for Q3	Multicenter RCT, phase 3 trial	Adult patients ≥18 y with an acute ischemic stroke within 4.5 hours of symptoms onset that qualified for thrombolytics; patients were randomized to receive 0.9 mg/kg (maximum 90 mg) alteplase or 0.4 mg/kg (maximum 40 mg) tenecteplase; primary outcome: mRS 0 to 1 at 90 d; secondary outcomes: any ICH and 3-month mortality	N=204 (tenecteplase 100); primary outcome: 32% tenecteplase versus 51% alteplase OR 0.45 (95% CI 0.25 to 0.80); secondary outcomes: any ICH was higher in tenecteplase versus alteplase (21% versus 7%, OR 3.68, 95% CI 1.49 to 9.11), 3-month mortality higher with tenecteplase (16% versus 5%, 3.56, 95% CI 1.24 to 10.21)	Open label; non-inferiority trial; stopped early due to prespecified safety criteria
Kvistad et al[57] (2019)	III for Q3	Study design is a post-hoc analysis of NOR-TEST of moderate (NIHSS 6–14) and severe (NIHSS ≥15)	Objective was to assess safety and efficacy of tenecteplase 0.4mg/kg versus 0.9 mg/kg alteplase with moderate and severe ischemic stroke; outcomes: favorable outcome (mRS 0 to 1 90 days, clinical improvement 7 d), sICH, death (7 and 90 d)	In 261 moderate stroke patients (123 tenecteplase versus 138 alteplase) no difference in outcome, sICH, or death, and in 87 severe stroke (40 tenecteplase vs 47 alteplase), no differences in outcome sICH or 7-d mortality but 90-d all-cause mortality increased in tenecteplase 26.3% (10) versus 9.1% (4)	Starts as design 2, while the patients are taken from an RCT, this is a subgroup analysis of patients identified retrospectively specifically with moderate and severe stroke, also open label; unclear if powered to detect a difference in only 87 severe patients or even in 261 severe patients

Evidentiary Table. (continued)

Author & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Rønning et al[58] (2019)	III for Q3	Prespecified secondary analysis of the NOR-TEST; multicenter randomized trial comparing tenecteplase to alteplase in patients with acute ischemic stroke arriving within 4.5 hours of symptom onset	This substudy only include that subset of patients arriving between 3 to 4.5 hours of onset time form the larger trial of all patients arriving within 4.5 hours of symptom onset; outcomes were the proportion of patients with a mRS of 0 to 1 at 3 mo	194 patients were treated between 3 and 4.5 hours of which 105 were randomized to tenecteplase and 89 to alteplase; the median NIHSS was 3 in both treatment groups at admission, and in total 66 % had an NIHSS score of 0 to 4; 60 (57%) of 105 patients that received tenecteplase and 47 (53%) of 89 patients that received alteplase reached good clinical out-come (mRS score of 0 to 1) at 3 mo (OR 1.19, 95% CI 0.68 to 2.10); the rates of any ICH within 48 hours were 5.7% in the tenecteplase group and 6.7% in the alteplase group (OR 0.84, 95% CI 0.26 to 2.70); there were 7 with sICH, 5 (4.8%) in the tenecteplase group and 2 (2.2%) in the alteplase group	Secondary analysis of another study; power and randomization were not performed based upon the population included in this study because it is a secondary analysis; no differences in outcomes were found but the study was not designed at the outset as a non-inferiority trial

Evidentiary Table. (continued)

Author & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Thommessen et al[59] (2020)	III for Q3	Multicenter RCT	Adult patients ≥80 years of age with acute stroke, and LKWT <4.5 hours; arms: tenecteplase (0.4 mg/kg) versus alteplase (0.9 mg/kg); primary outcome: mRS 0 to 1 at 90 d; secondary outcomes: sICH, mRS at 90 d, MNI at 24 h, death at 90 d	N=273 (tenecteplase 130); primary outcome: favorable neurological outcome 43% for tenecteplase versus 40% for alteplase (OR 1.14, 95% CI 0.70 to 1.9); no significant differences in secondary outcomes	Post-hoc subgroup analysis and not powered to test superiority; open label
Burgos et al[60] (2019)	II for Q3	Meta-Analysis	Objective of the study was to perform a formal non-inferiority meta-analysis of tenecteplase as an alternative to alteplase with AIS and no major intracranial occlusion; compared tenecteplase (0.1, 0.25, 0.4 mg/kg) versus alteplase (0.9 mg/kg); primary outcome: mRS 0 to 1 at 3 mo (non-inferiority); secondary outcomes: ICH and death (non-inferiority)	1,585 patients (5 studies); tenecteplase was non-inferior to alteplase in mRS 0 to 1; non-inferior to safety; baseline NIHSS mean=7; alteplase received 0.9 mg/kg; tenecteplase varied from 0.1 mg/kg (6.8%), 0.25 mg/kg (24.6%), 0.4 mg/kg (68.6%); crude effect for 3 mo mRS 0 to 1 was 57.9% versus 55.4%; risk difference random effects was 4% (-1 to 8%), which was within the prespecified noninferiority margin (set at -6.5%) and for mRS 0 to 2 it was tenecteplase 71.9% versus alteplase 70.5%, for risk difference 2% (-3-6%) and the mRS shift analysis common OR 1.21 (95% CI 0.93 to 1.57); random effects model used; safety end points were also consistent with noninferiority	Inclusion criteria are limited between January 2005 and August 2018 (nothing about language and only PubMed) and the treatment had to be administered up to 6 hours of LKWT; does not state that 2 investigators conducted the search, heterogeneity is only described for modification of treatment effect by TNKtenecteplase dose; the NOR-TEST study has 1,100/1,585 patients or 69% of the subjects

Evidentiary Table. (continued)

Author & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Xu et al[61] (2018)	II for Q3	Meta-analysis and systematic review assessing thrombolysis with tenecteplase to alteplase in acute ischemic stroke	Medline, Embase and Cochrane Library were searched for RCT comparing tenecteplase to alteplase in acute ischemic stroke between January 2001 to April 2018	Out of 513 titles and abstracts initially identified 4 RCT including 1,390 patients were included in the final analysis; tenecteplase showed a neutral effect on excellent functional outcome (58.7 versus 55.6% for tenecteplase vs alteplase; RR 1.04; 95% CI 0.96 to 1.14; *P*=.31) and good functional outcome (70.8 versus 68.6% for tenecteplase vs alteplase; RR 1.16; 95% CI 0.89 to 1.53; *P*=.275); tenecteplase showed a significantly early neurological improvement at 24 h (40.6 versus 33.9% for tenecteplase vs alteplase; RR 1.52; 95% CI 1.03 to 2.25; *P*=.035) compared with alteplase; in addition, tenecteplase showed a neutral effect on recanalization within 24 h or 24 to 48 h (61.8% versus 54.9% for tenecteplase vs alteplase; RR 1.26; 95% CI 0.53 to 3.01; *P*=.3); no significant differences in other safety outcomes were demonstrated	Main issues with the results from the meta-analysis are that at least 1 of the included trials included a high risk of bias associated with allocation concealment; 2 included high risk of bias associated with blinding of outcomes assessment

Evidentiary Table. (continued)

Author & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Thelengana et al[62] (2018)	II for Q3	Meta-Analysis of 1,344 patients from 4 RCT: Australian tenecteplase, NOR-TEST, TNK-S2B. ATTEST	Objective of study was to investigate whether tenecteplase is superior to alteplase for efficacy and safety outcomes for AIS; outcomes: early 24 h improvement with NIHSS ≥8, mRS 0 to 1 at 90 d, mRS 0 to 2 at 90 d, any ICH, sICH, and death; Cochrane risk of bias tool used. If I^2 >50%, random effects model used but otherwise fixed effects model; heterogeneity between inclusion and exclusion criteria	RR for early neuro improvement 1.56 (95% CI 1.0 to 2.43), no difference in mRS 0 to 1, RR 1.06 (95% CI 0.97 to 1.16) or mRS 0 to 2, RR 1.18 (85% CI 0.86 to 1.61); no difference in any ICH RR 0.84 (95% CI 0.61 to 1.15) or sICH RR 1.07 (95% CI 0.6 to 1.93) or death RR 1.03 (95% CI 0.69 to 1.52) at 90 d; sensitivity analysis removed Logallo and favored early neuro improvement RR 1.93 (95% CI 1.32 to 2.81)	Starts as design 1, sensitivity analysis consisted of removing Logallo study, and they say they accounted for heterogeneity by using random effects modeling, and again disproportionate number coming from the 1,100 Logallo patients

1034 **Evidentiary Table. (continued)**

Author & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Huang et al[63] (2016)	III for Q3	Meta-analysis using both summary and individual patient data from randomized studies to examine current evidence for efficacy and safety of tenecteplase compared with alteplase	Primary outcome mRS 0 to 1 at 3 mo (excellent out- come); secondary outcomes included good outcome (mRS 0 to 2 at 3 mo); all analyses were performed on an intention-to-treat basis including all randomized patients; group-level meta-analysis using the DerSimonian–Laird test and the Breslow–Day test to evaluate heterogeneity between studies with I^2 for inconsistency; random effects models were undertaken to account for study heterogeneity; outcomes were expressed as ORs and their 95% CIs	N=3 studies for inclusion having a total of 291 patients; 108 patients were allocated to 0.25 mg/kg tenecteplase, 56 patients to 0.1 mg/kg tenecteplase, and 19 patients to 0.4 mg/kg tenecteplase, and 108 patients to alteplase; the 0.25 mg/kg tenecteplase group showed significantly greater odds of early neurological improvement at 24 h (OR 3.4, 95% CI 1.6 to 7.4, P=0.002) compared with alteplase; no significant differences in other efficacy or safety outcomes were demonstrated; no significant heterogeneity was detected among studies; no significant differences were found in any outcome between 0.1 mg/kg tenecteplase and alteplase-treated patients; only 19 patients received tenecteplase 0.4 mg/kg and outcomes did not differ from alteplase	Limited search terms were used to identify papers; selection criteria were not well developed nor explained; no specification of number of investigators selecting/screening articles; quality of studies not assessed; no sensitivity analyses done;

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Evidentiary Table. (continued)

Author & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Kheiri et al[64] (2018)	III for Q3	Meta-analysis of RCTs	Efficacy outcomes included early neurological improvement, defined as ≥4 points reduction in the NIHSS; calculated summary ORs and 95% CIs using the Mantel–Haenszel method for dichotomous data; used a random-effects model to account for the between-study heterogeneity and we measured the heterogeneity using the Cochrane's Q statistic and I^2 statistic test; sensitivity analyses were performed by removing trials sequentially and based on study design (single/multiple centers, phase 2/3 trials, double-blinded/open-label trials, timing of symptom onset to thrombolysis); meta-regression analyses were conducted based on the study-level covariates (age and baseline NIHSS scores)	N=5 RCTs with 1,585 patients, of whom 828 received tenecteplase and 757 received alteplase; there was a significant increase in complete recanalization of the occluded vascular territory in the tenecteplase-treated patients (30% versus 15%; OR 2.01, 95% CI 1.04 to 3.87; P=.04; I^2=0%); although statistically nonsignificant, there was an increased rate of complete/partial recanalization with tenecteplase (54% versus 41%; OR 1.51, 95% CI 0.70 to 3.26; P=.30; I^2=50%); significant increase in early neurological improvement with tenecteplase-treated patients compared with the alteplase group (45% versus 41%; OR 1.43, 95% CI 1.01 to 2.03; P=.05; I^2=34%); sensitivity analysis showed no heterogeneity after removing one RCT that allowed up to 6 h from stroke onset to the start of treatment (I^2=0%), but with the loss of a statistically significant result (P=.10); network meta-analysis showed trend towards worse outcomes with advanced age (R^2=76%; b= −0.38; SE=0.25; P=.13)	Search terms seem cursory, no librarian assisted with the strategy; some trials were industry sponsored; treatment times varied from 3 to 4.5 hours; most trials (N=4) were open-label; 1 prematurely terminated trial was double-blinded

Evidentiary Table. (continued)

Author & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Zhang et al[65] (2016)	III for Q3	Systematic review and meta-analysis	Inclusion of participants included prospectively in controlled clinical trials; standardized extraction with random effects modeling to account for study heterogeneity; outcome = MNI) defined by an improvement in NIHSS of 8 or more points	N=6 studies; N=497 patients; N=276 received tenecteplase 0.25mg/kg tenecteplase had better MNI than 0.1mg/kg tenecteplase (*P*=.005); tenecteplase has better MNI than alteplase (*P*=.02) with decreased parenchymal hematoma (*P*=.009)	Comprehensive search; quality of evidence assessment; significant heterogeneity across studies but random effects modeling to account for study heterogeneity; sensitivity analysis to account for study quality and to evaluate influence of each individual study
Bivard et al[66] (2017)	III for Q3	Secondary analysis of 2 RCT (Australia-TNK and ATTEST); Australia-TNK included 3 sites; ATTEST included 1 site	Prospective enrollment of adult patients eligible for thrombolysis after clinical diagnosis of AIS within 4.5 hours for ATTEST and 6 hours for Australia-TNK from onset of symptoms; pooled analysis of patients receiving 0.25mg/kg tenecteplase versus 0.9 mg/kg alteplase; outcome=change in NIHSS	N=146 (96 from ATTEST and 50 from Australia-tenecteplase); 71 received alteplase 74 received tenecteplase; those who received tenecteplase had improved earlier outcomes vs alteplase (*P*=.02) with less ICH (*P*=.02); both groups had similar long-term mRS (*P*=.1)	Trials were open label; secondary analysis, pooling, and post hoc assessments; generalizability extended given pooling of two trials with different population characteristics

Evidentiary Table. (continued)

Author & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Katsanos et al[67] (2021)	III for Q3	Meta-analysis and systematic review assessing thrombolysis with tenecteplase to alteplase in acute ischemic stroke in patients with large vessel occlusion	Searched MEDLINE and Scopus for RCT in patients with acute ischemic stroke with confirmed LVO; primary outcome was mRS of 0 to 2 at 3 mo	4 RCT including a total of 433 patients; patients with confirmed LVO receiving tenecteplase had higher odds of mRS of 0 to 2 (OR 2.06 [95% CI 1.15 to 3.69]), successful recanalization (OR 3.05 [95% CI 1.73 to 5.40]), and functional improvement defined as 1-point decrease across all mRS (common OR 1.84 [95% CI, 1.18 to 2.87]) at 3 mo compared with patients with confirmed LVO receiving alteplase; no difference in the outcomes of early neurological improvement, sICH, any intracranial hemorrhage, and the rates of mRS 0 to 1 or all-cause mortality at 3 mo was detected between patients with LVO receiving intravenous thrombolysis with either tenecteplase or alteplase	Only reviewed 2 possible sources for available literature; no description of the quality of the included studies; many studies include patients who received thrombectomy

Evidentiary Table. (continued)

Author & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Kerber et al[75] (2015)	III for Q4	Prospective cohort study at one center in Michigan; target population was patients presenting for acute dizziness without an obvious cause who also had examination findings (ie, nystagmus [spontaneous or gaze-evoked] or imbalance when walking) that could be attributable to neurologic dysfunction	Evaluated the ability of the combination of bedside predictors of stroke-including both the ABCD2 score and the specialized OM examination-to stratify stroke risk using an MRI-based industry standard; study examinations were performed before the MRI whenever possible or blinded to the results of the MRI; OM examination was performed including a nystagmus assessment, assessment of skew deviation, and the head impulse test (HIT); primary outcome was an imaging-based definition of stroke, specifically any acute infarction or ICH on MRI as determined by a neuroradiologist	N=320 patients; stroke rate 11%; in multivariable logistic regression models, ABCD2 OR 1.74 (95% CI 1.20 to 2.5); HINTS positive OR 2.82 (95% CI 0.96 to 8.30); false-negative frequency (ie, frequency of stroke in the lowest-risk categories) was as follows: ABCD2 <4, 5.1% (8/157); OM assessment, 5.9% (9/152) (4.9% [4/82], for HINTS peripheral findings); other CNS features, 7.8% (17/219); and prior stroke, 10.8% (28/260); the OM assessment was positive for a central lesion in 20 of the 29 stroke patients (69%); of the 9 stroke patients who did not have the central OM findings, 7 patients were in the no-nystagmus category (5) and/or had an acute infarction that was possibly incidental (3)	15% did not receive MRI within 14 d; physical examination was performed in a structured fashion by a study investigator, either a neurologist fellowship trained in neuro-otology or vascular neurology, or an emergency medicine physician fellowship trained in vascular neurology - not generalizable to the general EM provider population

Evidentiary Table. (continued)

Author & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Ohle et al[76] (2020)	III for Q4	Systematic review and meta-analysis	Inclusion of participants included prospectively; standardized extraction by independent reviewers	N=5 studies; N=617 patients; HINTS examination with sensitivity=97% and specificity=95% when performed by neurologists; HINTS examination with sensitivity=83% and specificity=44% when performed by emergency physicians and/or neurologists	Comprehensive search; quality of evidence assessment; random effects modeling to account for study heterogeneity; no sensitivity analyses

3I-SS, 3-Item Stroke Scale; *A1*, first segment anterior cerebral artery; *A2*, second segment anterior cerebral artery; *ABCD2*, age, blood pressure, clinical features, duration, diabetes; *ACA*, anterior cerebral artery; *ACT-FAST*, Ambulance Clinical Triage for Acute Stroke Treatment; *AIS*, acute ischemic stroke; *ATTEST*, Alteplase-Tenecteplase Trial Evaluation for Stroke Thrombolysis; *AUC*, area under the curve; *AUROC*, area under the receiver operating characteristics; *BA*, basilar artery; *CPSS*, Cincinnati Prehospital Stroke Severity; *CSC*, comprehensive stroke center; *CT*, computed tomography; *CTA*, computed tomography angiography; *d*, day; *ED*, emergency department; *EMS*, emergency medical service; *EMSA*, Emergency Medical Stroke Assessment; *EVT*, endovascular thrombectomy; *FANG-D*, field cut, aphasia, neglect, gaze preference, and dense hemiparesis; *FAST*, face-arm-speech test; *FAST-PLUS*, Face-Arm-Speech-Time plus severe arm or leg motor deficit; *FAST-ED*, Field Assessment Stroke Triage for Emergency Destination; *G-FAST*, gaze-face-arm-speech-time; *HINTS*, Head Impulse-Nystagmus-Test of Skew; *ICA*, internal carotid artery; *ICH*, intercranial hemorrhage; *LAMS*, Los Angeles Motor Scale; *LKWT*, last known well time; *LVO*, large vessel occlusion; *M1*, first segment middle cerebral artery; *M2*, second segment middle cerebral artery; *MCA*, middle cerebral artery; *MNI*, major neurological improvement; *mo*, month; *MRA*, magnetic resonance imaging; *mRS*, modified Rankin scale score; *MSU*, mobile stroke unit; *MT*, mechanical thrombectomy; *NOR-TEST*, Norwegian Tenecteplase Stroke Trial; *NPV*, negative predictive value; *OM*, oculomotor; *OPM*, optimize prehospital management; *PASS*, Prehospital Acute Stroke Severity Scale; *PPV*, positive predictive value; *RACE*, Rapid Arterial Occlusion Evaluation; *RCT*, randomized controlled trial; *RR*, relative risk; *sICH*, symptomatic intracerebral hemorrhage; *VAN*, Vision-Aphasia-Neglect; *y*, year.