Clinical Policy: Use of Intravenous Tissue Plasminogen Activator for the Management of Acute Ischemic Stroke in the Emergency Department

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ABSTRACT

This clinical policy from the American College of Emergency Physicians is the revision of a clinical policy approved in 2012 addressing critical questions in the evaluation and management of patients with acute ischemic stroke.[1] A writing subcommittee conducted a systematic review of the literature to derive evidence-based recommendations to answer the following clinical questions: (1) Is intravenous tissue plasminogen activator safe and effective for patients with acute ischemic stroke if given within 3 hours of symptom onset? (2) Is intravenous tissue

plasminogen activator safe and effective for patients with acute ischemic stroke treated between 3 to 4.5 hours after symptom onset? Evidence was graded and recommendations were made according to the strength of the available data.

INTRODUCTION

Stroke is a leading cause of death in the United States, with approximately 800,000 new strokes documented each year.[2,3] Among survivors, stroke often results in disability, reducing mobility in half of those aged 65 years or older.[2] In 1996, the Food and Drug Administration approved intravenous (IV) tissue plasminogen activator (tPA) as a treatment for acute ischemic stroke. Despite their approval, the use of IV tPA for stroke has been polarizing[4] and continues to generate a large volume of published literature.

The last American College of Emergency Physicians (ACEP) clinical policy addressing the use of IV tPA for acute ischemic stroke was approved in 2012.[1] Since then, changes to the ACEP clinical policies development process have been implemented (ACEP's clinical policy development process can be found at http://www.acep.org/clinicalpolicies), the grading forms used to rate published research have continued to evolve, and newer research articles have been published.

The 2012 IV tPA clinical policy recommendation to "offer" tPA to patients presenting with acute ischemic stroke within 3 hours of symptom onset was consistent with other national guidelines (eg, those of the American Heart Association[5] and the American College of Chest Physicians[6]). Unfortunately, the committee's intent in using the term "offer" may not have conveyed the importance of having a discussion with the patient or family about the potential benefits and harms of IV tPA; therefore, we have expanded on this concept with recommendations addressing shared decisionmaking.

As in the previous ACEP clinical policy,[1] the 2 critical questions addressed in this clinical policy are: (1) Is IV tPA safe and effective for patients with acute ischemic stroke if given within 3 hours of symptom onset? (2) Is IV tPA safe and effective for patients with acute ischemic stroke treated between 3 to 4.5 hours after symptom onset?

METHODOLOGY

This clinical policy was created after careful review and critical analyses of the medical literature and was based on a systematic review of the literature. Searches of MEDLINE, MEDLINE InProcess and other nonindexed citations portion of MEDLINE, and the Cochrane Database were performed. All searches were limited to English-language sources, human studies, and adults, from January 2011 to September 2014; searches were conducted on January 27, 2014, and September 3, 2014. Specific key words/phrases and years used in the searches are identified under each critical question.

Study Selection: 1,765 references were identified in the updated literature search as potentially relevant to the critical questions (992 in the search on January 27, 2014, and 773 in the search on September 3, 2014). From these, 136 articles were selected from the January 27, 2014 search, and 59 articles from the September 3, 2014 search, resulting in a total of 195 new articles for full-text review.

Additionally, given recent changes to the ACEP clinical policy development process, articles rated as Class I or II in the 2012 policy[1] were also reviewed and graded by the committee methodologists using current grading forms (available at http://acep.org/clinicalpolicies). Finally, relevant articles from the bibliographies of included studies and more recent articles identified by committee members and reviewers were also included.

This policy is a product of the ACEP clinical policy development process and is based on the existing literature; when literature was not available, consensus of emergency physicians was used. Clinical policies are scheduled for revision every 3 years; however, interim reviews such as this revision are conducted when technology, methodology, or the practice environment changes significantly. ACEP was the funding source for this clinical policy.

Assessment of Classes of Evidence

All articles used in the formulation of this clinical policy were graded by at least 2 committee members or methodologists; all Class I and Class II articles were graded by at least 2 methodologists. Each article was assigned a design class with design 1 representing the strongest study design and subsequent design classes (eg, design 2, design 3) representing respectively weaker study designs for therapeutic, diagnostic, or prognostic clinical reports, or meta-analyses (Appendix A). Articles were then graded on dimensions related to the study's methodological features, such as randomization processes, blinding, allocation concealment, methods of data collection, outcome measures and their assessment, selection and misclassification biases, sample size, and generalizability. Using a predetermined process related to the study's design, methodological quality, and applicability to the critical question, articles received a final Class of Evidence grade (ie, Class I, Class II, Class III, or Class X) (Appendix B). Articles identified with fatal flaws or that were ultimately not applicable to the critical question received a Class of Evidence grade "X" and were not used in formulating recommendations for this policy. Grading was done with respect to the specific critical questions; thus, the level of

evidence for any one study may vary according to the question for which it is being considered. As such, it was possible for a single article to receive different Classes of Evidence as different critical questions were answered from the same study. Question-specific Classes of Evidence grading can be found in the Evidentiary Table (available online at www.annemergmed.com).

Translation of Classes of Evidence to Recommendation Levels

Strength of recommendations regarding each critical question were made by subcommittee members using results from strength of evidence grading, expert opinion, and consensus among subcommittee members according to the following guidelines:

Level A recommendations. Generally accepted principles for patient care that reflect a high degree of clinical certainty (ie, based on evidence from 1 or more Class of Evidence I or multiple Class of Evidence II studies).

Level B recommendations. Recommendations for patient care that may identify a particular strategy or range of strategies that reflect moderate clinical certainty (ie, based on evidence from 1 or more Class of Evidence II studies or strong consensus of Class of Evidence III studies).

Level C recommendations. Recommendations for patient care that are based on evidence from Class of Evidence III studies or, in the absence of any 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 heterogeneity of results, uncertainty about effect magnitude and consequences, and publication bias, among others, might lead to such a downgrading of recommendations.

For this policy, recommendations for question 1 were based on 1 Class I randomized controlled trial, 5 Class II articles, and 29 Class III studies. For question 2, recommendations were based on 1 Class II randomized controlled trial and 42 Class III studies.

When possible, clinically oriented statistics (eg, likelihood ratios, number needed to treat [NNT]) are presented to help the reader better understand how the results may be applied to the individual patient. For a definition of these statistical concepts, see Appendix C.

This policy is not intended to be a complete manual on the evaluation and management of patients with acute ischemic stroke but rather a focused examination of critical issues that have particular relevance to the current practice of emergency medicine.

It is the goal of the Clinical Policies Committee to provide an evidence-based recommendation when the medical literature provides enough quality information to answer a critical question. When the medical literature does not contain adequate empirical data to answer 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 defines for the physician those strategies for which medical literature exists to provide support for answers to the critical questions addressed in this policy.

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

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

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

A summary of potential benefits and harms of implementing the recommendations is presented in Appendix D.

CRITICAL QUESTIONS

1. Is IV tPA safe and effective for patients with acute ischemic stroke if given within 3 hours of symptom onset?

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. With a goal to improve functional outcomes, IV tPA should be offered and may be given to selected patients with acute ischemic stroke within 3 hours after symptom onset at institutions where systems are in place to safely administer the medication. The increased risk of symptomatic intracerebral hemorrhage (sICH) should be considered when deciding whether to administer IV tPA to patients with acute ischemic stroke.

Level C recommendations. When feasible, shared decisionmaking between the patient (and/or his or her surrogate) and a member of the health care team should include a discussion of potential benefits and harms prior to

Table. Modified Rankin Scale.* (Used with permission).

Score	Description
0	No symptoms
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities but able to look after own affairs without assistance
3	Moderate disability; requiring some help but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent, and requiring constant nursing care and attention
6	Dead

Rankin J. Cerebral vascular accidents in patients over the age of 60. II. Prognosis. *Scott Med J*. 1957;2:200-215. © Copyright 1957 Royal Society of Medicine Press, UK.
*The modified Rankin Scale is a 6-point clinical outcome scale that measures a patient's function and independence. A lower score indicates a better outcome.

the decision whether to administer IV tPA for acute ischemic stroke. (Consensus recommendation)

Key words/phrases for literature searches: stroke, cerebrovascular accident, thrombolytic, tPA, thrombolytic therapy, drug therapy, emergency department or emergency room, emergency service, hospital, and variations and combinations of the key words/phrases.

A study was considered directly applicable if IV tPA was administered within the specified timeframe (ie, within 3 hours of symptom onset). To be included, articles were required to report patient-centered outcomes such as sICH, mortality, or a validated measure for functional outcome. In terms of assessing the potential benefits of IV tPA, the subcommittee focused on the modified Rankin Scale (mRS) because it is both patient centered and consistently reported[1,7] (Table). An "excellent" functional outcome is typically equated to a score of 0 to 1 on the mRS; a score of 2 is considered a "good" functional outcome; and a score of 3 to 6 is considered "poor" functional outcome. To place this into context, an mRS score of 2 is defined as a slight disability that allows the patient to look after their affairs without assistance yet be unable to perform some previous activities (eg, drive a car, dance).[7]

The major harm associated with IV tPA therapy in this clinical setting is sICH, defined as bleeding associated with "any decline in neurological status" per the National Institute of Neurological Disorders and Stroke (NINDS) trials[8] and, when it occurs, sICH is ultimately associated with a substantial increase in the risk of an unfavorable outcome (mRS score 3 to 6).[9] Studies have used various definitions for sICH, such as those requiring a deterioration of 4 or more points on the National Institutes of Health Stroke Scale (NIHSS)[9] (Figure 1). When possible, the subcommittee reported results using the more inclusive NINDS definition.

Potential Benefits

It has been nearly 20 years since the last patient was enrolled in part 2 of the tPA for acute stroke trials sponsored by the NINDS. This trial provided the scientific basis for the Food and Drug Administration's approval of the use of IV tPA in acute stroke.[8] The results of the NINDS trial (part 2) (Class I) demonstrated an absolute difference of 13% with respect to excellent functional outcomes (ie, 39% with mRS score 0 to 1 for tPA versus 26% for control), thus rendering a NNT of 8; 95% confidence interval [CI] 4 to 31. Although the enrollment criteria for the NINDS trials (Figure 2) required a measurable deficit on the NIHSS, there was a paucity of patients presenting with mild stroke (NIHSS score 0 to 4).[10] In an effort to address the current state of equipoise for IV tPA in patients presenting with mild (NIHSS score 0 to 4) or rapidly improving symptoms, a randomized controlled trial is actively enrolling subjects.[11]

Data from the NINDS trials continue to be reanalyzed and despite inherent problems with post hoc reanalyses,[12] these studies highlight the strengths and limitations of the NINDS trials.[10,13-19] Although strict randomization was followed in the NINDS trials, there was an imbalance in baseline stroke severity scores between the intervention and control groups.[13,14] A subsequent reanalysis of the original NINDS data set showed that a larger proportion of patients with milder strokes with an NIHSS score of 0 to 5 (19% versus 4%) at 91 to 180 minutes were randomized to tPA.[14] Last, the NINDS trials were designed to enroll half of their subjects within 90 minutes of symptom onset, which has raised questions about the generalizability of their findings.[20]

The only other randomized controlled trial (Class II) that directly addressed the critical question enrolled subjects within 6 hours of stroke symptom onset, using block randomization stratified by 0 to less than 3 hours and 3 to 6 hours.[22] This study did not show benefit for tPA administered within 6 hours of symptom onset (the primary analysis), and the difference in the subgroup randomized to less than 3 hours (42% with mRS score 0 to 2 for tPA versus 38% for placebo) did not reach statistical significance (odds ratio [OR]=1.2; 95% CI 0.6 to 2.3).

A Class III open-label clinical trial, the Third International Stroke Trial (IST-3), by Sandercock et al,[23] enrolled patients within 6 hours of symptom onset. In this trial, patients did not meet the standard European Union license–approved protocol for IV tPA; a large percentage of

Level of consciousness 1a–1c:

1a. Alertness
0=alert and responsive
1=arousable to minor stimulation
2=arousable only to painful stimulation
3=reflex responses or unarousable

1b. Orientation: Ask the patient his or her age and the month; answers must be exact.
0=Both correct
1=One correct (or dysarthria, intubated, foreign language)
2=Neither correct

1c. Commands: Ask the patient to open/close eyes and to grip/release the nonparetic hand (or other 1-step command). Grip and release nonparetic
0=Both correct (OK if impaired by weakness)
1=One correct
2=Neither correct

2. Best Gaze: Only horizontal eye movements are checked by voluntary movement or reflective movement (doll's eyes, not by calorics).
0=Normal
1=Partial gaze palsy
2=Forced eye deviation or total paresis that cannot be overcome by doll's eyes

3. Visual Field: Test using confrontation (or visual threat if necessary).
0=No visual loss
1=Partial hemianopia, quadrantanopia, extinction
2=Complete hemianopia
3=Bilateral hemianopia or blindness (including cortical blindness)

4. Facial Palsy: If stuporous, check symmetry of grimace to pain.
0=Normal
1=Minor paralysis, flat nasolabial fold or asymmetric smile
2=Partial paralysis (lower face)
3=Complete paralysis (upper and lower face)

5. Motor Arm: arms outstretched 90 degrees (patient sitting) or 45 degrees (patient supine) for 10 seconds. Encourage patient for best effort. Assess both sides.
0=No drift for full 10 seconds
1=Drift but does not hit bed
2=Some antigravity effort but cannot sustain
3=No antigravity effort, but even minimal movement counts
4=No movement at all
X=Unable to assess because of amputation, fusion, fracture, etc

6. Motor Leg: Raise leg to 30 degrees and hold for 5 seconds; test both sides.
0=No drift for full 5 seconds
1=Drift but does not hit bed
2=Some antigravity effort but cannot sustain
3=No antigravity effort, but even minimal movement counts
4=No movement at all
X=Unable to assess because of amputation, fusion, fracture, etc

7. Limb Ataxia: Check finger to nose and heel to shin on both sides (ataxia is scored only if out of proportion to weakness).
0=No ataxia (or aphasic, hemiplegic)
1=Ataxia in 1 limb
2=Ataxia in 2 limbs
X=Unable to assess because of amputation, fusion, fracture, etc

8. Sensory: Use safety pin. Check grimace or withdrawal if stuporous. Score only stroke-related losses.
0=Normal
1=Mild to moderate unilateral loss but patient aware of touch (or aphasic, confused)
2=Total loss, patient unaware of touch, coma, bilateral loss

9. Best Language: Describe cookie jar picture, name objects, and read sentences (these standard items can be found on the Internet and at the American Heart Association Web site).
0=Normal
1=Mild to moderate aphasia (partly comprehensible)
2=Severe aphasia (almost no information exchanged)
3=Mute, global aphasia, coma

10. Dysarthria: Read list of words.
0=Normal
1=Mild to moderate, slurred but intelligible
2=Severe, unintelligible or mute
X=Intubation or mechanical barrier

11. Extinction/Inattention: Simultaneously touch patient on both hands, show fingers in both visual fields, ask whether patient recognizes own left hand.
0=Normal, none detected (visual loss alone)
1=Neglects or extinguishes to double simultaneous stimulation in any modality (visual, auditory, sensory, spatial, or body parts)
2=Profound neglect in more than 1 modality; does not recognize own hand

*The NIHSS is an 11-part scale that measures the neurologic examination in a codified manner. The scale ranges from 0 to 42. A score of less than 5 indicates a small stroke, and greater than 20 indicates a large stroke. Physicians can learn to perform the NIHSS on a training module on the Internet. Standard pictures (eg, the cookie jar picture) and lists of words can also be downloaded from the Internet.

Figure 1. National Institutes of Health Stroke Scale.*

patients were elderly (53% older than 80 years), had elevated systolic blood pressure (34% greater than 165 mm Hg), or had low baseline NIHSS scores (20% with scores 0 to 5). Because of slow enrollment, the trial was stopped early. Among the prespecified subgroups of subjects randomized at less than 3 hours of symptom onset (N=849), the tPA group achieved better functional outcomes compared with controls (31% with good functional outcomes for tPA versus 23% for controls; OR=1.64; 95% CI 1.03 to 2.62), resulting in a NNT of 13 (95% CI 7 to 51).

The literature search also identified an updated meta-analysis (Class II) of randomized controlled trials for IV tPA.[24] The pooled results of the prespecified subgroup analysis for treatment within 3 hours demonstrated benefit in terms of a good functional outcome (mRS score 0 to 2) with thrombolysis (OR=1.53; 95% CI 1.26 to 1.86). Although the authors of the meta-analysis concluded that the 12 studies analyzed were at low risk of bias, a sensitivity analysis based on the methodological and quality differences was not performed. The trial contributing the largest proportion of patient data to the pooled estimate of

effect (ie, Sandercock et al IST-3[23]) was rated Class III by the subcommittee. Another meta-analysis (Class III) based on individual patient-level data reported a similar effect size for tPA administered within 3 hours of symptom onset (OR=1.75; 95% CI 1.35 to 2.27).[25]

Although efficacy estimates in observational studies are often flawed, these studies may provide information on safety. Among the many registry studies identified in the updated searches, methodological limitations such as selection bias (eg, eligible patients missed or purposely not enrolled in a registry) and measurement bias (eg, mRS score assessed by research assistant telephone follow-up rather than an in-person interview by a neurologist) typically resulted in downgrading to Class III or Class X. The search identified a few randomized controlled trials comparing new interventions to standard IV tPA (serving as the control group), which provided data on safety and functional outcomes similar to that of prospective cohort studies. In summary, numerous Class III studies report prevalences of excellent functional outcomes (mRS score 0 to 1) with administration of IV tPA within 3 hours of symptom onset ranging from 37% to 53%.[26-36] However, registries typically included patients with less severe strokes (baseline mean or median NIHSS scores ranging from 11 to 13) compared with those enrolled in the NINDS trials.

Potential Harms

The NINDS trial, part 2[8] (Class I) demonstrated an absolute increase in the prevalence of sICH of 6% (ie, sICH=7% for tPA versus 1% for control), thus indicating a number needed to harm [NNH] of 17; 95% CI 12 to 34. The Class II meta-analysis by Wardlaw et al[24] reported a pooled estimate for sICH of 8% for tPA versus 1% for controls (OR=4.55; 95% CI 2.92 to 7.09); however, the definition for sICH varied among the included individual trials. Among Class III cohort studies, prevalences of sICH were remarkably consistent when based on the NINDS definition (approximately 5% to 7%).[33,35-44] As expected, reported rates of sICH are lower in studies that used standard doses of tPA and a definition requiring a deterioration of 4 or more points on the NIHSS (range of 4% to 6% for sICH).[28,30,31,39,45-49]

In the NINDS trials,[8] there was no statistically significant difference in 3-month mortality (17% for tPA versus 21% for control; OR=0.81; 95% CI 0.54 to 1.21). Similarly, 1 Class II and 1 Class III meta-analyses reported no difference in mortality for patients treated with IV tPA within 3 hours of symptom onset to the end of follow-up: Wardlaw et al[24] (OR=0.91; 95% CI 0.73 to 1.13) and Emberson et al[25] (OR=1.00; 95% CI 0.81 to 1.24), respectively. According to another Class III meta-analysis by Wardlaw et al[50] that included trials using tPA and other thrombolytic agents, there was again no difference in mortality when given within 3 hours of stroke onset (OR 0.99; 95% CI 0.82 to 1.21). Among the Class III cohort studies, there was substantial variability in the reported mortality prevalences, ranging from 1% to 24%.[27-31,33-37,40,45,51]

Appendix D contains information on key risk-benefit concepts.

2. Is IV tPA safe and effective for patients with acute ischemic stroke treated between 3 to 4.5 hours after symptom onset?

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. Despite the known risk of sICH and the variability in the degree of benefit in functional outcomes, IV tPA may be offered and may be given to carefully selected patients with acute ischemic stroke within 3 to 4.5 hours after symptom onset at institutions where systems are in place to safely administer the medication.

Level C recommendations. When feasible, shared decisionmaking between the patient (and/or his or her surrogate) and a member of the health care team should include a discussion of potential benefits and harms prior to the decision whether to administer IV tPA for acute ischemic stroke. (Consensus recommendation)

Key words/phrases for literature searches: stroke, cerebrovascular accident, thrombolytic, tPA, thrombolytic therapy, drug therapy, emergency department or emergency room, emergency service, hospital, and variations and combinations of the key words/phrases.

Potential Benefits

The Class II study, European Cooperative Acute Stroke Study (ECASS III) (Figure 2), by Hacke et al[21] demonstrated improvement in the prevalence of excellent functional outcomes (mRS score 0 to 1) with IV tPA administered within 3 to 4.5 hours after symptom onset (52% for tPA versus 45% for controls; OR=1.34; 95% CI 1.02 to 1.76; NNT=14; 95% CI 7 to 244). Reasons for downgrading ECASS III to a Class II level include baseline differences between groups and changes in the timing of tPA administration during the course of the study.

The Class III open-label clinical trial (IST-3) by Sandercock et al[23] enrolled patients not meeting the standard European Union–approved protocol for IV tPA as discussed under critical question 1 above. In the 3- to

NINDS Criteria[8]

Inclusion:
Acute ischemic stroke with clearly defined time of onset (who could be treated <3 hours of symptom onset)
Measurable deficit on the NIHSS
Baseline brain CT scan that showed no evidence of hemorrhage

Exclusion:
Another stroke or serious head injury within the preceding 3 months
Major surgery within prior 14 days
History of intracranial hemorrhage
Systolic BP >185 mm Hg or diastolic BP >100 mm Hg
Rapidly improving or minor symptoms
Symptoms suggestive of subarachnoid hemorrhage
Gastrointestinal or genitourinary hemorrhage within the previous 21 days
Arterial puncture at a noncompressible site within the previous 7 days
Seizure at onset of stroke
Use of anticoagulation: patients receiving heparin within the 48 hours preceding the onset of stroke who have an elevated PTT, patients with a PT >15 seconds (or INR >1.6), patients with a platelet count <100,000
Glucose level of <50 mg/dL or >400 mg/dL

ECASS III Criteria[21]

Inclusion:
Acute ischemic stroke with a clearly defined time of onset (who could be treated between 3 to 4.5 hours from symptom onset)
Age 18-80 years
Stroke symptoms present for at least 30 minutes without significant improvement prior to treatment
Baseline brain imaging that showed no evidence of hemorrhage

Exclusion:
Same as NINDS plus the following additional criteria:
Age >80 years
Severe stroke (NIHSS score >25) or by appropriate imaging techniques (defined as >1/3 of the middle cerebral artery territory)
Combination of previous stroke and diabetes mellitus
Any oral anticoagulant use (regardless of INR or PT)

BP, blood pressure; *CT*, computed tomography; *ECASS*, European Cooperative Acute Stroke Study; *INR*, International Normalized Ratio; *NIHSS*, National Institutes of Health Stroke Scale; *NINDS*, National Institute of Neurological Disorders and Stroke; *PT*, prothrombin time; *PTT*, partial thromboplastin time; *tPA*, tissue plasminogen activator.

Figure 2. NINDS and ECASS III inclusion and exclusion criteria for intravenous tPA for acute ischemic stroke.

4.5-hour subgroup (N=1,177), there was no statistically significant difference in functional outcomes in those randomized to the tPA arm (32% with good functional outcome in the tPA group versus 38% in the control group [OR=0.73; 99% CI 0.50 to 1.07]). The investigators reported this outcome using a 99% CI rather than a conventional 95% CI; use of a 95% CI would have resulted in a statistically significant association between patients in the placebo arm and good functional outcomes. An older Class III randomized trial also showed no difference in 90-day functional outcomes between the tPA and control groups.[52] A Class III meta-analysis by the Stroke Thrombolysis Trialists' Collaborative Group[25] that pooled individual patient data from multiple trials reported an effect size similar to that of ECASS III (OR=1.26; 95% CI 1.05 to 1.51) for the 3- to 4.5-hour subgroup. Among the Class III observational studies, there was wide variability in baseline stroke severity (mean NIHSS scores ranged from 5 to 17), making comparisons difficult.[33,36,37,39,53-67]

Potential Harms

The Class II study by Hacke et al[21] reported sICH prevalence of 8% for tPA versus 4% for placebo (OR=2.38; 95% CI 1.25 to 4.52; NNH=23; 95% CI 13 to 78); there was no difference in mortality between the 2 groups. The Class III individual patient data meta-analysis also reported no difference in mortality for the 3- to 4.5-hour subgroup (hazard ratio=1.14; 95% CI 0.95 to 1.36).[25] Among other Class III studies,[33,36,37,41,44,50,55,56,58,61,66,68-77] the prevalences of sICH associated with IV tPA administration within 4.5 hours ranged from 3% to 8% when based on the NINDS definition, whereas the prevalence was lower (2% to 6%) for those studies using an sICH definition requiring a change of 4 or more on the NIHSS.[39,53,54,57,60,62-65,67,78-84]

Future Research

Further research is needed to refine estimates for the effectiveness and safety of IV tPA across the entire acute stroke population (ie, heterogeneity of treatment effect) so

that clinicians and patients can have a more informed conversation about who is most likely to benefit from the administration of IV tPA, and clinicians can better identify those individuals at highest risk for sICH and other complications.[85-89] There is some evidence to suggest that lower weight-based doses of tPA may be effective and result in fewer adverse outcomes, warranting further studies in this area.[26,75,82,90] Advancement in precision medicine (eg, predicting risk based on systems biology) and more accurate assessment of patient weight may play a role in deciphering the appropriate treatment of stroke patients. Although trial results on endovascular interventions have been mixed,[78,91,92] more recent trials focusing on the subgroup of patients with large vessel occlusion have reported benefit,[83,84,93,94] thus representing an area of research that is likely to yield further improvements in acute stroke care.

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

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 report Other (eg, consensus, review)	Case series Case report Other (eg, consensus, review)	Case series Case report Other (eg, consensus, review)

*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 reductionx100, where absolute risk reduction is the risk difference between 2 events (ie, experimental and control groups).

Appendix D. Potential benefits and harms of implementing the recommendations

1. Is IV tPA safe and effective for patients with acute ischemic stroke if given within 3 hours of symptom onset?

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. With a goal to improve functional outcomes, IV tPA should be offered and may be given to selected patients with acute ischemic stroke within 3 hours after symptom onset at institutions where systems are in place to safely administer the medication. The increased risk of sICH should be considered when deciding whether to administer IV tPA to patients with acute ischemic stroke.

Level C recommendations. When feasible, shared decisionmaking between the patient (and/or his or her surrogate) and a member of the health care team should include a discussion of potential benefits and harms prior to the decision whether to administer IV tPA for acute ischemic stroke. (Consensus recommendation)

Potential Benefit of Implementing the Recommendations: Administration of IV tPA within 3 hours of stroke symptom onset increases the probability of better long-term functional outcome (NNT=8; 95% CI 4 to 31 when based on data from the Class I NINDS[8] trial part 2).

Potential Harm of Implementing the Recommendations: Administration of IV tPA within 3 hours of stroke symptom onset increases the risk of early sICH (NNH=17; 95% CI 12 to 34 when based on data from the Class I NINDS[8] trial part 2).

When considering administration of IV tPA for a patient with acute ischemic stroke within 3 hours of stroke symptom onset, the physician and patient (and/or the surrogate) should weigh the potential benefit in terms of long-term functional outcome against the increased risk of sICH while recognizing that IV tPA does not alter 90-day mortality.

Shared decisionmaking relies on a combination of the best available research evidence, the clinical expertise of the providers, and the unique attributes of the patient and the patient's family.[95-97] Patients tend to overestimate the benefits and underestimate the harms associated with medical interventions[98]; therefore, it is suggested that patient decision aids be used to improve decision quality.[95] Graphic risk communication tools such as person icon arrays have been developed for IV thrombolysis decisions in acute ischemic stroke.[99,100] Although these tools rely on group-level data from clinical trials rather than providing dynamic individualized estimates of risk, they may provide a starting point for shared decisionmaking.

2. Is IV tPA safe and effective for patients with acute ischemic stroke treated between 3 to 4.5 hours after symptom onset?

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. Despite the known risk of sICH and the variability in the degree of benefit in functional outcomes, IV tPA may be offered and may be given to carefully selected patients with acute ischemic stroke within 3 to 4.5 hours after symptom onset at institutions where systems are in place to safely administer the medication.

Level C recommendations. When feasible, shared decisionmaking between the patient (and/or his or her surrogate) and a member of the health care team should include a discussion of potential benefits and harms prior to the decision whether to administer IV tPA for acute ischemic stroke. (Consensus recommendation)

Potential Benefit of Implementing the Recommendations: Administration of IV tPA for patients with ischemic stroke within 3 to 4.5 hours of stroke symptom onset may increase the probability of better long-term functional outcome (NNT=14; 95% CI 7 to 244 when based on data from the Class II ECASS III[21] trial).

Potential Harm of Implementing the Recommendations: Administration of IV tPA for patients with ischemic stroke within 3 to 4.5 hours of stroke symptom onset increases the risk of early sICH (NNH=23; 95% CI 13 to 78 when based on data from the Class II ECASS III[21] trial).

When considering administration of IV tPA for a patient with ischemic stroke within 3 to 4.5 hours of stroke symptom onset, the physician and patient (and/or the surrogate) should weigh the potential benefit in terms of long-term functional outcome against the increased risk of sICH.

Evidentiary Table.

Study and Year Published	Class of Evidence	Setting and Study Design	Methods and Outcome Measures	Results	Limitations and Comments
NINDS rt-PA Stroke Study Group[8] (1995)	I (for Q1)	Multicenter randomized controlled trial	Adults with stroke measurable on the NIHSS, CT without evidence of ICH; double-blind, placebo controlled; 2 arms: tPA 0.9 mg/kg (maximum 90 mg) versus placebo with standard care stratified by <1.5 h and 1.5 h to 3 h; primary outcomes: Barthel index, mRS score, Glasgow Outcome Scale, NIHSS; part 1: improvement in NIHSS score (4 points) or neurologic deficit resolution within 24 h; part 2: global test statistic of all 4 outcomes at 3 mo; secondary outcomes: deaths and sICH within 36 h	Part 1: N=291 (144 tPA); part 2: N=333 (168 tPA); no significant difference between tPA (47%) and placebo (30%) groups in percentages of patients with neurologic improvement at 24 h; at 3 mo the global odds for a favorable outcome in the tPA group was 1.7 (95% CI 1.2 to 2.6) times the odds in the placebo group; symptomatic ICH <36 h of stroke onset 7% in tPA and 1% in placebo group (P=.001); 3-mo mortality 17% in the tPA group and 21% in the placebo group (P=.30)	Imbalances noted in baseline NIHSS scores in the 91- to 180-min treatment stratum (Marler et al, Table 3[14]); placebo with lower percentage in the 0 to 5 category (19% tPA versus 4% placebo) and higher percentage in the >20 (18% tPA versus 28% placebo); there was evidence of benefit with the global test statistic combining all 4 outcomes; Genentech supplied and distributed both the tPA and the placebo and was involved in monitoring the clinical sites
Hoffman and Schriger[10] (2009)	III (for Q1)	Secondary analysis of NINDS	Outcomes: Barthel index, mRS score, Glasgow Outcome Scale, NIHSS score at 90 days	Outcomes highly dependent on stroke severity; small differences favored tPA when baseline NIHSS score was in range of 5 to 22; no differences when 90-day change in NIHSS score was graphed; graphs fail to support benefit with using tPA	Graphs do not account for skewed data inherent in the outcome scales; total scores were graphed in lieu of normalized data or other means of handling skewed data

Evidentiary Table (continued).

Study and Year Published	Class of Evidence	Setting and Study Design	Methods and Outcome Measures	Results	Limitations and Comments
Feng et al[13] (2011)	II (for Q1)	Secondary analysis of NINDS	NIHSS score collected at 24 h, 7 days, and 90 days; Barthel Index score collected at 90 days, 6 mo, and 12 mo; mRS score collected at 7 days, 90 days, 6 mo, and 12 mo; Glasgow Outcome Scale score collected at 90 days, 6 mo, and 12 mo; model includes age, sex, study center, treatment group, race/ethnicity, stroke onset to treatment, baseline NIHSS score, time, and treatment group time interaction	Outcome variables strongly correlated with time; Pearson correlations for NIHSS score over time=0.5 to 0.7, mRS score over time=0.76 to 0.82, and Glasgow Outcome Scale score=0.9 to 0.96; at 24 h, 17% of tPA had NIHSS score of 0 to 1 versus 5% of controls; OR higher at all time points (2.1, 1.5 to 3.0); 2-fold benefit in all outcome measures	Baseline NIHSS score was imbalanced (tPA had lower NIHSS score), but authors stated that they incorporated baseline NIHSS score into the modeling
Marler et al[14] (2000)	II (for Q1)	Secondary analysis of NINDS	Adjusted for baseline patient characteristics to determine if onset-to-treatment time impacts hemorrhage and neurologic outcomes at 24 h and 3 mo	tPA treatment between 91 to 180 min had less severe strokes than placebo; after adjusting for NIHSS score as covariate, OR for 3-mo favorable outcome=2.1 between 0 to 90 min and 1.7 between 91 to 180 min; after adjusting for baseline NIHSS score, no effect of onset-to-treatment time detected on ICH	Baseline NIHSS score is predictor of outcome, and the imbalance in NIHSS score may have obscured or confounded increased tPA response in early versus later treatment group; the authors had to combine symptomatic and asymptomatic ICH because there were only 10 patients with this outcome

Evidentiary Table (continued).

Study and Year Published	Class of Evidence	Setting and Study Design	Methods and Outcome Measures	Results	Limitations and Comments
Saver et al[15] (2010)	II (for Q1)	Secondary analysis of NINDS	Authors describe a graph of normalized gain and loss scores	On average, patients treated with tPA in <3 h recovered 2/3, whereas placebo improved ½ toward fully normal	NIHSS and Δ NIHSS scores are ordinal, are severely skewed, and assume equal functional import of the NIHSS score over an integer scale
Hacke et al[21] (ECASS III, 2008)	II (for Q2)	Multicenter randomized controlled trial	Double-blind, placebo controlled; 0.9 mg/kg tPA versus placebo; primary endpoint: 90-day disability, dichotomized as favorable outcome (0 to 1 score on mRS versus 2 to 6); secondary outcome: global outcome analysis of 4 neurologic and disability scores combined: a score of 0 to 1 on mRS, >95 on Barthel Index, NIHSS score 0 to 1, and Glasgow Outcome Score 1; safety endpoints: death, ICH, adverse events; inclusion: 18 y to 80 y, tPA between 3 to 4 h (amended in 2005 to 4.5 h)	N=821; 418 tPA and 403 placebo; median time to administration=3 h 59 min; 10% treated 3 to 3.5 h, 47% 3.5 to 4 h, and 39% 4 to 4.5 h; OR for favorable outcome tPA=1.3, 95% CI 1.0 to 1.8 (52% versus 45%); global analysis OR=1.3, 95% CI 1.0 to 1.7, sICH 2% versus 0.2%; no mortality difference (8% versus 8%); post hoc analysis in intention-to-treat population adjusted for confounding variables using logistic regression, tPA OR=1.4, 95% CI 1.0 to 2.0, *P*=.04 for favorable outcome (score 0 to 1 on mRS), NNT=4	Significant differences between the groups before adjustment with respect to initial severity of the stroke and presence or absence of a history of a stroke; median NIHSS score=9 in tPA versus 10 in placebo, and history of stroke is 8% in tPA versus 14% in placebo; time had to be increased midway through trial to 4.5 h after pooled analysis was published and because of slow recruitment; monitoring and data management were undertaken by trial sponsor

Evidentiary Table (continued).

Study and Year Published	Class of Evidence	Setting and Study Design	Methods and Outcome Measures	Results	Limitations and Comments
Hacke et al[22] (ECASS II, 1998)	II (for Q1)	Multicenter randomized controlled trial	Double-blind, placebo controlled; adults 18 to 80 y with moderate to severe stroke with no or early signs on CT (<33% swelling of MCA territory); 2 arms: tPA 0.9 mg/kg versus placebo with standard care stratified by <3 h and 3 h to 6 h; primary outcome: mRS score at 90 days, dichotomized for favorable score (0 to 1) and unfavorable (2 to 6); secondary outcomes: deaths and symptomatic ICH	N=800 (409 tPA); 40% tPA and 37% placebo patients had favorable outcomes (difference 4%, *P*=.30); differences similar <3 h and 3 to 6 h to treatment; 11% of patients died with no difference between treatment groups at day 90 (SD 14 days); symptomatic ICH occurred for 9% tPA and 3% placebo group patients	Imbalances in baseline prevalences of myocardial infarction and aspirin use; there was no benefit for the primary outcome mRS score 0 to 1; post hoc analysis of mRS score 0 to 2 showed benefit, yet conclusions understate the negative result for the primary outcome; tPA randomization schedule controlled by the Clinical Trial Support Unit at Boehringer Ingelheim, the corporate partner
Sandercock et al[23] (IST-3, 2012)	III (for Q1) III (for Q2)	Multicenter pragmatic randomized controlled trial	Open label; patients received tPA at 0.9 mg/kg body weight versus placebo; primary outcome: alive and independent, defined as an Oxford Handicap Score of 0 to 2 at 6 mo	N=3,035; at 6 mo 554 (37%) in the tPA group versus 534 (35%) in the placebo group were alive and independent (OR 1.13; 95% CI 0.95 to 1.35, *P*=.20); ordinal analysis showed significant change in Oxford Handicap Score (OR 1.3; 95% CI 1.1 to 1.5)	Intervention not blinded to treating physicians; differences in post-tPA treatments, including aspirin, other antiplatelet agents, heparin, and intensive care (supplementary appendix); investigators revised recruitment target midway through trial because of inability to obtain original sample size

Evidentiary Table (continued).

Study and Year Published	Class of Evidence	Setting and Study Design	Methods and Outcome Measures	Results	Limitations and Comments
Wardlaw et al[24] (2012)	II (for Q1)	Systematic review and meta-analysis of randomized trials of tPA versus placebo within 6 h for acute ischemic stroke	Patients received tPA ranging from 0.6 mg/kg to 1.1 mg/kg according to standard guidelines; outcomes: good neurologic function (defined as an mRS score of 0 to 2), or poor neurologic function (defined as an mRS score of 3, 4, or 5); mortality within 7 days	12 trials (N=7,012); odds of good neurologic outcome: 1.2 (95% CI 1 to 1.3); odds of death within 7 days: 1.4 (95% CI 1.2 to 1.8); among patients treated <3 h, odds of good neurologic outcome: 1.5 (95% CI 1.3 to 1.9); among patients treated <3 h, odds of death within 7 days: 0.9 (95% CI 0.7 to 1.1); among patients treated <3 h, odds of symptomatic ICH: 4.6 (95% CI 2.9 to 7.1)	The authors judged the risk of bias to be low across all trials; however, there was substantial methodological heterogeneity among the studies; did not report sensitivity analyses based on quality; 43% of the combined sample resulted from a single study (IST-3 trial)

Evidentiary Table (continued).

Study and Year Published	Class of Evidence	Setting and Study Design	Methods and Outcome Measures	Results	Limitations and Comments
Emberson et al[25] (2014)	III (for Q1) III (for Q2)	Meta-analysis of individual patient data from 9 trials that included completed randomized controlled trial of tPA	Primary outcome measure was proportion of patients with good outcome defined by mRS score <2 at 3 to 6 mo (except IST-3, where there was no 3-mo assessment); secondary outcome included fatal ICH <7 days, any sICH, and 90-day mortality	N=6,756; 1 trial had 3,035 patients with open control group; 2,210/3,756 (31%) had mRS score <2 on discharge; tPA increased odds of good outcome with earlier treatment resulting in greater proportional benefit; after adjusting for treatment delay there was no evidence that stroke severity or age had effect on death or mRS score; tPA increased risk of sICH: 231/3,391 (6.8%) of those who received tPA versus 44/3,365 (1.3%) with no tPA; absolute increased risk of early death because of ICH from tPA=2%; increased disability-free survival of 10% treated <3 h and 5% in 3- to 4.5-h group	Large proportion from IST-3 (open label); 3,035/6,756 were assigned to tPA versus open control and individual data not available for 270 subjects (used imputation); imbalance: patients treated earlier had higher stroke severity, and older patients had higher stroke severity
Aoki et al[26] (2013)	III (for Q1)	Japan, multicenter cohort (registry), retrospective analysis	Prospectively collected data for patients receiving IV tPA ≤3 h; outcomes included sICH* and 3-mo mRS scores	N=526 for tPA ≤3 h with median baseline NIHSS score=12; sICH*=1.5%; excellent functional outcome (mRS score 0 to 1)=37%	The standard dose of tPA (0.6 mg/kg) in Japan is lower than in North America (0.9 mg/kg); patients with preexisting disability prior to stroke onset (N=74) were excluded

Evidentiary Table (continued).

Study and Year Published	Class of Evidence	Setting and Study Design	Methods and Outcome Measures	Results	Limitations and Comments
Hirano et al[27] (2012)	III (for Q1)	Japan, multicenter prospective cohort	Prospectively collected data for patients receiving IV tPA ≤3 h; outcomes included sICH*, 3-mo mortality, and 3-mo mRS score	N=103 for tPA ≤3 h with median baseline NIHSS score=15; sICH*=5.8%; mortality=9.7%; excellent functional outcome (mRS score 0 to 1)=36.9%	The standard dose of tPA (0.6 mg/kg) in Japan is lower than in North America (0.9 mg/kg); patients with early ischemic changes greater than 1/3 of the middle cerebral artery territory were excluded
Karlinski et al[28] (2012)	III (for Q1)	Central and Eastern Europe, multicenter prospective cohort (registry)	Prospectively collected data for patients receiving IV tPA ≤3 h; outcomes included sICH*, 3-mo mortality, and 3-mo mRS score	N=3,428 for tPA ≤3 h with median baseline NIHSS score=12; sICH*=5% based on N=3,316; mortality=18% based on N=2,702; excellent functional outcome (mRS score 0 to 1)=39%; good functional outcome (mRS score 0 to 2)=54% based on N=2,645	Study population appears to overlap with that of Ahmed et al[37]; however, the extent of duplication is unclear; the sample size for the outcomes varied because of incomplete data; the study also reported results for patients receiving tPA off label, but they were not included in this table
Lang et al[29] (2013)	III (for Q1)	Europe, multicenter, double-blind, randomized, controlled trial	Enrolled patients receiving IV tPA ≤3 h; outcomes included 3-mo mortality and 3-mo mRS score	N=59 for the control arm receiving tPA ≤3 h; mean baseline NIHSS score=11; mortality=7%; excellent functional outcome (mRS score 0 to 1)=53%; good functional outcome (mRS score 0 to 2)=66%	This was a randomized controlled trial comparing Cerebrolysin with tPA to a standard IV tPA regimen; the results of the control arm are relevant to the critical question but downgraded to Class III, given the multiple exclusion criteria (poor generalizability) and lack of clear reporting for sICH
Abilleira et al[30] (2011)	III (for Q1)	Catalonia, multicenter prospective cohort (registry)	Prospectively collected data for patients receiving IV tPA ≤3 h; outcomes included sICH, mortality, and mRS score at 3 mo	N=488 for tPA ≤3 h with median baseline NIHSS score=13; sICH*=3%; excellent functional outcome (mRS score 0 to 1)=39%; mortality=17%	Centers compared in subanalysis between centers with prior stroke experience and those with no prior experience

Evidentiary Table (continued).

Study and Year Published	Class of Evidence	Setting and Study Design	Methods and Outcome Measures	Results	Limitations and Comments
Antoncic et al[31] (2011)	III (for Q1)	Croatia, single-center prospective cohort	Prospectively reviewed data for patients receiving IV tPA ≤3 h with comparison to those >3 h from onset of symptoms and not receiving IV tPA; outcomes included sICH within 36 h, mortality, and mRS score at 3 mo	N=71 for tPA ≤3 h with median baseline NIHSS score=14; sICH*=4%; excellent functional outcome (mRS score 0 to 1)=65%; mortality=1.4%; N=71 for control group >3 h from symptom onset and no IV tPA with median baseline NIHSS score=14; sICH* reported; excellent functional outcome (mRS score 0 to 1)=23%; mortality=18%	Compared patients receiving IV tPA within 3 h onset of symptoms to those who present more than 3 h after stroke symptom onset and no IV tPA therapy; small study size in comparison groups, single center; very high rates of excellent functional outcome in IV tPA patients; no patients received tPA after 3 h
Bhatnagar et al[32] (2011)	III (for Q1)	Meta-analysis of observational cohorts	Comprehensive systematic review and analysis of observational patient cohorts receiving IV tPA within 3 h for ischemic stroke; comparison of patients <80 y or ≥80 y; outcomes included sICH, mortality, and 1- to 3-mo mRS score	13 studies identified; sICH OR=1.3; 95% CI 0.9 to 1.8; excellent functional outcome (mRS score 0 to 1) OR=0.5; 95% CI 0.4 to 0.6; death OR=2.8; 95% CI 2.3 to 3.4 in patients ≥80 y when compared with patients <80 y	Attempted to address question of safety and efficacy in patients older than 80 y; no randomization or comparison to controls in these cohort studies; no patients receiving tPA in excess of 3 h

Evidentiary Table (continued).

Study and Year Published	Class of Evidence	Setting and Study Design	Methods and Outcome Measures	Results	Limitations and Comments
Liao et al[33] (2013)	III (for Q1) III (for Q2)	Post hoc retrospective review of multicenter, Chinese stroke registry (TIMS-China)	Retrospectively reviewed data of patients given tPA within 4.5 h of symptoms; outcomes included NIHSS score at time of enrollment and 24 h, sICH at 24 and 36 h, mRS score on day 7 and day 90, and death by day 90	N=574 (409 received tPA between 0 and 3 h and 165 between 3 and 4.5 h); median NIHSS score (IQR) for patients treated within 3 to 4.5 h was 10 (6 to 15); sICH rates (NINDS definition) higher in patients who received tPA between 3 and 4.5 h compared with those receiving tPA between 0 and 3 h, 6% versus 5% (P=.90); mRS score 0 to 2 at 3 mo, 64% for patients treated between 0 and 3 h and 69% for patients treated between 3 and 4.5 h (P=.20); mRS score 0 to 1 at 3 mo 52% for patients treated between 0 h and 3 h and 61% for patients treated between 3 and 4.5 h (P=.10); mortality rates at 7 days and 90 days were 4% and 7% for patients receiving tPA within 3 h and 4% and 8% for patients treated between 3 and 4.5 h; P=.90 for 7 days and P=1.0 for 90 days	Data showed no significant difference in sICH rates with different administration times; favorable functional outcomes were nonsignificantly better; further analysis by the authors showed that most cases in the 3- to 4.5-h group came from medical centers with more experienced stroke physicians and better medical facilities

Evidentiary Table (continued).

Study and Year Published	Class of Evidence	Setting and Study Design	Methods and Outcome Measures	Results	Limitations and Comments
Martins et al[34] (2011)	III (for Q1)	Retrospective review of multicenter Brazilian stroke registry (Porto Alegre Stroke Network)	Retrospectively compared outcomes of elderly (≥80 y) and nonelderly stroke patients who received tPA within 3 h of symptom onset	N=238 stroke patients (55 elderly and 183 nonelderly) sICH: for elderly 11% versus nonelderly 7% (P=.30); mRS score of 0 to 1 at 90 days 58% in nonelderly versus 42% elderly (P=.04); mortality at 90 days 13% for nonelderly and 24% for elderly (P=.05)	NIHSS scores were higher on admission for elderly patients 15 (SD 7) and 11 (SD 6) for nonelderly (P<.001)
Sung et al[35] (2011)	III (for Q1)	Post hoc retrospective analysis of patients ≥80 y in the Taiwan Stroke Registry	Retrospective analysis of registry data assessing the safety and efficacy of tPA given within 3 h of symptoms in elderly (≥80 y)	N=71 patients ≥80 y with NIHSS score ≥6 (30 patients received tPA and 41 patients did not) any parenchymal hemorrhage 17% versus 2%, P=.08 sICH 7% versus 2%, P=.08; gastrointestinal bleeding 13% versus 12%, P=.90; discharge to home 57% versus 61%, P=.70; mRS score at discharge of 0 to 2, 20% versus 17%, P=.80 and inhospital mortality 3% versus 7%, P=.60	tPA dose changed during study period; initially tPA dose was 0.7 mg/kg, 10% bolus to 0.9 mg/kg after June 2009; in this study, IV tPA did not increase the chance of favorable outcome in the elderly

Evidentiary Table (continued).

Study and Year Published	Class of Evidence	Setting and Study Design	Methods and Outcome Measures	Results	Limitations and Comments
Park et al[36] (2014)	III (for Q1) III (for Q2)	Korea, secondary analysis of a multicenter national stroke registry	Patients who received IV tPA were selected from a registry of 10,828 stroke patients; primary outcomes included sICH and mRS score at 3 mo	N=616 tPA within 3 h; median NIHSS score=9; sICH=6%; mortality=12%; excellent functional outcome (mRS score 0 to 1)=42.9%; N=107 for tPA 3 to 4.5 h; median NIHSS score=10; sICH=8.4%; mortality=19.6%; excellent functional outcome (mRS score 0 to 1)=39.3%	Selection bias given that of the 979 patients who received IV tPA within 4.5 h, only 723 were included in the study; limited details related to data collection, data quality, and outcome assessment
Ahmed et al[37] (2013)	III (for Q1) III (for Q2)	Europe, multicenter prospective cohort (registry)	Prospectively collected data for patients receiving IV tPA within specified timeframes; outcomes included sICH, 3-mo mortality, and 3-mo mRS score	N=25,279 for tPA $\leq$3 h with median baseline NIHSS score=12; sICH=7%; mortality=12%; good functional outcome (mRS score 0 to 2)=58% N=4,056 for tPA 3 to 4.5 h with median baseline NIHSS score=9; sICH=7%; mortality=11%; good functional outcome (mRS score 0 to 2)=63%	Excluded stroke patients who received tPA treatment outside of the approved European Union treatment protocol (35% of those who received tPA within 4.5 h)

Evidentiary Table (continued).

Study and Year Published	Class of Evidence	Setting and Study Design	Methods and Outcome Measures	Results	Limitations and Comments
Sung et al[38] (2013)	III (for Q1)	Taiwan, prospective cohort (registry)	Prospectively collected data for patients receiving IV tPA ≤3 h; primary outcome was sICH	N=548 for tPA ≤3 h with mean baseline NIHSS score=13; sICH=7% (95% CI 4% to 8%)	The aim was to assess the accuracy of scoring systems for predicting sICH
Alias et al[39] (2011)	III (for Q1) III (for Q2)	United States, single center retrospective cohort	Retrospectively reviewed data for patients receiving IV tPA ≤3 h with comparison to those receiving it at >3 h; outcomes included sICH at 24 h, modified Barthel Index score at 3 mo, and inhospital mortality	N=251 for tPA ≤3 h with mean baseline NIHSS score=12; sICH*=4%; mean modified Barthel Index score at 3 mo=16.4; inhospital mortality=18%; N=39 for tPA 3 to 4.5 h with mean baseline NIHSS score=15; sICH*=8% (not statistically different from comparison group); mean modified Barthel Index score at 3 mo=16; inhospital mortality=27%	Retrospective design, single center with low patient numbers

Evidentiary Table (continued).

Study and Year Published	Class of Evidence	Setting and Study Design	Methods and Outcome Measures	Results	Limitations and Comments
Chao et al[40] (2013)	III (for Q1)	Taiwan, retrospective, single stroke center; included adults receiving 0.9 mg/kg <3 h	Renal dysfunction defined as GFR <60 mL/min and used registry data to determine sICH (defined by NINDS), mRS score, and death at 1 mo and 1 y; used multivariable regression to determine whether renal dysfunction predicted sICH, mRS score, and death; final model included age in years, GFR, sugar levels, triglycerides, and NIHSS score during ED evaluation	N=297; 65 with renal dysfunction versus 232 normal; ICH was more common in renal dysfunction (23% versus 13%); overall 14/297 (5%) had sICH; multivariable analysis did not demonstrate that renal dysfunction predicted ICH, dependence, or death at 1 mo or 1 y	Retrospective, observational, all included patients received tPA; no information on how mRS score was measured at 1 mo or 1 y; small sample with only 14 patients who had sICH; arbitrary categorization of renal dysfunction; authors lump together functional dependency and death so the number of deaths cannot be determined
Cronin et al[41] (2014)	III (for Q1) III (for Q2)	United States stroke registry patients receiving tPA within 4.5 h; data from 1,464 hospitals in United States participating in the Get With the Guidelines study	Study aimed to assess adherence to ECASS guidelines for administering tPA	N=32,019; sICH=5% in both the 0- to 3-h and >3- to 4.5-h groups	Data available only for patients receiving tPA

Evidentiary Table (continued).

Study and Year Published	Class of Evidence	Setting and Study Design	Methods and Outcome Measures	Results	Limitations and Comments
Flint et al[42] (2014)	III (for Q1)	Europe, stroke registry patients receiving tPA with 3 h; data from 285 centers in 14 European countries	Study aimed to assess the THRIVE score to predict sICH after tPA	N=5,970; sICH 7% (468/5,970)	Data available only for patients receiving tPA
Mehrpour et al[43] (2013)	III (for Q1)	Iran, prospective stroke registry at single medical center	Consecutive patients receiving tPA according to NINDS protocol	N=37; sICH=5%	Small sample size; limited details related to data collection, data quality, and outcome assessment
Saver et al[44] (2013)	III (for Q1) III (for Q2)	United States stroke registry of patients receiving tPA within 4.5 h; data from 1,395 hospitals in United States participating in Get With the Guidelines	Voluntary registry of stroke patients; logistic regression models used to assess the association between time to tPA treatment and inhospital outcomes such as sICH and mortality	N=51,158 patients with acute ischemic stroke treated with IV tPA with median NIHSS score=11; sICH=4% (193/4,818) treated ≤90 min; sICH=5% (1,965/39,398) treated 1.5 to 3 h, sICH=5.1% (351/6,942) treated 3 to 4.5 h	Analysis based only on subjects with baseline NIHSS score recorded in database (ie, 12% of cohort excluded because of missing NIHSS data); functional outcomes and mortality at 30 or 90 days were not reported; likely substantial overlap with subjects included in other Get With the Guidelines registry studies such as Cronin et al[41]
Chowdhury et al[45] (2012)	III (for Q1)	United Kingdom, single-center cohort	Retrospective analysis of cohort receiving IV tPA ≤3 h with approximately 46% treated by telemedicine after 5 PM or on weekends; outcomes included sICH,* 3-mo mortality, and 3-mo mRS score	N=97 for tPA ≤3 h with median baseline NIHSS score=12 for telemedicine group and 13 for face-to-face group; sICH=6%; mortality=13%; good functional outcome (mRS score 0 to 2)=39%	Majority of patients recruited from a single ED; however, a few inpatients treated for acute stroke were included

Evidentiary Table (continued).

Study and Year Published	Class of Evidence	Setting and Study Design	Methods and Outcome Measures	Results	Limitations and Comments
Saarinen et al[46] (2012)	III (for Q1)	Finland, retrospective cohort	Retrospective analysis of anterior circulation stroke confirmed by CT angiography receiving tPA in <3 h; outcomes included sICH*, 3-mo mortality, and 3-mo mRS score	N=105 for tPA received in <3 h with mean baseline NIHSS score=13; sICH*=5%; good functional outcome (mRS score 0 to 2)=51%	The aim of the study was to compare those with thrombus in the internal carotid artery or proximal M1 segment of the middle cerebral artery to those with more distal thrombus; results indicate that those with a more distal thrombus have a better prognosis
Kono et al[47] 2013	III (for Q1)	Japan, multicenter, retrospective registry cohort	Retrospectively collected data for patients receiving IV tPA within 3 h at 4 hospitals; outcomes included sICH, and median NIHSS score at 3 days and 7 days postonset	N=114 (11 treated without IV tPA and 103 with treatment) with median baseline NIHSS score of 10 in IV tPA patients and 16 in nontreated patients; sICH*=3% in IV tPA patients and 0% in nontreated patients (P=.70); median NIHSS score at 7 days after onset=2 in IV tPA patients and 10 in nontreatment patients (P=.02)	Small study size; IV tPA not randomly allocated between treatment groups; no patients received tPA after 3 h from symptom onset
Seet et al[48] (2014)	III (for Q1)	Retrospective cohort study from single center	Primary goal to assess the impact of BMI categories on stroke outcomes of patients receiving tPA within 3 h of symptom onset; safety outcome=sICH defined by ECASS II criteria	N=169; 9 (5%) sICH	Data extrapolated from tables having values separated by BMI categories; 70% of patients were either overweight or obese and received <0.9 mg/kg of tPA

Evidentiary Table (continued).

Study and Year Published	Class of Evidence	Setting and Study Design	Methods and Outcome Measures	Results	Limitations and Comments
McKinney et al[49] (2012)	III (for Q1)	France, Spain, and United States, multicenter case series	Retrospective analysis of stroke cases receiving tPA in ≤3 h following a recent TIA; primary outcome was sICH*	N=16 for tPA in ≤3 h with median baseline NIHSS score=12; sICH*=6%	All patients had TIA within 7 days of stroke; data for patients who received intra-arterial or mechanical thrombolysis were not included in the evidentiary table
Wardlaw et al[50] (2014)	III (for Q1) III (for Q2)	Meta-analysis of Cochrane Stroke Group Trials Register, MEDLINE, EMBASE, and hand-searched conferences, etc for all randomized trials of thrombolytic compared with placebo or open control in AIS patients	Primary goal was to determine whether IV tPA is effective and safe for the treatment of AIS; primary outcome measures were death or dependency as defined by mRS score of 3 to 6 or death, sICH with 7- to 10-day fatal ICH; contacted investigators for missing data and tested for heterogeneity using the I2 statistic; also attempted to assess for publication bias using the funnel plot; also looked at effect of stroke severity, younger or older than age 80 y, time from stroke to treatment, effect of large infarct on outcomes	27 trials with 10,187 patients receiving urokinase, streptokinase, tPA, recombinant urokinase, or desmoteplase, ranging from 0 h to 6 h from symptom onset; 44% of trials and 70% of patients received IV tPA; most trials only administered tPA in <6 h; 16% of participants >80 y; 0 to 3 h from symptom onset using tPA: 6 trials, 1,779 patients for efficacy, resulting in 9% (95% CI 5% to 14%) (NNT=11; 95% CI 7 to 22) absolute increase in good neurologic function; 5 trials, 1,155 patients for safety, resulting in 7% (95% CI 5% to 10%) (NNH=14; 95% CI 10 to 21) absolute increase in sICH; 3 to 4.5 h from symptom onset using tPA: 1 trial, 821 patients (see results for ECASS III[21])	Heterogeneity between trials with different doses, ages, timeframes, drugs, routes (4 included intra-arterial), and definitions of outcome (mRS score, Barthel Index, Oxford Handicap); concomitant use of other antithrombotics, and different definitions of sICH; 5 trials were single-blind without a placebo, and in IST-3,[23] except for the first 276 patients, 2,759 were open label

Evidentiary Table (continued).

Study and Year Published	Class of Evidence	Setting and Study Design	Methods and Outcome Measures	Results	Limitations and Comments
Topakian et al[51] (2011)	III (for Q1)	Retrospective analysis of SITS-MOST (Austria) and SITS-ISTR (International) registry data	Retrospective comparison of patients treated with tPA within 3 h of symptoms in Austria compared with other international countries; reported outcomes included time to treatment, functional outcomes, sICH, and mortality	N=16,049; Austrian patients had a significantly shorter stroke onset–to-treatment time; median, IQR: 135, 105 min to 160 min versus 145, 115 min to 170 min, $P<.001$); sICHs* were observed in 2% of Austrian and 2% of non-Austrian patients ($P=.80$); at 3 mo 51% of Austrian and 53% of non-Austrian patients were independent (mRS score 0 to 2; $P=.20$) but death was less frequent in Austrian patients (12% versus 15%; $P=.03$)	Post hoc retrospective analysis of registry data comparing the subgroup of patients enrolled in Austria to those enrolled in other countries; selection bias

Evidentiary Table (continued).

Study and Year Published	Class of Evidence	Setting and Study Design	Methods and Outcome Measures	Results	Limitations and Comments
Clark et al[52] (1999)	III (for Q2)	Multicenter randomized controlled trial	Double-blind, placebo-controlled; patients received tPA at 0.9 mg/kg versus placebo from 3 to 5 h after symptom onset; primary outcome: excellent neurologic function at 90 days as defined by NIHSS score of 0 or 1; secondary outcomes included Barthel Index, mRS score, and Glasgow Outcome Scale scores at 30 days and 90 days	N=613; 35% of tPA group versus 34% of controls had good neurologic function at 90 days (P=.90)	Some imbalances in baseline characteristics, including diabetes mellitus more common among patients who received tPA; multiple modifications to the study protocol and enrollment processes; no prespecified stopping criteria; sponsor (Genetech) involved in management and analyses
Ebinger et al[53] (2012)	III (for Q2)	Germany single-center cohort	Subgroup analysis of MRI study; enrolled patients receiving IV tPA in ≤4.5 h and MRI; outcomes included sICH, mortality, and 3-mo mRS score	N=131 for tPA in ≤4.5 h with median NIHSS score=8; sICH*=3%; mortality=15%; mRS score (0 to 2)=50%	Study did not separately report results for tPA in <3 h or 3 to 4.5 h

Evidentiary Table (continued).

Study and Year Published	Class of Evidence	Setting and Study Design	Methods and Outcome Measures	Results	Limitations and Comments
Garcia-Bermejo et al[54] (2012)	III (for Q2)	Spain single-center prospective cohort	Compared patients receiving IV tPA in ≤4.5 h with those receiving IV tPA in >4.5 h; outcomes included sICH and 3-mo mRS score	N=172 for tPA ≤4.5 h with median NIHSS score=11; sICH*=3%; mRS score (0 to 2)=65%	Study did not separately report results for tPA in <3 h or 3 to 4.5 h
Paliwal et al[55] (2012)	III (for Q2)	Singapore, single-center retrospective analysis of cohort (registry)	Included patients receiving IV tPA in ≤4.5 h; outcomes included sICH and 3-mo mRS score	N=226 for tPA in ≤4.5 h with median NIHSS score=17; sICH=5%; mRS score (0 to 2)=52%	Study did not separately report results for tPA in <3 h or 3 to 4.5 h; excluded posterior circulation strokes
Sairanen et al[56] (2011)	III (for Q2)	Finland, cohort	Included patients receiving IV tPA in ≤4.5 h at community hospitals by the telestroke network; outcomes included sICH, mortality, and 3-mo mRS score	N=57 for tPA in ≤4.5 h with median NIHSS score=10; sICH=7%; mortality=12% (based on N=60); mRS score (0 to 1)=29%; mRS score (0 to 2)=49%	Study did not separately report results for tPA in <3 h or in 3 to 4.5 h; excluded basilar artery strokes; neurology consultations were done by televideo conferencing
Sobolewski et al[57] (2013)	III (for Q2)	Poland, single-center retrospective analysis of cohort	Included patients receiving IV tPA in ≤4.5 h by telestroke network; outcomes included sICH, mortality, and 3-mo mRS score	N=200 for tPA in ≤4.5 h with mean NIHSS score=12; sICH*=5%; mortality=16%; mRS score (0 to 2)=58%	Study did not separately report results for tPA in <3 h or 3 to 4.5 h

Evidentiary Table (continued).

Study and Year Published	Class of Evidence	Setting and Study Design	Methods and Outcome Measures	Results	Limitations and Comments
Strbian et al[58] (2013)	III (for Q2)	Europe, multicenter cohort (registry)	Merged individual patient-level data for those receiving IV tPA in ≤4.5 h; aim was to assess the outcomes of patients receiving ultra-early tPA (<90 min); outcomes included sICH and 3-mo mRS score	N=6,856 for tPA in ≤4.5 h with mean NIHSS score=11; sICH=4%; mRS score (0 to 1)=29%; ultra-early administration of tPA (<90 min) was associated with excellent functional outcomes among those with moderate to severe stroke (ie, NIHSS score 7 to 12); adjusted OR=1.4 (95% CI 1.1 to 1.7)	Study did not separately report results for tPA in <3 h or 3 to 4.5 h
Turc et al[59] (2013)	III (for Q2)	France, single-center cohort	Included patients receiving IV tPA in ≤4.5 h with anterior circulation stroke by MRI to develop an imaging-based scoring system; outcome was 3-mo mRS score	N=228 for tPA in ≤4.5 h with median NIHSS score=14, mRS score (0 to 2)=57%	Study did not separately report results for tPA in <3 h or 3 to 4.5 h; patients not having MRI were excluded
Vujkovic et al[60] (2012)	III (for Q2)	Bosnia, single-center cohort	Included patients receiving IV tPA in ≤4.5 h; outcomes were sICH and inhospital mortality	N=100 for tPA in ≤4.5 h with mean NIHSS score=11; sICH*=5%; inhospital mortality=6%	Study did not separately report results for tPA in <3 h (N=96) or 3 to 4.5 h (N=4)

Evidentiary Table (continued).

Study and Year Published	Class of Evidence	Setting and Study Design	Methods and Outcome Measures	Results	Limitations and Comments
Xian et al[61] (2012)	III (for Q2)	United States, multicenter cohort (registry)	Enrolled patients receiving IV tPA in ≤4.5 h to compare outcomes of those on warfarin with those who were not; outcome was sICH	N=23,437 for tPA in ≤4.5 h with NIHSS score=14 if on warfarin and NIHSS score=11 if not; overall sICH=5%; the unadjusted risk for sICH among those on warfarin was higher (6%) versus those not on warfarin (5%) but not statistically different when adjusted for baseline clinical factors (OR=1.0)	Study did not separately report results for tPA in <3 h or 3 to 4.5 h; patients with INR >1.7 or with missing data about INR or warfarin use were excluded
Zinkstok and Roos[62] (2012)	III (for Q2)	Netherlands, control arm of open-label randomized controlled trial	Enrolled patients receiving IV tPA in ≤4.5 h to compare outcomes of those randomized to early IV aspirin therapy to those without; outcomes included sICH, 3-mo mortality, and 3-mo mRS score	N=320 for tPA in ≤4.5 h that did not receive IV aspirin (control arm) with mean NIHSS score=9; sICH*=1.6%; mortality=10%; mRS score (0 to 2)=57%	Study did not separately report results for tPA in <3 h or 3 to 4.5 h; trial was stopped early because of excess sICH in the early IV aspirin arm

Evidentiary Table (continued).

Study and Year Published	Class of Evidence	Setting and Study Design	Methods and Outcome Measures	Results	Limitations and Comments
Dharmasaroja et al[63] (2011)	III (for Q2)	Thailand, single-center retrospective cohort	Retrospectively reported data for patients receiving IV tPA in ≤4.5 h; outcomes included sICH, mortality, and mRS score at 3 mo	N=197 with median baseline NIHSS score=12; sICH*=18% (asymptomatic in 14% and symptomatic in 4%); excellent functional outcome (mRS score 0 to 1)=47%; mortality=12%	Study did not separately report results for tPA in <3 h or 3 to 4.5 h; relatively small study size
Fischer et al[64] (2012)	III (for Q2)	Bern, multicenter prospective cohort	Prospectively collected data for patients receiving IV tPA in ≤3 h; outcomes included sICH, mortality, and mRS scores at 3 mo and 12 mo	N=107 (13%) of total patients in study underwent thrombolysis with 35 receiving IV tPA in ≤4.5 h, 41 intra-arterial within 6 h, and 5 mechanical thrombectomy within 8 h; median baseline NIHSS score=5; sICH*=3.3%; excellent functional outcome (mRS score 0 to 1)=48.2% at 3 mo and 44.6% at 12 mo; mortality=20.6 at 3 mo, 27.4% at 12 mo	Small number of IV tPA patients; selected patients received IV, intra-arterial, or mechanical thrombolysis, with no separate data reporting for outcomes in these groups; no sICH data reported; study did not separately report results for tPA in <3 h or 3 to 4.5 h
Al-Khaled et al[65] (2014)	III (for Q2)	Germany, secondary analysis of stroke registry of AIS treated in <4.5 h over 4-y period	Defined sICH as any bleeding and increase in NIHSS score by 4 points; used logistic regression to determine predictors of death and sICH and used significance testing on bivariate to select multivariable predictors	N=1,007; mean NIHSS score=12; 83 (8%) died during hospitalization; sICH*=58 (6%); mortality predictors included ≥80 y, aphasia, altered consciousness, hypertension, sICH, pneumonia; sICH predictors included age, NIHSS score, and atrial fibrillation	No control group, observational, and multivariable model based on statistical significance; with only 58 with sICH outcome, possible overfitting with 14 covariates

Evidentiary Table (continued).

Study and Year Published	Class of Evidence	Setting and Study Design	Methods and Outcome Measures	Results	Limitations and Comments
Tong et al[66] (2014)	III (for Q2)	CDC Stroke Registry; state health department data, including that from Georgia, Illinois, Massachusetts, North Carolina, Michigan, Minnesota, and Ohio	Study aimed to assess risk factors associated with inhospital death and sICH among patients who received tPA within 4.5 h of symptom onset	N=7,193; median NIHSS score=11; sICH=5%	Study failed to use imputation for missing data; 13% had missing NIHSS scores
Yeo et al[67] (2013)	III (for Q2)	Secondary analysis of prospective registry from a single center	Primary goal was to evaluate whether neurologic improvement at 2 h and 24 h after IV tPA was associated with 3-mo functional outcomes (mRS score) and sICH	N=263; median baseline NIHSS score=17; sICH*=4%; excellent functional outcomes (mRS score 0 to 1)=49%	Limited details related to data collection, data quality, and outcome assessment
Dharmasaroja et al[68] (2012)	III (for Q2)	Thailand, single-center prospective cohort (registry)	Enrolled patients receiving IV tPA ≤4.5 h; outcomes included sICH, mortality, and 3-mo mRS score	N=194 for tPA ≤4.5 h; sICH=6%; mortality=12%; mRS score (0 to 1)=46%	Study did not separately report results for tPA in <3 h or 3 to 4.5 h

Evidentiary Table (continued).

Study and Year Published	Class of Evidence	Setting and Study Design	Methods and Outcome Measures	Results	Limitations and Comments
Meurer et al[69] (2013)	III (for Q2)	Michigan, retrospective analysis of multicenter cluster randomized trial	Included patients who received IV tPA and were either on antiplatelet therapy or not; outcome was sICH	N=830, with 47% on antiplatelet therapy prior to receiving IV tPA; overall sICH=8%; there was a 3% absolute increased risk of sICH among those on antiplatelet therapy compared with those who were not	Study did not separately report results for tPA in <3 h or 3 to 4.5 h
Paciaroni et al[70] (2012)	III (for Q2)	Italy, multicenter cohort (registry)	Enrolled patients receiving IV tPA in ≤4.5 h; this was a subgroup analysis to compare those with an extracranial internal carotid occlusion to those without; outcomes included sICH, mortality, and 3-mo mRS score	N=1,856 for tPA in ≤4.5 h; sICH=8%; mortality=11%; mRS score (0 to 1)=46%; mRS score (0 to 2)=60%	Study did not separately report results for tPA in <3 h or 3 to 4.5 h
Messe et al[71] (2012)	III (for Q2)	Retrospective review of US quality improvement database (Get With the Guidelines—Stroke)	Retrospectively compared outcomes of patients with AIS treated with IV tPA in the 3- to 4.5-h time window before and after publication of ECASS III	N=5,254 stroke patients (1,322 patients pre–ECASS III and 3,932 patients post–ECASS III); sICH pre–ECASS III 7% and post–ECASS III 5% (P=.002); ambulatory at discharge 33% versus 35% (P<.001); died 10% versus 8% (P<.001)	There were no significant differences in inhospital mortality, ambulatory status at discharge, or discharge home after ECASS III

Evidentiary Table (continued).

Study and Year Published	Class of Evidence	Setting and Study Design	Methods and Outcome Measures	Results	Limitations and Comments
Wong et al[72] (2012)	III (for Q2)	Hong Kong, historical cohort study	Retrospective comparison of patients during the same period who received thrombolysis versus patients who did not because stroke team was not available	N=111 (48 thrombolysis and 63 nonthrombolysis patients); 52% of the thrombolysis group achieved functional independence compared with 24% of nonthrombolysis group (P=.003), without significant increase in mortality (15% versus 13%, P=.50) or sICH (4% versus 2%, P=.60); 29% of the thrombolysis group patients were discharged home directly versus 6% of nonthrombolysis group (P<.001); mean length of stay was shorter for the thrombolysis group (25 versus 35 days; P=.03)	Baseline characteristics of both groups were comparable except for onset-to-door time, prior anticoagulant, and acute stroke unit care; tPA dose was not standardized; weight was not recorded for 16 patients, each of whom received 50 mg; 6 patients received <0.9 mg/kg; of the patients who received 0.9 mg/kg, 1 received more than the recommended maximum dose
Ebinger et al[73] (2014)	III (for Q2)	Germany, quasi-randomized trial of prehospital stroke vehicles versus standard care	Alternating weeks of Stroke Emergency Mobile ambulances that included CT scanner, point-of-care laboratory, and telemedicine versus standard of care; primary outcome: alarm to thrombolysis time; secondary outcomes: thrombolysis rate, sICH, and 7-day mortality	N=730 (received IV tPA); sICH=5%	This study did not assess the efficacy of tPA; instead, it evaluated the use of a specialized prehospital ambulance and time to administration of tPA; this prospective study did include a cohort of patients who received IV tPA (0.9 mg/kg) within 4.5 h and reported sICH, defined as any new hemorrhage by CT with decline in neurologic status as defined in the original NINDS trial

Evidentiary Table (continued).

Study and Year Published	Class of Evidence	Setting and Study Design	Methods and Outcome Measures	Results	Limitations and Comments
Fonarow et al[74] (2014)	III (for Q2)	United States, stroke registry patients receiving tPA within 4.5 h; data from the Get With the Guidelines registry	Study aimed to assess the impact of an educational program on door-to-needle times and outcomes for registry patients with a pre- and postintervention design	sICH=5% (3,514/71,169)	Retrospective registry data; participation representative of stroke centers with experience administering tPA; no control
Hsieh et al[75] (2014)	III (for Q2)	Taiwan, stroke registry from 4 hospitals	Study aimed to assess the impact of renal insufficiency on outcomes of patients who received tPA within 4.5 hours; outcome determined by a senior stroke neurologist at each hospital, who was blinded to the renal function status	N=657; sICH=8%	Numerator not reported, but calculated from the data in the article; all patients had renal insufficiency; patients received variable dosage of tPA (0.6 to 0.9 mg/kg), given data suggesting Asian patients may have better outcomes with a lower dose

Evidentiary Table (continued).

Study and Year Published	Class of Evidence	Setting and Study Design	Methods and Outcome Measures	Results	Limitations and Comments
Reiter et al[76] (2014)	III (for Q2)	Austria, secondary analysis of a prospective stroke registry	Primary goal was to compare outcome data of patients matched according to tPA administration and whether patient had diabetes mellitus; data collection standardized and performed by trained neurologists; primary outcome=mRS score at 3 mo; safety outcome=sICH as defined by the NINDS criteria; multivariable logistic regression analysis to estimate associations between tPA and functional outcomes while adjusting for confounders; interaction terms included to assess for modification of diabetes	N=1,464 matched pairs used for primary outcome assessment; no significant differences in matching for age, sex, functional impairment before stroke, stroke severity, and stroke history; functional outcome better in patients with diabetes who received tPA compared with those who did not ($P<.01$); functional outcomes also better in patients without diabetes who received tPA when compared with those who did not ($P=.01$); sICH=4%	Observational study without blinding or randomization; potential selection bias given restriction to patients with available data; although they were matched across a number of important characteristics, it is possible other characteristics existed that confounded the relationship between tPA and the outcomes
Strbian et al[77] (2014)	III (for Q2)	Finland, secondary analysis of prospectively collected data from 7 centers	Primary goal to compare various scores in predicting sICH after receiving tPA within 4.5 h; safety outcome was sICH	N=3,012; sICH=7%	Retrospective analysis of a merged cohort with no control group

Evidentiary Table (continued).

Study and Year Published	Class of Evidence	Setting and Study Design	Methods and Outcome Measures	Results	Limitations and Comments
Ciccone et al[78] (2013)	III (for Q2)	Italy, multicenter, open-label, randomized, controlled trial	Trial enrolled patients receiving IV tPA ≤4.5 h versus endovascular therapy; outcomes included sICH, mortality, and 3-mo mRS score	N=181 for IV tPA ≤4.5 h control arm; sICH*=6%; mortality=10%; mRS score (0 to 1)=35%, mRS score (0 to 2)=46%	Study did not separately report results for IV tPA in <3 h or 3 to 4.5 h
Matijevic et al[79] (2012)	III (for Q2)	Croatia, multicenter retrospective cohort	Included patients receiving IV tPA in ≤4.5 h; outcome was sICH	N=166 for tPA ≤4.5 h; sICH*=5%	Study did not separately report results for tPA in <3 h or 3 to 4.5 h
Lahoti et al[80] (2014)	III (for Q2)	United States, Europe, and India, retrospective multicenter (8 centers) over 5 y with no evidence of occlusion on imaging	Divided patients into tPA versus no tPA; primary outcome was excellent clinical outcome (mRS score 0 to 1) at 90 days	N=256; 103 tPA and 153 no tPA; multivariable logistic regression: tPA had OR for excellent outcome of 4, but tPA had more sICH* (5% versus 1% without tPA); excellent outcomes with tPA were better with nonlacunar (OR=4.9) and lacunar (OR=9.3) stroke compared with that of all of those receiving tPA; estimated NNT=6 for excellent functional outcome; NNH=24 for sICH	Retrospective, highly select group of AIS patients who did not have an occlusion at baseline, and imbalanced groups at baseline with respect to age, diabetes mellitus, NIHSS score; excluded patients who had preexisting mRS score >2

Evidentiary Table (continued).

Study and Year Published	Class of Evidence	Setting and Study Design	Methods and Outcome Measures	Results	Limitations and Comments
Lylerly et al[81] (2014)	III (for Q2)	Secondary analysis of University of Alabama stroke registry; retrospective, single, tertiary care center chart review	Primary goal to determine safety of IV tPA among patients with contraindications to tPA; defined protocol violation as any contraindication listed in original tPA stroke study; multiple outcomes were reported including sICH; unfavorable outcome defined by mRS score 3 to 6 at discharge	N=212; sICH*=2%; protocol violations occurred in 76 (36%), with most common violations being >3 h, aggressive blood pressure control, elevated PT/PTT, resolving deficits, unclear onset time, and prior stroke within 3 mo; no difference in safety outcome or discharge disposition between patients with and without protocol violations	Retrospective, single center, observational, no control group; outcomes based on chart review yet chart review methods not clearly described (ie, no description of who performed the mRS assessment or read the scans)

Evidentiary Table (continued).

Study and Year Published	Class of Evidence	Setting and Study Design	Methods and Outcome Measures	Results	Limitations and Comments
Murao et al[82] (2014)	III (for Q2)	France and Japan, secondary analysis of stroke registry	Primary goal to evaluate prestroke cognitive impairment on outcomes of patients who received IV tPA within <4.5 h; dose in Japan=0.6 mg/kg; France=0.9 mg/kg; excluded thrombolytic therapy administered intra-arterially, patients with an mRS score ≥2 at baseline and inability to perform the IQCODE; defined PSCI as score >3 on the IQCODE; primary outcome was mRS score 0 to 1 at 3 mo, secondary outcome included sICH, mRS score 0 to 2, and 3-mo mortality; mRS assessment done face-to-face or by telephone	N=205; sICH*=6%; mortality=5%; excellent functional outcome (mRS score 0 to 1)=49%; 62 (30%) had PSCI score ≥3 and were 11 y older, had more sICH, and higher median baseline NIHSS score (9 versus 8); analysis adjusted for age, NIHSS score, and time to needle, demonstrated no association with sICH, mRS score 0 to 1, mRS score 0 to 2, or death	Small sample size; no control group; inadequate power to perform multivariable analysis; finding no effect should not be interpreted as IQCODE having no predictive value; PSCI was evaluated retrospectively and was categorized at a threshold of 3 because the investigators wanted to increase the sensitivity of the test to diagnose mild cognitive impairment; dose of tPA differed between France and Japan, and no consideration for clustering by center
Goyal et al[83] (ESCAPE, 2015)	III (for Q2)	Worldwide; open-label randomized controlled trial compared endovascular intervention with IV tPA alone (control arm)	Enrolled subjects with acute anterior circulation stroke with small infarct core on CT; all patients received IV tPA ≤4.5 h; outcomes included sICH,* 3-mo mortality, and 3-mo mRS score	N=150 patients who received tPA ≤4.5 h and who did not receive endovascular intervention (control arm) with median NIHSS score=17; sICH*=2.7%; mortality=19%; mRS score (0 to 2)=29%	Trial stopped early for efficacy; patients with large infarct core or poor collateral circulation were excluded; although most control subjects received tPA within 3 h, some received tPA up to 4.5 h

Evidentiary Table (continued).

Study and Year Published	Class of Evidence	Setting and Study Design	Methods and Outcome Measures	Results	Limitations and Comments
Campbell et al[84] (EXTEND-IA, 2015)	III (for Q2)	Australia and New Zealand; open-label randomized controlled trial compared endovascular intervention and IV tPA with IV tPA alone	Enrolled subjects with acute large-vessel anterior circulation stroke with salvageable tissue and infarct core <70 mL on CT perfusion; all patients received IV tPA ≤4.5 h; outcomes included sICH,* 3-mo mortality, and 3-mo mRS score	N=30 patients who received tPA ≤4.5 h and who did not receive endovascular intervention (control arm) with median NIHSS score=13; sICH*=6%; mortality=20%; mRS score (0 to 2)=40%	Stopped early for efficacy; 25% of eligible subjects were excluded on the basis of CT perfusion criteria; most patients received tPA within 3 h but some received it in up to 4.5 h

*When sICH was reported, the NINDS definition of sICH was used (ie, any neurologic deterioration associated with hemorrhage on imaging); however, some studies (marked with *) reported sICH if associated with a neurologic deterioration of greater than or equal to 4 points on NIHSS, or death.

AIS, acute ischemic stroke; *BMI*, body mass index; *CI*, confidence interval; *CT*, computed tomography; *ECASS*, European Cooperative Acute Stroke Study; *ED*, emergency department; *EXTEND-IA*, Extending the Time for Thrombolysis in Emergency Neurological Deficits — Intra-Arterial; *GFR*, glomerular filtration rate; *h*, hour; *ICH*, intracranial hemorrhage; *INR*, International Normalized Ratio; *IQCODE*, Informant Questionnaire on Cognitive Decline in the Elderly; *IQR*, interquartile range; *IST-3*, the Third International Stroke Trial; *ISTR*, International Stroke Thrombolysis Register; *IV*, intravenous; *kg*, kilogram; *MCA*, middle cerebral artery; *mg*, milligram; *min*, minute; *mL*, milliliter; *mo*, month; *MOST*, MOnitoring STudy; *MRI*, magnetic resonance imaging; *mRS*, modified Rankin Scale; *N*, number of patients; *NIHSS*, National Institutes of Health Stroke Scale; *NINDS*, National Institute of Neurological Disorders and Stroke; *NNH*, number needed to harm; *NNT*, number needed to treat; *OR*, odds ratio; *PSCI*, prestroke cognitive impairment; *PT*, prothrombin time; *PTT*, partial thromboplastin time; *Q*, question; *SD*, standard deviation; *sICH*, symptomatic intracranial hemorrhage; *SITS*, Safe Implementation of Thrombolysis in Stroke; *THRIVE*, Totaled Health Risks in Vascular Events; *TIA*, transient ischemic attack; *TIMS*, Thrombolysis Implementation and Monitor of acute ischemic Stroke; *tPA*, tissue plasminogen activator; *y*, year.