

Scientific Rationale for the Inclusion and Exclusion Criteria for Intravenous Alteplase in Acute Ischemic Stroke

A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association

The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists.

Endorsed by the American Association of Neurological Surgeons and Congress of Neurological Surgeons

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Purpose—To critically review and evaluate the science behind individual eligibility criteria (indication/inclusion and contraindications/exclusion criteria) for intravenous recombinant tissue-type plasminogen activator (alteplase) treatment in acute ischemic stroke. This will allow us to better inform stroke providers of quantitative and qualitative risks associated with alteplase administration under selected commonly and uncommonly encountered clinical circumstances and to identify future research priorities concerning these eligibility criteria, which could potentially expand the safe and judicious use of alteplase and improve outcomes after stroke.

Methods—Writing group members were nominated by the committee chair on the basis of their previous work in relevant topic areas and were approved by the American Heart Association Stroke Council's Scientific Statement Oversight Committee and the American Heart Association's Manuscript Oversight Committee. The writers used systematic literature reviews, references to published clinical and epidemiology studies, morbidity and mortality reports, clinical and public health guidelines, authoritative statements, personal files, and expert opinion to summarize existing evidence and to indicate gaps in current knowledge and, when appropriate, formulated recommendations using standard American Heart Association criteria. All members of the writing group had the opportunity to comment on and approved the final version of this document. The document underwent extensive American Heart Association internal peer review, Stroke

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

This statement was approved by the American Heart Association Science Advisory and Coordinating Committee on September 24, 2015, and the American Heart Association Executive Committee on October 5, 2015. A copy of the document is available at <http://my.americanheart.org/statements> by selecting either the "By Topic" link or the "By Publication Date" link. To purchase additional reprints, call 843-216-2533 or e-mail kelle.ramsay@wolterskluwer.com.

The online-only Data Supplement, which contains literature search strategies and Figures A, B, and C, is available with this article at <http://circ.ahajournals.org/lookup/suppl/doi:10.1161/STR.0000000000000086/-/DC1>.

The American Heart Association requests that this document be cited as follows: Demaerschalk BM, Kleindorfer DO, Adeoye OM, Demchuk AM, Fugate JE, Grotta JC, Khalessi AA, Levy EI, Palesch YY, Prabhakaran S, Saposnik G, Saver JL, Smith EE; on behalf of the American Heart Association Stroke Council and Council on Epidemiology and Prevention. Scientific rationale for the inclusion and exclusion criteria for intravenous alteplase in acute ischemic stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2016;47:XXX-XXX.

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DOI: 10.1161/STR.0000000000000086

Council Leadership review, and Scientific Statements Oversight Committee review before consideration and approval by the American Heart Association Science Advisory and Coordinating Committee.

Results—After a review of the current literature, it was clearly evident that the levels of evidence supporting individual exclusion criteria for intravenous alteplase vary widely. Several exclusionary criteria have already undergone extensive scientific study such as the clear benefit of alteplase treatment in elderly stroke patients, those with severe stroke, those with diabetes mellitus and hyperglycemia, and those with minor early ischemic changes evident on computed tomography. Some exclusions such as recent intracranial surgery are likely based on common sense and sound judgment and are unlikely to ever be subjected to a randomized, clinical trial to evaluate safety. Most other contraindications or warnings range somewhere in between. However, the differential impact of each exclusion criterion varies not only with the evidence base behind it but also with the frequency of the exclusion within the stroke population, the probability of coexistence of multiple exclusion factors in a single patient, and the variation in practice among treating clinicians. (*Stroke*. 2016;47:00-00. DOI: 10.1161/STR.0000000000000086.)

Key Words: AHA Scientific Statements ■ brain ischemia ■ cerebral infarction ■ fibrinolytic agents ■ stroke ■ thrombolytic therapy ■ tissue plasminogen activator

For our exclusion criteria, we elected to focus only on American Heart Association (AHA)/American Stroke Association (ASA) guidelines and exclusions, warnings, risks, and contraindications based on the US Food and Drug Administration (FDA) package insert, specifically for the only tissue-type plasminogen activator licensed for use in acute ischemic stroke, alteplase. We did not include international guidelines or other international governmental restrictions on the use of alteplase because it was beyond the scope of this document. However, we included data from international studies in our review of the literature for each exclusion. Literature search strategies are published as an online-only Data Supplement.

We have also intentionally focused on alteplase rather than on any or all types of thrombolytic agents. We have concentrated on intravenous use of alteplase rather than on any interventional or intra-arterial strategies for recanalization. The controversies and approvals for these different approaches are many and currently are not as generalizable as the FDA-approved intravenous administration of alteplase.

Recommendations were formulated with the use of standard AHA criteria (Tables 1 and 2). All members of the writing group had the opportunity to comment on the recommendations and approved the final version of this document. The document underwent extensive AHA internal peer review, Stroke Council Leadership review, and Scientific Statements Oversight Committee review before consideration and approval by the AHA Science Advisory and Coordinating Committee.

Introduction

Recombinant tissue-type plasminogen activator (alteplase) was first approved by the FDA in the United States in 1996 and remains the only medication proven to affect outcomes when given in the hyperacute time frame after ischemic stroke.¹ Since the pivotal alteplase trial was published, numerous other trials and governmental stroke registries have confirmed the benefit of alteplase in improving rates of disability after ischemic stroke.²⁻⁶

Unfortunately, although the benefit of alteplase is well established, the minority of patients with acute ischemic

stroke actually receive this medication across the United States. Although some hospital and quality registry estimates of alteplase treatment rates can range as high as 20% to 30%,^{7,8} national estimates of use have ranged only from 3% to 5% since 2004.^{9,10} Although these rates of treatment are quite low, they are improving slowly over time. This low use is likely attributable to a number of reasons, including the paucity of community public education about recognition and response to acute stroke symptoms and signs, the slow adoption of the medication in the medical community, and the complexity of large system changes at the hospital level that are necessary for this medication to be provided in a safe and timely manner.¹¹ However, although these issues are all extremely important, we believe that one of the most likely reasons for low rates of alteplase treatment is the low eligibility rate for this medication.

Estimates of eligibility for alteplase within a population of ischemic stroke patients range from 6% to 8% of all strokes, with slightly higher estimates in cross-sectional studies.¹²⁻¹⁵ The most common exclusion for alteplase is dominated by delays in presentation to medical attention. Within a population, only 22% to 31% of patients with ischemic stroke present to an emergency department within 3 hours from symptom onset. In addition, arrival times to presentation are not linearly distributed. Most patients arrive either <2 or >8 hours from onset. This has been confirmed in multiple population-based and cohort studies, shown in Table 3.¹⁶⁻²³

However, given the hemorrhage risk associated with alteplase, there are numerous other clinical, radiological, and laboratory-related exclusion criteria for alteplase that are considered standard of care and are listed in the AHA/ASA acute stroke management guidelines (Table 4).²⁴

Some of these exclusions are much more common than others, and some are potentially treatable, modifiable, or reversible before alteplase administration. The prevalence rates of individual exclusion criteria among patients presenting to an emergency department within 3 hours from onset are listed in Table 5. In this study, even if all ischemic stroke patients arrived within the treatment time window, only 29% would have been eligible for alteplase.

Table 1. Applying Classification of Recommendations and Level of Evidence

ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT	SIZE OF TREATMENT EFFECT				
	CLASS I <i>Benefit >>> Risk</i> Procedure/Treatment SHOULD be performed/ administered	CLASS IIa <i>Benefit >> Risk</i> <i>Additional studies with focused objectives needed</i> IT IS REASONABLE to per- form procedure/administer treatment	CLASS IIb <i>Benefit ≥ Risk</i> <i>Additional studies with broad objectives needed; additional registry data would be helpful</i> Procedure/Treatment MAY BE CONSIDERED	CLASS III <i>No Benefit</i> or CLASS III <i>Harm</i>	
				Procedure/ Test	Treatment
				COR III: No benefit	No Proven Benefit
				COR III: Harm	Excess Cost w/o Benefit or Harmful
LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	<ul style="list-style-type: none"> Recommendation that procedure or treatment is useful/effective Sufficient evidence from multiple randomized trials or meta-analyses 	<ul style="list-style-type: none"> Recommendation in favor of treatment or procedure being useful/effective Some conflicting evidence from multiple randomized trials or meta-analyses 	<ul style="list-style-type: none"> Recommendation's usefulness/efficacy less well established Greater conflicting evidence from multiple randomized trials or meta-analyses 	<ul style="list-style-type: none"> Recommendation that procedure or treatment is not useful/effective and may be harmful Sufficient evidence from multiple randomized trials or meta-analyses 	
LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	<ul style="list-style-type: none"> Recommendation that procedure or treatment is useful/effective Evidence from single randomized trial or nonrandomized studies 	<ul style="list-style-type: none"> Recommendation in favor of treatment or procedure being useful/effective Some conflicting evidence from single randomized trial or nonrandomized studies 	<ul style="list-style-type: none"> Recommendation's usefulness/efficacy less well established Greater conflicting evidence from single randomized trial or nonrandomized studies 	<ul style="list-style-type: none"> Recommendation that procedure or treatment is not useful/effective and may be harmful Evidence from single randomized trial or nonrandomized studies 	
LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	<ul style="list-style-type: none"> Recommendation that procedure or treatment is useful/effective Only expert opinion, case studies, or standard of care 	<ul style="list-style-type: none"> Recommendation in favor of treatment or procedure being useful/effective Only diverging expert opinion, case studies, or standard of care 	<ul style="list-style-type: none"> Recommendation's usefulness/efficacy less well established Only diverging expert opinion, case studies, or standard of care 	<ul style="list-style-type: none"> Recommendation that procedure or treatment is not useful/effective and may be harmful Only expert opinion, case studies, or standard of care 	
Suggested phrases for writing recommendations	should is recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established	COR III: No Benefit is not recommended is not indicated should not be performed/ administered/ other is not useful/ beneficial/ effective	COR III: Harm potentially harmful causes harm associated with excess morbidity/mortality should not be performed/ administered/ other
Comparative effectiveness phrases†	treatment/strategy A is recommended/indicated in preference to treatment B treatment A should be chosen over treatment B	treatment/strategy A is probably recommended/indicated in preference to treatment B it is reasonable to choose treatment A over treatment B			

A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Although randomized trials are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

*Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as sex, age, history of diabetes, history of prior myocardial infarction, history of heart failure, and prior aspirin use.

†For comparative effectiveness recommendations (Class I and IIa; Level of Evidence A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

The current exclusion criteria listed in the AHA/ASA 2013 acute stroke management guidelines²⁴ remain based largely on the criteria listed in the pivotal National Institute of Neurological Disorders and Stroke (NINDS) alteplase trial published in 1996,²¹ with a few modifications over the years. These exclusion criteria were developed for the original alteplase pilot studies, many of which were borrowed from the cardiac literature from cardiac thrombolysis trials and others from basic science publications.^{25–30}

However, some of these exclusions for alteplase are controversial. Many stroke experts across the country consider some of these exclusion criteria (or contraindications) to be “relative” and others to be “absolute.” A recent survey of

stroke experts within the Specialized Program of Translational Research in Acute Stroke (SPOTRIAS; n=47), a National Institutes of Health–funded acute stroke treatment trial network, found that there was a broad variation among these experts in which criteria they would or would not consider treating, as shown in the Figure.³¹

Another example of varying practice patterns with regard to alteplase exclusions includes those patients with mild stroke. Registry data from the SPOTRIAS network found that treatment of patients with mild stroke ranged from 2.7% to 18% among the 8 centers contributing data.³²

However, thrombolysis science has continued to evolve, and there is substantial and growing literature on the indications,

Table 2. Definition of Classes and Levels of Evidence Used in AHA/ASA Recommendations

Class I	Conditions for which there is evidence for and/or general agreement that the procedure or treatment is useful and effective
Class II	Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment
Class IIa	The weight of evidence or opinion is in favor of the procedure or treatment
Class IIb	Usefulness/efficacy is less well established by evidence or opinion
Class III	Conditions for which there is evidence and/or general agreement that the procedure or treatment is not useful/effective and in some cases may be harmful
Therapeutic recommendations	
Level of Evidence A	Data derived from multiple randomized, clinical trials or meta-analyses
Level of Evidence B	Data derived from a single randomized trial or nonrandomized studies
Level of Evidence C	Consensus opinion of experts, case studies, or standard of care
Diagnostic recommendations	
Level of Evidence A	Data derived from multiple prospective cohort studies using a reference standard applied by a masked evaluator
Level of Evidence B	Data derived from a single grade A study, ≥ 1 case-control studies, or studies using a reference standard applied by an unmasked evaluator
Level of Evidence C	Consensus opinion of experts
AHA/ASA indicates American Heart Association/American Stroke Association.	

benefits, and risks associated with alteplase that was not available at the time of the design of the original alteplase trial. The intent of this advisory statement is to critically review and evaluate the science behind each of the alteplase eligibility criteria (indications and contraindications alike) and to explore some popular myths about treatment. If successful, we will help with alteplase eligibility decision making today and identify research priorities for the future that potentially could broaden the eligibility for and treatment with alteplase. This advisory statement is expected to be an adjunct to, not a replacement for, the AHA/ASA acute stroke management guidelines.

The need for a document to specifically go through the science behind each of the individual inclusion and exclusion criteria for alteplase administration is further highlighted by the recent changes to the prescribing information (PI) of alteplase by the FDA in February 2015 (see the Appendix). To clarify, these changes were made as part of a routine update to the PI to ensure that the information is consistent with the Physician Labeling Rule instituted in 2006.³³ No new data were requested from the company that produced alteplase or were reviewed by the FDA as part of this PI update. The Physician Labeling Rule outlines regulations governing content and format of the PI for human drug and biological products. Thus, it provides a standardized format with the goal of

providing clear and concise PI that is easier for healthcare professionals to access, read, and use. In particular, the definitions of contraindications and warnings and precautions have been changed and are as follows:

- **Contraindications:** A drug should be contraindicated only in those clinical situations for which the risk from use clearly outweighs any possible therapeutic benefit. Only known hazards, not theoretical possibilities, can be the basis for a contraindication.
- **Warnings and precautions:** The warnings and precautions section is intended to identify and describe a discrete set of adverse reactions and other potential safety hazards that are serious or are otherwise clinically significant because they have implications for prescribing decisions or for patient management. For an adverse event to be included in the section, there should be reasonable evidence of a causal association between the drug and the adverse event, but a causal relationship need not have been definitively established.

The alteplase PI has been recategorized and simplified to be consistent with the Physician Labeling Rule requirements, and these changes are summarized in the Appendix. Most of the changes have been made to contraindications and warnings and to precautions. Specifically, many have been removed or made less specific if there are no known hazards as defined by the Physician Labeling Rule. However, this AHA/ASA statement writing group feels strongly that the AHA/ASA acute stroke management guidelines, in combination with the science presented in this document, should be what clinicians access and apply to their acute ischemic stroke treatment and management decisions. This is especially true because the PI changes were made by the FDA in the context of no substantial new information compared with the rigorous process undertaken by these authors.

It is our intent to help inform the decision-making process for clinicians in terms of the absolute and relative risks and benefits of alteplase treatment, to dispel uncertainty and myths about particular exclusion criteria, and to further quantify estimates of benefit and risk in zones of former uncertainty. We anticipate that this scientific statement will assist the clinician to better engage with patients experiencing an acute stroke and their families in a shared decision-making model with an up-to-date understanding of the current literature.

Age Issues

According to the FDA label, intravenous thrombolysis with alteplase is indicated within 3 hours after the onset of stroke symptoms for the management of acute ischemic stroke in adults for improving neurological recovery and reducing the incidence of disability after exclusion of intracranial hemorrhage. The label also identifies advanced age as a warning, stating that for patients >75 years of age, the risks of alteplase therapy may be increased and should be weighed against the anticipated benefits. The updated label additionally emphasizes that the safety and effectiveness of alteplase in pediatric patients have not been established. The 2013 AHA/ASA guidelines for the early management of patients with acute ischemic stroke recommend intravenous alteplase as early as possible

Table 3. Eligibility for rtPA Within a Population of Patients With Ischemic Stroke Who Arrived 0 to 3 Hours or 3 to 4.5 Hours After Symptom Onset¹³

2007 AHA Guidelines Exclusion Criteria	Time From Symptom Onset to ED Arrival (n=1838), n (%)	
	0–3 h (n=395, 22%)	3–4.5 h (n=66, 3.4%)
Minor symptoms (NIHSS score <5)	208 (11.5)	40 (2.1)
SBP >185 mm Hg or DBP >110 mm Hg	61 (3.2)	7 (0.4)
Stroke/head trauma in previous 3 mo	20 (2.6)	1 (0.1)
INR >1.7	26 (2.1)	4 (0.2)
aPTT >40 s	22 (1.1)	7 (0.4)
Seizure in acute setting	13 (0.7)	4 (0.2)
Major surgery in preceding 14 d	11 (0.6)	1 (0.1)
Previous intracranial hemorrhage	9 (0.5)	1 (0.1)
Aneurysm	7 (0.4)	0 (0)
Platelet count <100 000	5 (0.3)	2 (0.1)
MI in previous 3 mo	2 (0.1)	0 (0)
Gastrointestinal/urinary tract hemorrhage in previous 21 d	1 (0.1)	0 (0)
Serum glucose <50 mg/dL	1 (0.1)	0 (0)
Brain tumor	1 (0.1)	0 (0)
AVM	0	0
Active bleeding/acute trauma	0	0
Noncompressive arterial puncture in previous 7 d	0	0
ECASS III exclusion criteria		
Age >80 y	...	15 (0.8)
History of diabetes mellitus and prior stroke	...	3 (0.2)
Any OAC use or heparin use with aPTT >40 s	...	2 (0.1)
NIHSS score >25	...	2 (0.1)
Eligibility, standard criteria	115 (5.9)	14 (0.7)
Eligibility, ECASS III criteria	...	9 (0.5)

Data are presented as raw number (weighted percent of the 1838 strokes). Each criterion is not mutually exclusive. AHA indicates American Heart Association; aPTT, activated partial thromboplastin time; AVM, arteriovenous malformation; DBP, diastolic blood pressure; ECASS III, European Cooperative Acute Stroke Study III; ED, emergency department; INR, international normalized ratio; MI, myocardial infarction; NIHSS, National Institutes of Health Stroke Scale; OAC, oral anticoagulant; rtPA, recombinant tissue-type plasminogen activator; and SBP, systolic blood pressure.

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for eligible adult stroke patients who may be treated within 3 hours of symptom onset (Class I; Level of Evidence A). The effectiveness of intravenous treatment with alteplase is not well established (Class IIb; Level of Evidence C) and requires further study for patients >80 years of age who can be treated in the time period of 3 to 4.5 hours after symptom onset.²⁴

Age is one of the most important factors influencing the incident risk of stroke and the associated outcomes.^{34,35} The risk of ischemic stroke doubles for each successive decade after 55 years of age.^{36,37} In a large cohort study including >500 000 stroke patients participating in the AHA/ASA Get With The Guidelines (GWTG), death at discharge was 2- to 3-fold (7.7% and 10.3% versus 4.0%; $P<0.0001$) higher among octogenarians and those >90 years of age, respectively, compared with younger individuals.³⁸ The gap in clinical outcomes between <80 and >80 years of age is larger when long-term outcomes (eg, death at 1 year) are compared.^{39–41} Consequently, it is not surprising that some of the landmark randomized, controlled trials (RCTs) testing the efficacy of

thrombolytic agents excluded older patients.^{42–45} This section explores the benefits and safety of intravenous thrombolysis with alteplase within the 3-hour window by age. The eligibility for intravenous alteplase for the 3- to 4.5-hour window is discussed in the section on expanding the time window.

Efficacy of Intravenous Alteplase Among Stroke Patients ≥80 Years of Age

The benefits of alteplase in stroke patients ≥80 years of age were assessed in 3 randomized trials and 12 observational studies. The most relevant comparison to determine the benefit of intravenous alteplase in older patients is from RCTs because they provide information on clinical outcomes between patients taking alteplase and control subjects in each age strata. In contrast, most observational studies, aimed at monitoring the safety of thrombolytic therapy in the real world, provided only comparative information on stroke outcome between patients >80 and those <80 years of age receiving intravenous alteplase (usually lacking non-alteplase-treated patients).

Table 4. Inclusion and Exclusion Characteristics of Patients With Ischemic Stroke Who Could Be Treated With Intravenous rtPA Within 3 Hours From Symptom Onset

Inclusion criteria

Diagnosis of ischemic stroke causing measurable neurological deficit

Onset of symptoms <3 h before treatment begins

Age ≥18 y

Exclusion criteria

Significant head trauma or prior stroke in the previous 3 mo

Symptoms suggest SAH

Arterial puncture at noncompressible site in previous 7 d

History of previous intracranial hemorrhage

Intracranial neoplasm, AVM, or aneurysm

Recent intracranial or intraspinal surgery

Elevated blood pressure (systolic >185 mm Hg or diastolic >110 mm Hg)

Active internal bleeding

Acute bleeding diathesis, including but not limited to

Platelet count <100 000/mm³

Heparin received within 48 h resulting in abnormally elevated aPTT above the upper limit of normal

Current use of anticoagulant with INR >1.7 or PT >15 s

Current use of direct thrombin inhibitors or direct factor Xa inhibitors with elevated sensitive laboratory tests (eg, aPTT, INR, platelet count, ECT, TT, or appropriate factor Xa activity assays)

Blood glucose concentration <50 mg/dL (2.7 mmol/L)

CT demonstrates multilobar infarction (hypodensity >1/3 cerebral hemisphere)

Relative exclusion criteria

Recent experience suggests that under some circumstances, with careful consideration and weighting of risk to benefit, patients may receive fibrinolytic therapy despite ≥1 relative contraindications. Consider risk to benefit of intravenous rtPA administration carefully if any of these relative contraindications is present

Only minor or rapidly improving stroke symptoms (clearing spontaneously)

Pregnancy

Seizure at onset with postictal residual neurological impairments

Major surgery or serious trauma within previous 14 d

Recent gastrointestinal or urinary tract hemorrhage (within previous 21 d)

Recent acute myocardial infarction (within previous 3 mo)

Notes

The checklist includes some FDA-approved indications and contraindications for administration of intravenous rtPA for acute ischemic stroke. Recent guideline revisions have modified the original FDA-approved indications. A physician with expertise in acute stroke care may modify this list.

Onset time is defined as either the witnessed onset of symptoms or the time last known normal if symptom onset was not witnessed.

In patients without recent use of OACs or heparin, treatment with intravenous rtPA can be initiated before availability of coagulation test results but should be discontinued if INR is >1.7 or PT is abnormally elevated by local laboratory standards.

In patients without a history of thrombocytopenia, treatment with intravenous rtPA can be initiated before availability of platelet count but should be discontinued if platelet count is <100 000/mm³

aPTT indicates activated partial thromboplastin time; AVM, arteriovenous malformation; CT, computed tomography; ECT, ecarin clotting time; FDA, US Food and Drug Administration; INR, international normalized ratio; OAC, oral anticoagulant; PT, partial thromboplastin time; rtPA, recombinant tissue-type plasminogen activator; SAH, subarachnoid hemorrhage; and TT, thrombin time.

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Only 3 multicenter, randomized stroke trials included patients ≥80 years^{1,6,46} (Table 6).

Overall, 1711 stroke patients ≥80 years of age participated in these trials. The 2 NINDS alteplase trials included only 69 patients ≥80 years of age.¹ The Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET) included 25 older patients.⁴⁶ The Third International Stroke Trial (IST-3) is the largest randomized trial (n=1515 in the alteplase group versus 1520 in the control group) providing evidence of the benefits of alteplase for older patients with an acute ischemic stroke.

The IST-3 suggests some benefit in the primary outcome (alive and independent at 6 months) among stroke patients ≥80 years of age (odds ratio [OR], 1.35; 95% confidence interval [CI], 0.97–1.88) but not in those <80 years of age (OR, 0.92; 95% CI, 0.67–1.26; *P*<0.029; Table 7).⁶

A recent meta-analysis including 6 randomized trials within a 3-hour time window suggests a benefit in favor of intravenous alteplase for both younger (OR, 1.51; 95% CI, 1.18–1.93) and older (OR, 1.68; 95% CI, 1.20–2.34) patients.⁴⁸ Among patients treated within 3 hours, for every 1000 patients

Table 5. Time to Presentation for Acute Ischemic Stroke

Study	Location	Study Population	n	Median NIHSS Score	0-3 h, %	3-6 h, %	6-24 h, %	>24 h, %	Unknown
de Los Rios la Rosa et al, ¹³ 2012	Ohio/Kentucky	Population based, including 1 academic center	2210	NR	22	3-4.5 h: 3.4		>4.5 h: 74.6	
Majersik et al, ²¹ 2007	Southeast Texas	Population based	2347	4	31	13	27	24	4
Owe et al, ²² 2006	Bergden, Norway	3 Selected hospitals	88	4	23	8		>6 h: 69	
Qureshi et al, ²³ 2005	Western New York	11 Selected hospitals, including 8 academic centers	1590	3-5	21	11	19	26	22
California Acute Stroke Pilot Registry, ¹⁷ 2005	California	11 Selected hospitals, including 3 academic centers	374	7	24	6		40	30
Koennecke et al, ¹⁹ 2001	Berlin, Germany	Single academic center	504	13	32	8		20	40
Azzimondi et al, ¹⁶ 1997	Bologna, Italy	Single teaching hospital	204	NR	40	12	31	9	7

NIHSS indicates National Institutes of Health Stroke Scale; and NR, not reported.

>80 years of age, there would be 96 more patients alive and independent at the end of follow-up (28.9% of patients taking tissue-type plasminogen activator versus 19.3% of control subjects; $P<0.003$). Similar findings were observed for those <80 years of age (49.6% of patients taking alteplase versus 40.1% of control subjects; $P<0.001$), which translates to 95 more patients alive and independent per 1000 people ≤80 years of age treated within 3 hours.⁴⁸

Data from observational studies revealed similar results. The largest observational study evaluating the benefits of alteplase by age was the Safe Implementation of Treatments in Stroke—International Stroke Thrombolysis Registry (SITS-ISTR).⁴⁹

A study combining SITS-ISTR and the Virtual International Stroke Trials Archive (VISTA) included 29 500

patients; 3472 (11.8%) of them were ≥80 years of age.⁵⁰ A shift analysis showed a distribution similar to those observed in clinical trials on the modified Rankin Scale (mRS) scores with alteplase at 3 months (for patients ≤80 years of age: OR, 1.6; 95% CI, 1.5–1.7; $n=25\,789$; for those >80 years of age: OR, 1.4; 95% CI, 1.3–1.6; $n=3439$).⁵⁰ A sensitivity analysis revealed similar results favoring alteplase over control when the mRS scores were dichotomized (for an mRS score of 0–2: OR, 2.1; 95% CI, 1.7–2.5; for excellent outcome defined as an mRS score of 0–1: OR, 1.9; 95% CI, 1.5–2.3). Similar estimations in favor of alteplase were observed when the analysis was restricted to patients participating in VISTA (for older patients: OR, 1.34; 95% CI, 1.05–1.70; for patients ≤80 years of age: OR, 1.42; 95% CI, 1.26–1.59),⁵¹ in the SITS-ISTR study,⁴⁹ and when patients

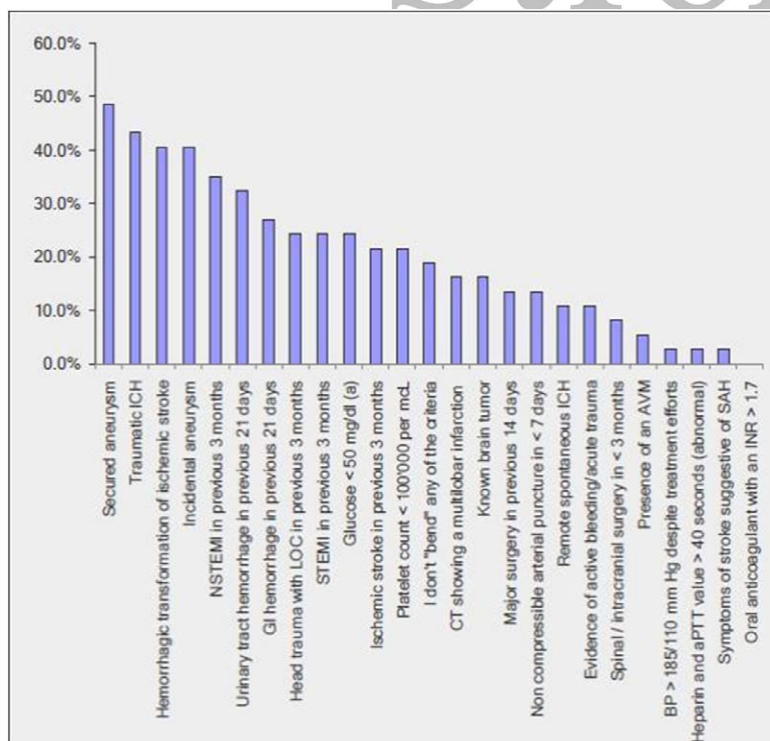


Figure. Survey of US stroke clinicians on their willingness to treat with recombinant tissue-type plasminogen activator (rtPA) in the setting of each individual rtPA exclusion criteria.³¹ aPTT indicates activated partial thromboplastin time; AVM, arteriovenous malformation; BP, blood pressure; CT, computed tomography; GI, gastrointestinal; ICH, intracerebral hemorrhage; INR, international normalized ratio; LOC, loss of consciousness; NSTEMI, non-ST-segment-elevation myocardial infarction; SAH, subarachnoid hemorrhage; and STEMI, ST-segment-elevation myocardial infarction. Reproduced from De Los Rios et al³¹ with permission from Elsevier. Copyright © 2014, National Stroke Association.

Table 6. Age Range and Proportion of Patients >80 Years of Age Among Randomized Trials Testing Intravenous tPA Within 3 Hours From Stroke Onset

Study	n	Dose, mg/kg (maximum, mg)	Control	Age Range, y	Age >80 y, n (%)	Stroke Type	Exclusion Criteria	Time, h	Follow-Up, mo
ECASS, 1995 ⁴⁷	620	1.1 (100)	Placebo	18–80	0	Carotid territory	Visible infarction >1/3 of MCA territory	<6	3
NINDS, 1995 ¹	624	0.9 (90)	Placebo	18–80	69 (11.1)	Any	None	<3	3
ECASS II, 1998 ⁴⁵	800	0.9 (90)	Placebo	18–80	0	Carotid territory	Visible infarction >1/3 of MCA territory	<6	3
ATLANTIS A, 2000 ⁴²	142	0.9 (90)	Placebo	18–80	0	As for NINDS	None	<6	3
ATLANTIS B, 1999 ⁴⁴	613	0.9 (90)	Placebo	18–80	0	As for NINDS	Visible infarction >1/3 of MCA territory	<5	3
IST-3, 2012 ⁶	3035	0.9 (90)	Placebo*	≥18	1617 (53.3)	All subtypes	Visible infarct only if it appears >6 h after stroke	<6	6
Total	5834	...	Placebo	...	1711 (29.3)

ATLANTIS indicates Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke; ECASS II, European Cooperative Acute Stroke Study II; IST-3, Third International Stroke Trial; MCA, middle cerebral artery; NINDS, National Institute of Neurological Diseases and Stroke; and tPA, tissue-type plasminogen activator.

*Only the first 276 patients received placebo; open control thereafter.

with potential exclusions for alteplase were analyzed.⁵² The magnitude of benefit with intravenous alteplase showed minimal variation by deciles of age (for 41–50 years of age: OR, 1.5; 95% CI, 1.2–1.8; for 51–60 years of age: OR, 1.6; 95% CI, 1.4–1.8; for 61–70 years of age: OR, 1.5; 95% CI, 1.4–1.7; 71–80 years of age: OR, 1.6; 95% CI, 1.5–1.8; and for 81–90 years of age: OR, 1.5; 95% CI, 1.3–1.7).⁵⁰ Another meta-analysis including 13 observational studies comprising 3178 patients receiving alteplase (2414 patients <80 years old and 764 patients ≥80 years old) revealed that those ≥80 years of age had a 50% lower chance of achieving a favorable outcome at 3 months (OR, 0.49; 95% CI, 0.40–0.61) compared with their younger counterparts.⁵³ Similar findings were observed in a reanalysis including 2 RCTs and 10 observational studies reporting favorable outcome at 3 months (see Figure A in online-only data supplement). It is not surprising that older patients are less likely to achieve good outcomes compared with younger individuals regardless of alteplase administration. Caution should be exercised because most observational studies evaluating age disparities compare older and younger patients receiving alteplase instead of comparing outcomes in older individuals receiving and not receiving alteplase.

Mortality

In the 2 NINDS alteplase stroke trials, there was no significant difference in death at 3 months between alteplase patients and control subjects for the same age stratum (for patients ≤80 years of age: 21.0% of alteplase patients versus 26.9% of control subjects; $P=0.10$; for patients >80 years of age: 52.5% of alteplase patients versus 48.3% control subjects; $P=0.73$).^{1,54} Neither the EPITHET nor the IST-3 reported death differences in these age groups.^{6,46}

Results from the SITS-ISTR and VISTA combined ($n=29500$) revealed a reduction of death at 3 months among patients receiving alteplase (OR, 0.85; 95% CI, 0.78–0.92).⁵⁰ Among patients ≥80 years of age ($n=2628$), 3-month mortality was 13.6% in the alteplase group ($n=21099$) and 14.8% in the control group ($n=4929$). In the older age group ($n=3472$), death was also lower among alteplase patients (32.6%) compared with control subjects (35.3%). The adjusted analysis revealed a similar death reduction in favor of alteplase treatment as reflected by the similar ORs for younger (OR, 0.87; 95% CI, 0.79–0.95) and older (OR, 0.89; 95% CI, 0.76–1.0) patients.⁵⁰

The analysis of VISTA ($n=5817$: 1585 alteplase patients and 4232 control subjects) revealed higher survival among patients ≤80 years of age in favor of alteplase (OR, 1.44;

Table 7. Comparison of Favorable Outcomes at 90 Days Between tPA and Control Among Participants <80 and >80 Years of Age in the NINDS and IST-3 Trials

Study	Age Group, y	tPA, n	Control, n	Favorable Outcome at 3 mo		
				tPA, n (%)	Control, n (%)	OR (95% CI)
NINDS ¹	≤80	272	283	142 (52.2)	102 (36.0)	1.94 (1.38–2.72)
	>80	40	29	9 (22.5)	6 (20.7)	1.11 (0.35–3.37)
IST-3 ⁶	≤80	698	719	331 (47.4)	346 (48.1)	0.92 (0.67–1.26)
	>80	817	799	223 (27.3)	188 (23.5)	1.35 (0.97–1.88)
Total	≤80	970	1002	473 (48.8)	433 (43.2)	1.25 (1.04–1.50)
	>80	857	828	232 (27.1)	194 (23.4)	1.21 (0.97–1.52)

Favorable outcome defined as a modified Rankin Scale score of 0 to 2 in the NINDS trials and as an Oxford Handicap Score of 0 to 2 in the IST-3 trial. CI indicates confidence interval; IST-3, Third International Stroke Trial; NINDS, National Institute of Neurological Diseases and Stroke; OR, odds ratio; and tPA, tissue-type plasminogen activator.

95% CI, 1.18–1.76). No significant improvement in survival was observed for those >80 years of age (OR, 1.20; 95% CI, 0.90–1.65).⁵¹

In SPOTRIAS, 3378 patients were treated with intravenous alteplase.⁵⁵ After adjustment, stroke patients ≥80 years of age treated with intravenous alteplase alone had a 2-fold higher risk of in-hospital mortality compared with their younger counterparts receiving alteplase (adjusted OR [aOR] 2.13; 95% CI, 1.60–2.84). Similarly, older stroke patients had a higher mortality rate (30% versus 12%; aOR, 1.53; 95% CI, 1.43–1.65) compared with those ≤80 years of age in the SITS-ISTR observational study (n=1831 patients >80 years of age and n=19411 patients ≤80 years of age).⁴⁹

A meta-analysis of observational studies (n=3178) showed that stroke patients ≥80 years of age receiving alteplase had a 3-fold higher chance of death (OR, 2.77; 95% CI, 2.25–3.40) compared with the younger group.⁵³ Comparative information for control subjects is not available because patients not receiving alteplase were not included.

A more recent meta-analysis including 3035 patients participating in randomized trials revealed a higher probability of death within 7 days among patients receiving alteplase (11% versus 7%; OR, 1.60; 95% CI, 1.22–2.08) compared with those receiving placebo. Age differences were not reported. The inclusion of the IST (death at 7 days for alteplase versus nonalteplase: OR, 1.58; 95% CI, 1.23–2.03) may explain the differences with previous meta-analysis.⁴⁸

Safety: Hemorrhagic Complications

Symptomatic intracerebral hemorrhage (sICH) is the most feared complication after intravenous alteplase. All studies consistently showed an increased risk of hemorrhagic conversion after alteplase compared with no alteplase. A recent meta-analysis including 6 RCTs comprising 1779 patients revealed that alteplase given within 3 hours was associated with a nearly 5-fold risk (OR, 4.55; 95% CI, 2.92–7.09; absolute risk, 8.04%; risk difference, 6.79%) of sICH.⁴⁸

A more relevant question concerns the risk of intracerebral hemorrhage (ICH) after alteplase among those ≥80 years of age compared with the younger group (see Figure B in online-only data supplement). Data from 2 RCTs and 15 observational studies provide relevant information. To best answer this question, it is important to differentiate the use of different definitions to characterize ICH in randomized and observational studies. Table 8 describes different types of ICHs and their definitions. For example, hemorrhagic transformation was categorized into hemorrhagic infarction (HI1, HI2), parenchymal hemorrhage (PH1, PH2), and remote parenchymal hemorrhage (PH1, PH2) in the European Cooperative Acute Stroke Study (ECASS) III trial.⁴³

Symptomatic hemorrhage was defined as ≥4-point increase in the National Institutes of Health Stroke Scale (NIHSS) from baseline or death within 36 hours and PH2 or PH2 hemorrhage. A comparison of the prevalence of sICH in those >80 and <80 years of age according to the ECASS III definition is summarized in Table 9.

In the 2 NINDS trials, sICH is defined as ICH within 36 hours, documented by computed tomography or magnetic resonance imaging (MRI) and by the treating physician's

Table 8. Classification of Intracerebral Hemorrhages After Intravenous Alteplase

Intracerebral Hemorrhage Type	Definition
HI1, hemorrhagic infarct type 1	Small petechial hemorrhage along the margins of the infarct
HI2, hemorrhagic infarct type 2	More confluent petechial hemorrhage within the infarct area but without space-occupying effect
PH1, primary intracerebral hemorrhage type 1	Parenchymal hemorrhage not exceeding 30% of the infarct area with some mild space-occupying effect
PH2, primary intracerebral hemorrhage type 2	Parenchymal hemorrhage exceeding 30% of the infarct area with significant space-occupying effect
PHr1, remote primary intracerebral hemorrhage type 1	Small or medium-sized blood clots located remote from the actual infarct; a mild space-occupying effect could be present
PHr2, remote primary intracerebral hemorrhage type 2	Large, confluent, dense blood clots in an area remote from the actual infarct; significant space-occupying effect may be present

notes indicating clinical deterioration attributable to hemorrhage.¹ The frequency of sICH after alteplase as per the NINDS definition reported in different studies is summarized in Table 10.

A meta-analysis including studies comparing the risk of sICH in patients receiving alteplase who were >80 and <80 years of age demonstrated no statistically significant difference in risk between groups (OR, 1.31; 95% CI, 0.93–1.84).⁵³ An analysis including only studies with a sample size of ≥100 stroke patients revealed an increased risk of bleeding for those ≥80 years of age when the ECASS definition (OR, 1.38; 95% CI, 1.12–1.69; n=28560) or the NINDS definition (OR, 1.40; 95% CI, 1.22–1.61; n=24327) of symptomatic hemorrhage was applied (see Figure C in online-only data supplement). The benefit of alteplase in this group remains despite the higher risk of intracranial bleeding.

Thrombolysis in the Pediatric Population

Pediatric stroke is defined as stroke occurring in patients 1 month to 18 years of age. Stroke may also occur in patients <1 month of age (newborns and neonates). The incidence of ischemic stroke in children <18 years of age in the United States is 0.63 to 6.4 per 100 000 per year.^{69–73}

Stroke diagnosis and treatment in children and neonates have several peculiarities (Table 11).

The initial diagnosis of stroke in children may be challenging considering the diverse presenting symptoms (eg, coma, seizures, and hemiparesis) common to nonvascular causes of stroke. All major randomized trials evaluating the benefits of intravenous alteplase have excluded stroke patients ≤18 years of age.^{1,42–45} Stroke mechanisms in children differ from those in adults. For example, prothrombotic factors account for two thirds of strokes in newborns and for >50% in infants and children,⁷⁹ and congenital heart malformations, vascular abnormalities, and infectious diseases are more frequent causes in children than in adults.⁷¹ There are important physiological

Table 9. Risk of sICH by Age Group Among Patients Receiving rtPA According to the ECASS III Definition

Study	Center	Design	Age Group, y	Receiving tPA, n	sICH, n (%)	OR (95% CI)*
Chen et al, ⁵⁶ United States	Single	Observational	<80	127	8 (6.3)	1.14 (0.28–4.45)
			≥80	56	4 (7.1)	
Berrouschot et al, ⁵⁷ Germany	Multicenter (3)	Observational	<80	190	5 (2.6)	1.0 (0.04–9.25)
			≥80	38	1 (2.6)	
Toni et al, ⁵⁸ Italy	Multicenter (6)	Observational	≤80	207	10 (4.8)	1.01 (0.15–5.21)
			>80	41	2 (4.8)	
VISTA-SITS, ⁵⁰ Europe, Australia, Asia	Multicenter	Observational	≤80	20 759	298 (1.9)	1.30 (0.96–1.8)
			>80	2163	54 (2.5)	
Gómez-Choco et al, ⁵⁹ Spain	Single	Observational	≤80	108	6 (5.5)	1.11 (0.21–5.30)
			>80	49	3 (6.1)	
CASES, Canada ⁶⁰	Multicenter	Observational	<80	865	40 (4.6)	1.04 (0.52–2.1)
			≥80	270	12 (4.4)	
Bray et al, ⁶¹ England	Multicenter	Observational	≤80	2487	107 (4.3)	1.19 (0.78–1.79)
			>80	671	34 (5.1)	
Boulouis et al, ⁶² France	Single	Observational	<80	302	18 (6.0)	1.03 (0.35–2.86)
			≥80	98	6 (6.1)	
Meseguer et al, ⁶³ France	Single	Observational	<80	107	8 (7.5)	1.95 (0.37–9.25)
			≥80	22	3 (13.6)	

CASES indicates Canadian Alteplase for Stroke Effectiveness Study; CI, confidence interval; ECASS III, European Cooperative Acute Stroke Study III; OR, odds ratio; rtPA, recombinant tissue-type plasminogen activator; sICH, symptomatic intracerebral hemorrhage; and VISTA-SITS, Virtual International Stroke Trials Archive–Safe Implementation of Treatments in Stroke.

*OR (95% CI) for the risk of sICH among patients >80 years of age compared with their younger counterparts.

differences between children (particularly neonates) and adults affecting the clinical response and risk of complications after thrombolysis. For example, neonates have reduced plasminogen levels compared with older children and adults.^{80–84} Consequently, response to alteplase in neonates is impaired. Increasing doses of alteplase would not improve the response to thrombolysis but would be associated with an increase in the neonatal plasminogen concentration.^{85,86} Evidence of thrombolysis in children is limited to single centers, case series, or other medical indications (eg, flow restoration for blocked hemodialysis catheters, intrasinus thrombolysis for cerebral venous thrombosis). In terms of the legal framework, the FDA has approved alteplase only for individuals ≥18 years of age.

At this time, there are no published randomized trials using alteplase in neonates and children. Most of the evidence of alteplase in the pediatric population is from observational studies. A large retrospective study from the National Inpatient System Database revealed that only 46 of 2904 pediatric patients (1.6%) with stroke included in the study received intravenous or intra-arterial alteplase.⁸⁷ The International Pediatric Stroke Study (IPSS) reported similar findings (15 of 687 pediatric patients [2.2%] with stroke received alteplase). The median time to treatment from stroke onset was 3.3 hours (range, 2.0–52.0 hours) for intravenous alteplase and 4.5 hours (range, 3.8–24.0 hours) for intra-arterial alteplase. Two patients died (1 of massive infarction and brain herniation and 1 of brainstem infarction). At discharge from hospital, 1 patient was healthy and 12 patients had neurological deficits. Intracranial hemorrhage after alteplase occurred in 4 of 15 patients, although none of the bleeding events was judged to be acutely symptomatic.⁸⁸

A population-based study among 1.3 million residents of the Greater Cincinnati/Northern Kentucky region identified 29 pediatric ischemic strokes during 3 separate study periods (1993–1994, 1999, and 2005).⁸⁹ The ischemic strokes included 7 neonates (≤28 days old), 4 infants (>28 days to <1 year old), 11 children between 1 and 14 years of age, and 7 children between 15 and 17 years old. The authors applied the 2007 AHA/ASA guidelines for the management of acute ischemic stroke in adults^{89a} to determine the potential eligibility for alteplase in those children. Only 1 of 29 pediatric strokes (3%) would have been eligible for alteplase according to adult criteria. The authors also suggested that ≈178 children would meet eligibility for alteplase in the United States every year by exclusion of relative contraindications such as seizure at onset.

The AHA/ASA pediatric stroke guidelines also do not recommend intravenous alteplase treatment for children with ischemic strokes outside a clinical trial except for older adolescents who otherwise meet adult eligibility criteria and for whom consensus is lacking.⁷¹ The most recent AHA/ASA guidelines for the management of acute ischemic stroke²⁴ mentioned age >18 years as part of the inclusion criteria for intravenous alteplase. This eligibility criterion was based on FDA approval and guidelines. It is noted that a physician with expertise in acute stroke care may modify the list.²⁴

A systematic review reported 17 children who underwent intravenous thrombolysis (n=6), intra-arterial thrombolysis (n=10), or mechanical thrombolysis (n=1).⁹⁰ No symptomatic intracranial hemorrhage occurred, but 2 asymptomatic intracranial hemorrhages were present. Sixteen children (94%) survived, and 12 (71%) had a good outcome (mRS score, 0 or 1). Currently, a dose-escalation clinical trial

Table 10. Risk of sICH by Age Group Among Patients Receiving tPA According to the NINDS Definition

Study	Center	Design	Age Group, y	Receiving tPA, n	sICH, n (%)	OR (95% CI)*
NINDS, ¹ United States	Multicenter	RCT	≤80	272	18 (6.6)	3.00 (1.16–7.70)
			>80	40	7 (17.5)	
VISTA-SITS, ⁵⁰ Europe, Australia, Asia	Multicenter	Observational	≤80	20 220	1670 (8.3)	1.4 (1.2–1.6)
			>80	2087	229 (11.0)	
Tanne et al, ⁶⁴ United States	Multicenter	Observational	<80	159	10 (6)	0.51 (0.02–4.17)
			≥80	30	1 (3)	
Uyttenboogaart et al, ⁶⁵ Netherlands	Single	Observational	<80	111	4 (3.6)	2.87 (0.47–16.4)
			≥80	31	3 (9.7)	
Ringleb et al, ⁶⁶ Germany	Single	Observational	<80	378	20 (5.3)	1.28 (0.44–3.50)
			≥80	90	6 (6.7)	
Engelter et al, ⁶⁷ Switzerland	Multicenter	Observational	<80	287	24 (8)	1.66 (0.52–5.01)
			≥80	38	5 (13)	
Van Oostenbrugge et al, ⁶⁸ Netherlands	Single	Observational	<80	139	4 (2.9)	4.22 (0.93–19.9)
			≥80	45	5 (11.1)	
Boulouis et al, ⁶² France	Single	Observational	<80	302	29 (9.6)	1.31 (0.60–2.82)
			≥80	98	12 (12.2)	

CI indicates confidence interval; NINDS, National Institute of Neurological Diseases and Stroke; OR, odds ratio; RCT, randomized, controlled trial; sICH, symptomatic intracerebral hemorrhage; tPA, tissue-type plasminogen activator; and VISTA-SITS, Virtual International Stroke Trials Archive–Safe Implementation of Treatments in Stroke.

*OR (95% CI) for the risk of sICH among patients >80 years of age compared with their younger counterparts.

of intravenous alteplase for the pediatric population has recently been funded by the NINDS. This study is based on the results of a multicenter observational study (IPSS).^{88,91} The Thrombolysis in Pediatric Stroke (TIPS) trial is a 5-year, multicenter, international study of intravenous alteplase in children with acute ischemic stroke to determine the maximal safe dose of intravenous alteplase among 3 doses (0.75, 0.9, and 1.0 mg/kg) for children 2 to 17 years of age within 4.5 hours from stroke onset.⁹¹ The primary end point is sICH defined as any PH2 or any intracranial hemorrhage judged to be the most important cause of neurological deterioration (a minimum of change of ≥2 points on the Pediatric NIHSS) that occurred within 36 hours from alteplase administration. Unfortunately, the study was terminated prematurely because of lack of patient accrual.⁹²

Age Issues: Recommendations

1. **For otherwise medically eligible patients ≥18 years of age, intravenous alteplase administration within 3 hours is equally recommended for patients <80 and >80 years of age. Older age is an adverse prognostic factor in stroke but does not modify the treatment effect of thrombolysis. Although older patients have poorer outcomes, higher mortality, and higher rates of sICH than those <80 years of age, compared with control subjects, intravenous alteplase provides a better chance of being independent at 3 months across all age groups (Class I; Level of Evidence A).**
2. **The efficacy and risk of intravenous alteplase administration in the pediatric population (neonates, children, and adolescents <18 years of age) are not well established (Class IIb; Level of Evidence B).**

Stroke Severity and the NIHSS

The previous version of the FDA label does not recommend alteplase treatment of patients with minor neurological deficits, emphasizing that its safety and efficacy in this circumstances have not been evaluated. According to the label, the risks of alteplase therapy to treat acute ischemic stroke may be increased in patients with severe neurological deficit (eg, NIHSS score >22) at presentation and should be weighed against the anticipated benefits. Of note, the updated version of the FDA label in February 2015 has removed both of these warnings about stroke severity. The 2013 AHA/ASA guidelines recommend that patients with acute ischemic stroke have measurable neurological deficit to be considered eligible for intravenous alteplase.²⁴ Furthermore, the guidelines list minor stroke symptoms as a relative exclusion criterion. Severe stroke (eg, NIHSS score >25) is a relative exclusion criterion for intravenous alteplase within 3 to 4.5 hours from symptom onset. The effectiveness of intravenous alteplase is not well established (Class IIb; Level of Evidence C) for patients who can be treated within 3 to 4.5 hours but have a severe stroke (eg, NIHSS score >25). The guidelines also state that use of intravenous alteplase in patients with mild stroke deficits may be considered, but the potential risk should be weighed against the anticipated benefits (Class IIb; Level of Evidence C).

Initial stroke severity is known to be the strongest predictor of functional outcome and mortality for ischemic stroke patients.^{93–98} The use of standardized scales to describe stroke severity greatly improves communication about patient care and interpretation of clinical trials in ischemic stroke. The most commonly used scale, the NIHSS, describes severity ranging from 0 (no measurable symptoms) to 42 (comatose). The NIHSS was originally developed for the alteplase pilot trials,⁹⁹ has been validated in many studies,^{100–102} and can be

Table 11. Comparison of Stroke Diagnosis and Treatment Between Children and Adults

Characteristic	Pediatric Population	Adult Population
Prevalence of ischemic stroke	Lower 0.63–1.2/100 000 ^{69,72} 1.2/100 000 per year ^{70,71}	Higher, doubles for each decade after 55 y of age ^{35,74} <64 y: 2.4/100 000 65–74 y: 7.6/100 000 >75 y: 11.2/100 000
Clinical presentation	Seizures, coma, and hemiparesis also common in nonvascular origins	Seizures or coma at onset is less common in adults
Stroke mechanism: prothrombotic factors	1/3 of stroke in newborns and 50% of stroke in children	Less common
Plasminogen levels	Reduced (neonates)	Normal
Response to tPA	Impaired (neonates), unknown efficacy	1/3 would have a better outcomes
Evidence of tPA	Limited to case reports or case series; no RCTs	6 RCTs and several observational studies
Dose of intravenous tPA	Unknown	0.9 mg/kg, 10% bolus
Legal framework	Off-label use	Approved for individuals ≥18 y of age
Guideline recommendations	AHA, ²⁴ United Kingdom, ⁷⁵ CHEST ⁷⁶ : not recommended ESO ⁷⁷ : Class III, Level of Evidence C	AHA, ²⁴ ESO, ⁷⁷ CHEST, ⁷⁶ Japanese ⁷⁸ : Class IA

AHA indicates American Heart Association; CHEST, American College of Chest Physicians; ESO, European Stroke Organisation; RCT, randomized, controlled trial; and tPA, tissue-type plasminogen activator.

used by health professionals with various levels of training.^{103,104} Some literature suggests that the NIHSS is weighted more toward language deficits, hence giving higher scores to left compared with right hemispheric ischemic strokes with equivalent volumes of infarct.¹⁰⁵

Although the NIHSS was developed by the investigators of the original 2 NINDS alteplase trials, the exclusion criteria for minor stroke were not based purely on the NIHSS. In the manual of operations from the original trial, minor stroke is defined as "...a stroke that is sensory only, or ataxia only. Also, if the patient has a motor score on the NIHSS of '1' for one limb and '0' for all other limbs, this is also a minor stroke." As a result, there were only 58 patients enrolled in the trial with an NIHSS score <5 (generally considered a mild stroke). There were also relatively few patients enrolled with an NIHSS score >25, likely because of the relative rarity of these massive ischemic strokes in populations.¹⁰⁶ Therefore, there are ongoing controversy and conflicting recommendations between the AHA guidelines and the FDA indications for alteplase for ischemic stroke in terms of stroke severity and intravenous alteplase treatment.

Severe Strokes and Alteplase Treatment

In an analysis of the predictors of good outcome from the 2 original NINDS alteplase trials, milder stroke severity (NIHSS score <20) was one of the most important predictors of good outcome.¹⁰⁷ However, a significant and independent alteplase treatment effect was also seen for those strokes with an NIHSS score >20.⁵⁴ Even when age-severity interaction terms were considered, there were no pretreatment factors that influenced the response to therapy, and no thresholds for withholding therapy could be determined. The authors concluded that treatment of severe strokes was warranted because, although the chances of a good outcome were less overall, severe stroke patients still had a better chance of a good outcome with alteplase treatment than without treatment. This has been confirmed in several other analyses, most recently in the IST-3.⁶ In IST-3, prespecified subgroup analyses of presenting NIHSS found an overall significant difference in treatment effect by

NIHSS strata ($P=0.003$). Overall, the estimated aOR for a good outcome increased with increasing severity, although the individual strata did not reach statistical significance and were not adjusted for time to treatment. Although this analysis was not statistically significant, there clearly was not a decreasing response to alteplase in the more severe patients.

The original FDA approval of alteplase included a warning statement that patients with an NIHSS score >22 be treated "with caution." This warning was included in the approval because it was noted that more severe ischemic stroke patients were more likely to have hemorrhagic transformation after receiving alteplase in the 2 NINDS trials. In fact, higher stroke severity has been associated with increased risk of hemorrhagic transformation, with or without alteplase treatment.¹⁰⁸ However, in a subgroup analysis of the 2 original NINDS alteplase trials, stroke severity and brain edema on initial head computed tomography (CT) scan were the only 2 independent predictors of risk of hemorrhage.¹⁰⁹ It should be noted, however, that despite increasing the frequency of early hemorrhage, the alteplase substantially improves the final functional outcome for more severe strokes, including the higher risk of hemorrhage, and accordingly, the increased risk of hemorrhage should not be interpreted as a rationale for nontreatment. More recently, scores have been created to risk stratify patients, such as the Ischemic Stroke Predictive Risk Score (iSCORE), Stroke Prognostication using Age and NIHSS (SPAN-100), SEDAN (a prediction rule for assessment of the risk for an sICH), Safe Implementation of Treatments in Stroke–Intracerebral Hemorrhage (SITS-ICH), and Hemorrhage After Thrombolysis (HAT) scores.^{110–114} However, these risk scores are not intended to drive decisions about the use of alteplase. Instead, these scores are best used to understand complication rates after treatment as a benchmark for risk adjustment.^{114,115} On the basis of the available literature, there should be no upper limit of NIHSS score for patients otherwise eligible for alteplase presenting to medical attention within 3 hours. Patients with stroke severity >25 in the 3- to 4.5-hour window are discussed below.

Mild Strokes and Alteplase Treatment

As with more severe strokes, there was also no lower limit of NIHSS score for enrollment in the original 2 NINDS trials, and investigators were instructed to enroll patients with ischemic stroke “causing a measurable neurologic deficit defined as impairment of language, motor function, cognition, and/or gaze, vision or neglect” (personal communication, J. Spilker, as written in the NINDS alteplase trial protocol). However, knowing which patients with milder stroke will have long-term disability is not as straightforward as with more severe strokes. A review of the rates of disability among milder stroke patients demonstrates that there is significant disability among patients (defined variably) at 3 months in multiple studies.^{116–118} Some of this disability was related to motor deficits as expected; however, there was a significant component of cognitive dysfunction, fatigue, and depression, deficits that are not captured by the presenting NIHSS score. Although there are several stroke syndromes that most stroke physicians agree would be disabling (such as severe monoparesis or aphasia), a significant proportion of mild stroke patients remain who are at significant risk for poor outcome despite relatively mild presenting stroke severity.^{118–121} The reasons for these poorer outcomes in milder stroke events are varied and include the possibility of recurrent strokes during the follow-up period, neurological deterioration of the original mild event, or unanticipated disability from deficits not well measured by the NIHSS. Patients with higher initial stroke severity and visible arterial occlusion on brain imaging are at higher risk for neurological deterioration.^{122,123}

Alteplase may be beneficial for milder stroke cases judged as potentially disabling despite low NIHSS scores. The NINDS trialists explored 5 different definitions of minor stroke in a post hoc analysis and found benefit for alteplase across all definitions.¹²⁴ However, data are not available on the effect of alteplase for milder stroke cases judged as not potentially disabling at presentation. Because nearly 3000 such cases of ischemic stroke were excluded from the 2 NINDS trials for mild symptoms, any analysis of mild symptoms within the 2 NINDS trials is difficult to interpret. Single-center studies and a large registry study in Austria also suggested benefit for thrombolytic treatment of mild strokes.^{125,126}

Risk of hemorrhagic transformation in milder stroke patients is significantly lower than for more severe strokes, ranging from 0% to 2% in the literature.^{127–130} However, these estimates were obtained from smaller studies and have wide CIs. Given that relatively few patients were enrolled in clinical trials of intravenous alteplase that included milder cases, the risk-to-benefit ratio for administration of intravenous alteplase in milder stroke cases is unknown and requires further study. There is currently wide variation in clinical practice of stroke-treating physicians in the use of alteplase in patients with mild but judged nondisabling strokes, which further reflects this uncertainty.³²

Stroke Severity: Recommendations

1. **For severe stroke symptoms, intravenous alteplase is indicated within 3 hours from symptom onset of ischemic stroke. Despite increased risk of hemorrhagic transformation, there is still proven clinical**

benefit for patients with severe stroke symptoms (Class I; Level of Evidence A).

2. **For patients with mild but disabling stroke symptoms, intravenous alteplase is indicated within 3 hours from symptom onset of ischemic stroke. There should be no exclusion for patients with mild but nonetheless disabling stroke symptoms in the opinion of the treating physician from treatment with intravenous alteplase because there is proven clinical benefit for those patients (Class I; Level of Evidence A).**
3. **Within 3 hours from symptom onset, treatment of patients with milder ischemic stroke symptoms that are judged as nondisabling may be considered. Treatment risks should be weighed against possible benefits; however, more study is needed to further define the risk-to-benefit ratio (Class IIb; Level of Evidence C).**

Rapidly Improving

The original FDA PI did not recommend alteplase treatment of patients with rapidly improving symptoms, emphasizing that its safety and efficacy in this circumstance have not been evaluated. However, the updated FDA label has removed this warning. The 2013 AHA/ASA guidelines²⁴ recommend that patients with acute ischemic stroke have measurable neurological deficit to be considered eligible for intravenous alteplase. Furthermore, the guidelines list rapidly improving stroke symptoms (clearing spontaneously) as a relative exclusion criterion. The guidelines state that use of intravenous alteplase in patients with rapidly improving stroke symptoms may be considered, but the potential risk should be weighed against the anticipated benefits (Class IIb; Level of Evidence C).

Rapid improvement is one of the most common reasons for exclusion from intravenous alteplase for acute ischemic stroke, yet it is an often misinterpreted exclusion criterion.^{118,121,131} The original rationale in the 2 NINDS trials was to exclude rapidly improving stroke symptoms so that patients with transient ischemic attacks did not receive unnecessary treatment.¹ Accordingly, the investigators excluded patients who had major, substantial improvements and improved to a severity that, in their judgment, would not lead to substantial disability; they did not exclude patients with only mild to moderate improvements.

Rapid clinical improvement has a number of pathophysiological explanations and can be quite dynamic. Often, improvement can be incomplete with disabling deficits remaining once improvement plateaus. A patient who improves from an NIHSS score of 15 to 10 is unlikely to fully resolve and will frequently remain disabled. Deterioration can also follow spontaneous improvement¹³² as a result of persistent occlusion or partial recanalization with subsequent reocclusion¹³³ and often results in a worsening of deficits back to baseline severity. Lacunar strokes involving the pons commonly fluctuate¹³⁴ yet often lead to progressive worsening of deficits later.¹³⁵ Many patients with stroke with initial rapid improvement are ultimately disabled.^{118,121,131} Early clinical improvement is a risk factor for subsequent deterioration in patients not treated with alteplase because of mild or improving stroke.^{119,136}

The Re-Examining Acute Eligibility for Thrombolysis (TREAT) Task Force recently examined in detail the exclusion criterion and provided recommendations to guide treating physicians¹³⁷ (Table 12). It was the unanimous consensus of this task force that patients with moderate to severe stroke who do not improve to a nondisabling state should be treated with intravenous alteplase unless other contraindications are present. The task force further emphasized that treatment should not be delayed to monitor for improvement beyond the extent of time needed to prepare and administer the intravenous alteplase bolus.

Rapidly Improving: Recommendations

1. Intravenous alteplase treatment is reasonable for patients who present with moderate to severe ischemic stroke and demonstrate early improvement but remain moderately impaired and potentially disabled in the judgment of the examiner (*Class IIa; Level of Evidence A*).
2. Because time from onset of symptoms to treatment has such a powerful impact on outcome, delaying treatment with intravenous alteplase to monitor for further improvement is not recommended (*Class III; Level of Evidence C*).

Time From Symptom Onset

According to the FDA label, treatment should be initiated only within 3 hours after the onset of stroke symptoms and after exclusion of intracranial hemorrhage by a cranial CT scan or other diagnostic imaging method sensitive for the presence of hemorrhage.

Recommendations According to the 2013 AHA/ASA Guidelines²⁴

1. Intravenous alteplase (0.9 mg/kg; maximum dose, 90 mg) is recommended for selected patients who may be treated within 3 hours of onset of ischemic stroke (*Class I; Level of Evidence A*). Physicians should review the criteria outlined in Tables 10 and 11 (which are modeled on those used in the 2 NINDS trials) to determine the eligibility of the patient.
2. In patients eligible for intravenous alteplase, benefit of therapy is time dependent, and treatment should be initiated as quickly as possible. The door-to-needle time (time of bolus administration) goal should be within 60 minutes from hospital arrival (*Class I; Level of Evidence A*).
3. Intravenous alteplase (0.9 mg/kg; maximum dose, 90 mg) is recommended for administration to eligible patients who can be treated in the time period of 3 to 4.5 hours after stroke onset (*Class I; Level of Evidence B*). The eligibility criteria for treatment in this time period are similar to those for people treated at earlier time periods within 3 hours, with the following additional exclusion criteria: patients >80 years old, those taking oral anticoagulants (OACs) regardless of international normalized ratio (INR), those with a baseline NIHSS score >25, those with imaging evidence of ischemic injury involving more than one third of the

middle cerebral artery (MCA) territory, or those with a history of both stroke and diabetes mellitus.

Time from symptom onset is the most important exclusion criterion for intravenous alteplase and is the most frequent reason why patients are ineligible for treatment. It is important for treating physicians to obtain corroborating history on time because families often confuse the time of symptom onset with the time the patient was found. Asking the family to remember when the last time the patient was seen normal or at their baseline state of health will often clarify. See the introductory section for a full description of the frequency of this exclusion within populations and the AHA/ASA guidelines for the early management of patients with acute ischemic stroke²⁴ for a full description of the controversies surrounding time from symptom onset. The scientific rationale for choosing such a restrictive time window by the original NINDS trialists came from models of ischemic stroke in rodents and primates. Within an awake primate model, they found that after 2 to 3 hours, occlusion of the MCA led to permanent, larger infarcts compared with ischemia for 15 to 30 minutes.¹³⁸

In the years since the completion of the 2 NINDS trials, the importance of time and the appropriateness of the 3-hour window has been demonstrated in several studies.^{5,139,140} It has become clear that the earlier thrombolytic treatment can be started, the better the chances are of a good outcome for the patient. Several pooled combined analyses have been performed. The most recent study-level meta-analysis included 7012 patients from 12 different randomized, clinical trials treated within 6 hours of symptom onset. Overall, there was a significant benefit, but it was much more pronounced for patients treated in <3 hours from symptom onset (mRS score of 0–2, 40.7% versus 31.7%; OR, 1.53; 95% CI, 1.26–1.86; $P<0.0001$).⁴⁸

Because every patient's collateral circulation is different and individuals have varying thresholds for permanent ischemia, the ideal way to establish the allowable time from symptom onset to treatment would be to evaluate the tissue viability or the ischemic penumbra in each patient. Multimodal imaging techniques designed to image the penumbra, including such modalities as MRI perfusion/diffusion mismatch, CT perfusion, and oxygen extraction ratios,

Table 12. Task Force Consensus: Definition and Clinical Context of Rapidly Improving Stroke Symptoms as an Exclusion Criterion for Intravenous Alteplase¹³⁷

Improvement to a mild stroke such that any remaining deficits seem nondisabling

The following typically should be considered disabling deficits:

Complete hemianopsia (≥ 2 on NIHSS question 3) or severe aphasia (≥ 2 on NIHSS question 9), or

Visual or sensory extinction (≥ 1 on NIHSS question 11) or

Any weakness limiting sustained effort against gravity (≥ 2 on NIHSS question 6 or 7) or

Any deficits that lead to a total NIHSS score >5 or

Any remaining deficit considered potentially disabling in the view of the patient and the treating practitioner. Clinical judgment is required.

NIHSS indicates National Institutes of Health Stroke Scale.

Modified from Levine et al.¹³⁷ Copyright © 2013, American Heart Association, Inc.

have the promise to establish the “tissue time clock” rather than using a standard time window for all patients.^{141–143} It is beyond the scope of this statement to review all of the literature on the utility of multimodal imaging in thrombolytic therapy. However, to date, these techniques have not been shown definitively in RCTs to be a valid selection tool for thrombolytic therapy in patients with ischemic stroke and have the potential to significantly delay treatment times.^{144–146} Therefore, we must still use the information obtained from the patient and family members about when the patient was last known to be normal or at baseline state of health and can be confident that intravenous alteplase is effective only when started within 4.5 hours from symptom onset. Please see the section below for further data on strokes present on awakening.

Extended Time Window

The ECASS III trial, performed in Europe, included thrombolytic therapy from 3 to 4.5 hours, with the addition of 4 exclusion criteria: age >80 years, NIHSS score >25, history of diabetes mellitus and prior stroke, and taking OACs (Please see below for a description of the scientific rationale behind these additional exclusion criteria in the extended time window).⁴ The degree of benefit seen in ECASS III was an OR for global favorable outcome (1.28; 95% CI, 1.00–1.65). This pivotal trial led to a revision of the AHA/ASA acute stroke management guidelines, which now recommended intravenous alteplase out to 4.5 hours from symptom onset, provided that the additional exclusion criteria are followed. However, the FDA did not approve a change in indication after reviewing the trial results and unpublished data from the company that produces alteplase. The writing committee of the acute stroke management guidelines commented:

To inform this update of the guidelines, the AHA/ASA Writing Committee leadership requested and was granted by the US manufacturer (Genentech) partial access to the FDA decision correspondence. The degree of evidence that AHA/ASA requires for a Grade B recommendation is less than for a Grade A recommendation, and the latter generally more closely approximates the level of evidence that the FDA requires for label approval. On the basis of the review, it is the opinion of the writing committee leadership that the existing Grade B recommendation remains reasonable.²⁴

Time From Symptom Onset: Recommendations

1. The time from last seen normal to treatment with intravenous alteplase should be <3 hours for eligible patients with the use of standard eligibility criteria (Class I; Level of Evidence A).
2. Intravenous alteplase treatment in the 3- to 4.5-hour time window is also recommended for those patients <80 years of age without a history of both diabetes mellitus and prior stroke, NIHSS score <25, not taking any OACs, and without imaging evidence of ischemic injury involving more than one third of the MCA territory (Class I; Level of Evidence B).

3. Treatment should be initiated as quickly as possible within the above listed time frames because time to treatment is strongly associated with outcome (Class I; Level of Evidence A).
4. In patients in the 0- to 4.5-hour time window who meet criteria for treatment with intravenous alteplase, substantially delaying intravenous alteplase treatment to obtain penumbral imaging before treatment is not recommended (Class III; Level of Evidence C).

Acute Intracranial Hemorrhage on CT

The FDA label and 2013 AHA/ASA guidelines indicate that the presence of an acute intracranial hemorrhage on CT (or by other diagnostic imaging sensitive to the presence of hemorrhage) is an absolute contraindication to intravenous alteplase.²⁴ Acute intracranial hemorrhage includes ICH, subarachnoid hemorrhage (SAH), intraventricular hemorrhage, subdural hematoma, epidural hematoma, and acute hemorrhagic transformation of a cerebral infarction. No studies or case reports have been published assessing the safety of intravenous alteplase in such a setting.

Acute Intracranial Hemorrhage on CT: Recommendation

1. Intravenous alteplase should not be administered to a patient whose CT reveals an acute intracranial hemorrhage (Class III; Level of Evidence C).

Pregnancy and Postpartum

The FDA label includes pregnancy and obstetrical delivery as examples of the conditions for which “the risks of alteplase therapy may be increased and should be weighed against the anticipated benefits.” Alteplase is listed as pregnancy category C, indicating possible embryocidal risk based on animal experiments at high doses. However, animal studies of alteplase at 1 mg/kg did not show fetal toxicity or teratogenicity, indicating that clinical doses used for stroke are probably not teratogenic. Therefore, the most relevant risks of alteplase in pregnancy relate to the risk of bleeding. The label specifies that there are no adequate or well-controlled studies in pregnant women and that alteplase should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus. The 2013 AHA/ASA guidelines list pregnancy as a relative exclusion criterion and suggest that under some circumstances, with careful consideration and weighting of risk to benefit, pregnant patients may receive thrombolytic therapy.²⁴

There is minimal experience with intravenous or intra-arterial alteplase for stroke in pregnancy. Our systematic review identified only 12 reported cases of pregnant women with arterial stroke who were treated with intravenous alteplase or endovascular therapy.^{147,148} Of these 12 patients, 8 were in the first trimester, 2 were in the second trimester, and 2 were in the third trimester (both at 37 weeks). Most case reports described proximal arterial occlusions in the M1 or M2 MCA branches with moderate to severe stroke deficits (NIHSS score, 6–25). Six were treated with intravenous

alteplase, and 6 were treated with intra-arterial alteplase, with doses of intra-arterial alteplase ranging from 15 to 25 mg or urokinase ranging from 600 000 to 700 000 U. No studies reported cases of clot aspiration or retrieval. There were 2 sICHs (16.7%): 1 fatal sICH resulting from arterial dissection during angioplasty in a patient who also received intravenous alteplase¹⁴⁹ and 1 mild sICH after intra-arterial alteplase that resolved with a good neurological outcome.¹⁵⁰ There were 2 systemic bleeding complications in 6 patients treated with intravenous alteplase (33%): 1 case of intrauterine hematoma that required surgical drainage and was associated with medical termination of pregnancy, although the relationship between the hematoma and the medical termination of pregnancy was not specified, and 1 case of a buttock hematoma that was managed conservatively, resulting in the delivery of a healthy infant.¹⁴⁹ Overall outcomes among the 12 fetuses were as follows: 2 fetal demise (1 in the woman with fatal sICH and 1 as a result of spontaneous abortion; 16.7%), 2 medical terminations of pregnancy (16.7%), and 8 healthy infants (67%). A review of all cases of thrombolysis reported in pregnancy included 18 cases with thrombolysis for other indications, including pulmonary embolism, cardiac valve thrombosis, and myocardial infarction (MI).¹⁵¹ Among these 18 cases, there was 1 additional serious systemic bleeding complication in a mother with abruptio utero and fetal demise.

We identified only 2 case reports of acute stroke reperfusion therapy in mothers in the early postpartum period, neither of whom received intravenous alteplase. One was a case report of intra-arterial alteplase (20 mg) 6 days postpartum,¹⁵² and the other was a case report of intra-arterial urokinase (110 000 U) 15 hours after cesarean section.¹⁵³ Neither was complicated by sICH or vaginal bleeding.

Pregnancy and Postpartum: Recommendations

1. **Intravenous alteplase administration for ischemic stroke may be considered in pregnancy when the anticipated benefits of treating moderate to severe stroke outweigh the anticipated increased risks of uterine bleeding (Class IIb; Level of Evidence C).**
2. **The safety and efficacy of intravenous alteplase in the early postpartum period (<14 days after delivery) have not been well established (Class IIb; Level of Evidence C).**
3. **Urgent consultation with an obstetrician-gynecologist and potentially a perinatologist to assist with management of the mother and fetus is recommended (Class I; Level of Evidence C).**

Platelets

According to the updated label, alteplase is contraindicated in any circumstances of known bleeding diathesis. Originally, the FDA label defined bleeding diathesis as including, but not limited to, current use of anticoagulants, an INR >1.7, or a prothrombin time (PT) >15 seconds; administration of heparin within 48 hours with an elevated partial thromboplastin time (pTT) or platelet count <100 000/mm³. The 2013 AHA/

ASA guidelines²⁴ list exactly these contraindications as exclusion criteria. Additionally, the current use of direct thrombin inhibitors or direct factor Xa inhibitors with elevated sensitive laboratory tests is an exclusion criterion.

Thrombocytopenia

A platelet count <100 000/mm³ is a contraindication for the administration of intravenous alteplase for acute ischemic stroke. This threshold was derived from expert consensus. The risk of hemorrhagic complications is expected to be increased in the setting of severe thrombocytopenia, but the precise relationship between platelet count and bleeding risk is not well studied. Notably, because unsuspected thrombocytopenia is rare,¹⁵⁴ clinicians should not await the platelet count results before administering intravenous alteplase to patients with acute stroke unless there is a suspected bleeding abnormality, thrombocytopenia, or coagulopathy.²⁴ Whether a platelet count of 100 000 mm³ is a justified threshold for withholding intravenous thrombolysis remains unclear.

The risk of bleeding complications in patients with platelet counts <100 000 mm³ who receive intravenous alteplase has not been evaluated in a prospective study or randomized trial. Very few such patients are reported in the English literature. Of 9613 patients in pooled trial data, only 10 patients with platelets <100 000 mm³ who received intravenous alteplase despite this contraindication were identified.⁵² With the addition of several smaller studies^{155–157} comprising 4693 stroke patients treated with intravenous alteplase, 21 patients with platelets <100 000 mm³ have been reported with sufficient details (Table 13). sICH was documented in 1 of these 21 patients (4.8%). Overall, the extremely small number of published cases precludes solid conclusions.

Abnormal Coagulation Values

Similarly, data on the efficacy or safety of administering intravenous alteplase to patients with acute stroke who have abnormal coagulation tests are not robust. The risk of all types of hemorrhage may be increased with intravenous alteplase if a patient is systemically anticoagulated. In the cardiology literature, higher activated partial thromboplastin time (aPTT) values (and higher heparin doses) have been associated with higher rates of ICH in cardiac patients treated with fibrinolysis.¹⁶²

In most published stroke studies on INR levels and intravenous alteplase, INR >1.7 is attributable to medication effect and not attributable to other causes of coagulopathy, including liver failure, sepsis, or nonmedication coagulopathy. A combined 115 warfarin-treated stroke patients with INR >1.7 at the time of intravenous alteplase administration have been reported in the English literature, derived from large registries and a few small case series.^{52,111,155,157–161} (Table 13) Of these, sICH was reported in only 1 patient. Most studies did not provide information about the rates of all types of ICH or functional outcomes in these small subsets of patients. Other disorders such as hepatic disease or hematologic disorders can cause an INR >1.7, but the safety of intravenous alteplase in patients with elevated INR resulting from these disorders is also not well studied. In 1 large analysis of 2755 thrombolized patients, 138 patients had an INR >1.7 as a result of

Table 13. Thrombocytopenia

Study	Study Design	n/Total Lysed, N	Any ICH, n	sICH, n	mRS Score of 0–2
Frank et al ⁵²	Data pooled from observational studies	10/2755	NA	0	NA
Meretoja et al ¹⁵⁷	Observational, single-center registry	7/985	NA	1	3
Brunner et al ¹⁵⁵	Observational, single-center registry	3/688	0	0	NA
Kvistad et al ¹⁵⁶	Observational, single-center registry	1/265	NA	0	NA
Prolonged aPTT					
Frank et al ^{52*}	Data pooled from observational studies	139/2755	NA	6	NA
Albers et al ¹⁵⁸ (STARS)	Prospective, multicenter	13/389	NA	0	NA
Brunner et al ^{155†}	Observational, single-center registry	7/688	0	0	NA
Meretoja et al ¹⁵⁷	Observational, single-center registry	2/985	NA	0	0
Lopez-Yunez et al ¹⁵⁹	Retrospective, multicenter	1/50	0	0	NA
INR >1.7 or PT >15					
Frank et al ^{52*}	Data pooled from observational studies	152/2755	NA	7	NA
Albers et al ¹⁵⁸ (STARS)	Prospective, multicenter	10/389	NA	0	NA
Breuer et al ¹⁶⁰	Observational, single-center prospective	22	NA	NA	NA
Brunner et al ¹⁵⁵	Observational, single-center registry	8/688	0	0	NA
Meretoja et al ¹⁵⁷	Observational, single-center registry	3	NA	0	2‡
Lopez-Yunez et al ¹⁵⁹	Retrospective, multicenter	1/50	1	0	NA
Xian et al ¹⁶¹	Observational, large, multicenter registry	33	NA	1	NA
Mazya et al ¹¹¹	Observational, large, multicenter registry	24	NA	0	NA

aPTT indicates activated partial thromboplastin time; ICH, intracerebral hemorrhage; INR, international normalized ratio; mRS, modified Rankin Scale; NA, not applicable; PT, prothrombin time; sICH, symptomatic intracerebral hemorrhage; and STARS, Standard Treatment With Alteplase to Reverse Stroke.

*Elevated aPTT was defined as >39 seconds.

†One patient had a prestroke mRS score >2.

‡Elevated aPTT was defined as >37 seconds.



any cause and 14 had an INR >1.7 resulting from OAC therapy.⁵² In the 138 patients with high INR, the odds for a more favorable outcome for thrombolized patients compared with control subjects after adjustment for age and baseline NIHSS slightly favored the patients with an INR >1.7, but this difference was not statistically significant (likely because of small sample size; OR, 1.21; 95% CI, 0.82–1.78).

Data pertaining to patients with a prolonged aPTT with intravenous alteplase are comparably scarce. In total, 164 such patients have been reported in the English literature, and 6 of them had sICH.^{52,155,157–159,163} All 6 patients with sICH were from the VISTA database, which contributed most of the patients (n=139 with aPTT >39 seconds). Counterintuitively, in that analysis, there was a statistically significant difference in the odds of a favorable outcome with intravenous alteplase that favored the patients with prolonged aPTT (OR, 1.57; 95% CI, 1.02–2.41).⁵² One of the larger single studies to contribute was a prospective study of thrombolysis in clinical practice in 57 US medical centers.¹⁵⁸ The specific aPTT at the time of intravenous alteplase administration in these studies was generally not specified. Most referred to a prolonged aPTT as >40 seconds; 1 study used a cutoff of 37 seconds¹⁵⁵; and an exact threshold was not always specified.¹⁵⁸

Although in much of the literature the subgroups of patients with disturbed hemostasis who received intravenous alteplase had higher crude rates of sICH, this did not seem to necessarily translate to worse functional outcomes. There is no literature to support or refute the practice of correcting coagulopathies

with protamine, fresh-frozen plasma, or clotting factors before the administration of alteplase. Given that so few patients have been reported and that much of the data come from large voluntary registries or observational studies in which selection bias and publication bias are likely, no firm conclusions on the safety or efficacy of intravenous alteplase in patients with INR >1.7, aPTT >40 seconds, or PT >15 seconds can be made.

Of note, studies have found that abnormal platelet counts or abnormal INR values are exceedingly rare if not previously suspected to be low among stroke patients presenting to emergency departments. Cucchiara et al¹⁵⁴ found that among 1752 stroke patients, only 6 had platelet counts <100 000 (0.3%) that were not suspected on the basis of the initial history. Saposnik et al¹¹⁴ described that of 470 patients with ischemic stroke arriving at an emergency department within 3 hours from symptom onset, only 2 (0.4%) had high INR values that were not suspected on the basis of the initial history (eg, a history of warfarin or heparin use, end-stage renal disease, metastatic cancer, bleeding history, sepsis/shock presentation). Therefore, the AHA/ASA acute stroke management guidelines recommend not waiting for laboratory tests before treatment unless there is reason to suspect that the tests might be abnormal.²⁴

Platelets and Coagulation Studies: Recommendations

1. The safety and efficacy of intravenous alteplase for acute stroke patients with platelets <100 000/mm³,

INR >1.7, aPTT >40 seconds, or PT >15 seconds are unknown, and intravenous alteplase is not recommended (Class III; Level of Evidence C).

- Given the extremely low risk of unsuspected abnormal platelet counts or coagulation studies in a population, it is reasonable that urgent intravenous alteplase treatment not be delayed while waiting for hematology or coagulation testing if there is no reason to suspect an abnormal test (Class IIa; Level of Evidence B).

History of Bleeding Diathesis or Coagulopathy

According to both the current FDA label and the 2013 AHA/ASA guidelines, the presence of a preexisting known or acute bleeding diathesis or coagulopathy is a contraindication to the administration of intravenous alteplase for the treatment of acute ischemic stroke.²⁴ In clinical practice, suspected coagulopathies are commonly attributable to anticoagulant therapy, and these situations are discussed in this statement. Other potential causes of coagulopathies include liver cirrhosis, end-stage renal disease, hematologic malignancy, vitamin K deficiency, sepsis, antiphospholipid antibody syndrome, and congenital disorders.

Renal Failure

End-stage renal disease can cause a bleeding tendency by several mechanisms. Although thrombocytopenia can occur, it is rarely severe enough to contribute, and it is rather the abnormal platelet function that is more significant in clinical bleeding.¹⁶⁴ Furthermore, impaired clot retraction, altered endothelium, and reductions in inhibitors of blood coagulation such as antithrombin III and protein C occur in patients with end-stage renal disease.¹⁶⁴ Only a few studies have examined stroke treatment with intravenous alteplase in patients with renal failure, and various definitions of renal failure have been used (Table 14).

An analysis of a large US database compared 1072 patients treated with thrombolysis who had dialysis-dependent renal failure with 81070 patients without dialysis-dependent renal failure.¹⁶⁵ The dialysis group had more comorbidities (including unspecified coagulopathies), but after adjustments for age, sex, and comorbidities, dialysis-dependent renal failure was associated with a higher rate of in-hospital mortality in patients treated with intravenous alteplase (OR, 1.9; 95% CI, 1.33–2.78) and lower rates of moderate to severe disability (OR, 0.6; 95% CI, 0.43–0.8) compared with those without dialysis-dependent renal failure.¹⁶⁵ Dialysis-dependent patients with renal failure who did not receive intravenous alteplase had statistically significant higher mortality rates (10% versus 4%) compared with those without dialysis dependence who did not

receive intravenous alteplase. This suggests that the higher mortality in this group was not related to the administration of alteplase.

In a multicenter, retrospective study of thrombolized patients using a lower dose of alteplase (0.6 mg/kg), patients with renal dysfunction (estimated glomerular filtration rate <60 mL·min⁻¹·1.73 m⁻²) had higher risks of ICH (OR, 1.81; 95% CI, 1.16–2.84) and sICH (OR, 2.64; 95% CI, 1.10–6.56) compared with patients without renal dysfunction.¹⁶⁷ Notably, patients with renal dysfunction were older and had higher rates of prior use of antithrombotic agents, atrial fibrillation, hypertension, and ischemic heart disease.¹⁶⁷ Other observational studies have found no statistically significant difference between rates of ICH or sICH in patients with renal dysfunction treated with intravenous alteplase compared with those with normal renal function receiving intravenous alteplase, even when mortality rates or frequency of unfavorable functional outcomes was higher.^{166,168} It is known that renal failure is an independent predictor of poor outcomes in patients with acute stroke, but the cumulative evidence does not support withholding intravenous alteplase from patients with end-stage renal disease who have acute stroke.

Liver Failure

Hepatic cirrhosis causes various disruptions to the endogenous procoagulant and anticoagulant pathways. Many factors contribute to an anticoagulant effect, including a decreased production of coagulation factors (factors II, V, VII, IX, X, XI, and XIII), impaired platelet function, fibrinogen abnormalities, and thrombocytopenia. However, this can be offset by decreased levels of anticoagulant factors such as protein C, protein S, and antithrombin. The anticoagulant effects may be evident because they prolong conventional laboratory parameters such as PT, INR, or aPTT, but the procoagulant factors are not similarly reflected.¹⁶⁹ End-stage liver disease is also accompanied by a state of clinically evident hyperfibrinolysis in up to 5% to 10% of patients with decompensated cirrhosis.¹⁷⁰ Hyperfibrinolysis could delay hemostasis and theoretically aggravate bleeding complications after administration of intravenous alteplase for acute stroke in patients with end-stage liver disease, but this has not been studied. Overall, the hemostatic phenotype of patients with liver failure may be either prothrombotic or antithrombotic. In patients with a clinical history of end-stage liver disease with normal PT, INR, and pTT values, there is no existing evidence for withholding intravenous alteplase for acute ischemic stroke.

Table 14. Summary of Studies Evaluating Intravenous rtPA for Acute Stroke Treatment in Patients With Renal Failure

Study	Study Design	Renal Impairment, n/		Renal Impairment Description	ICH, n (%)	sICH, n (%)
		Total, N				
Tariq et al ¹⁶⁵	National database	1072/82 142		Dialysis dependent	56 (5.2)	NA
Lyrer et al ¹⁶⁶	Single-center database	138/196		eGFR <90 mL·min ⁻¹ ·1.73 m ⁻²	NA	11 (8)
Naganuma et al ¹⁶⁷	Retrospective, multicenter	186/578		eGFR <60 mL·min ⁻¹ ·1.73 m ⁻²	51 (27.4)	15 (8.1)
Power et al ¹⁶⁸	Retrospective, multicenter	65/229		eGFR <60 mL·min ⁻¹ ·1.73 m ⁻²	4 (6.2)	3 (4.6)

eGFR indicates estimated glomerular filtration rate; ICH, intracerebral hemorrhage; NA, not applicable; rtPA, recombinant tissue-type plasminogen activator; and sICH, symptomatic intracerebral hemorrhage.

Hematologic Disorders

A history of a hematologic disorder may be considered a bleeding diathesis that could potentially exclude stroke patients from receiving intravenous alteplase. Although clinical bleeding is one of the dominant complications of disorders such as leukemia, it is noteworthy that the incidence of thrombosis in malignant hematologic disorders is as high as or higher than in solid tumors.¹⁷¹ The increased bleeding risk in patients with hematologic malignancies results from multiple factors, including thrombocytopenia, disseminated intravascular coagulation, and excessive fibrinolysis.¹⁷¹

Very few data are available to guide the decision on whether to administer intravenous alteplase to a stroke patient with a history of a hematologic disorder. Results from small observational studies indicate that a general history of cancer should not preclude stroke patients from receiving treatment with intravenous alteplase, assuming other criteria are met.^{172,173} In a single-center, retrospective study of 44 thrombolized stroke patients with cancer, 5 patients with a hematologic malignancy were included. Diseases such as chronic myelogenous leukemia, chronic lymphocytic leukemia, non-Hodgkin lymphoma, and essential thrombocythemia were included, but the complication rate and outcomes of this subset were not reported.¹⁷³ A single case report of a 24-year-old man with lymphoblastic leukemia treated with intravenous alteplase for acute stroke after correction of thrombocytopenia (pretransfusion platelet count, 43 000/mm³) found that his course was not complicated by sICH and his mRS score at 3 months was 0.¹⁷⁴

In summary, there is a dearth of evidence to support or refute the usefulness of administering intravenous alteplase to stroke patients with known hematologic disorders. As in other cases, hemorrhagic risks and potential benefits should be considered on an individual basis.

History of Bleeding Diathesis/Coagulopathy: Recommendation

1. **The safety and efficacy of intravenous alteplase for acute stroke patients with a clinical history of potential bleeding diathesis or coagulopathy are unknown. Intravenous alteplase may be considered on a case-by-case basis (Class IIb; Level of Evidence C).**

History of Anticoagulant Use

Patients with acute stroke frequently have a history of anticoagulant use, and the administration of intravenous alteplase in these patients has been controversial. Current AHA/ASA guidelines state that current use of anticoagulant with INR >1.7 or PT >15 seconds is a contraindication to administering intravenous alteplase within 3 hours of symptom onset.²⁴ For patients considered for alteplase within 3 to 4.5 hours, taking OAC regardless of INR is an exclusion criterion. Given that the number of people in the United States who have atrial fibrillation is projected to reach 5.6 to 10 million by the year 2050,¹⁷⁵ this issue will become even more relevant. Many studies include patients on vitamin K antagonists or heparins and separate patients according to presenting INR, PT, or aPTT

level, discussed further below. In contrast, some studies lump patients into the more general category of prior treatment with anticoagulants. In the largest of these, based on the SITS registry in which treatment deviated from the European license for alteplase, 212 stroke patients who were on prior OAC were treated with intravenous alteplase.¹⁷⁶ Forty-five patients had an INR >1.7. After adjustment for independent predictors, there was no significant difference in the odds of sICH based on either SITS criteria (aOR, 1.6; 95% CI, 0.4–6.9) or ECASS criteria (aOR, 1.4; 95% CI, 0.7–3.0), 3-month mortality (aOR, 0.7; 95% CI, 0.3–1.3), or unfavorable outcome (aOR, 1.0; 95% CI, 0.6–1.8) for patients with a history of OAC compared with patients not receiving OAC.¹⁷⁶

Similarly, in a study using data from the VISTA database of 68 patients on OAC who were treated with intravenous alteplase, there was no difference in odds of favorable outcome compared with those not on OAC after adjustment for risk factors.⁵² Another study of 70 patients on OAC from 5 Spanish hospitals found no difference in the rate of sICH in patients on OAC compared with those not taking OAC but did find that those on OAC had lower rates of independence and higher mortality rates. However, patients on OAC in this study were older, had higher glucose levels, and were treated later.¹⁷⁷ Among these 70 patients, the mean INR before alteplase administration was 1.3 (range, 0.9–2), and only 7 patients had an INR ≥1.7.

Warfarin

The safety of intravenous alteplase in stroke patients who take warfarin who have subtherapeutic INR at the time of stroke has been disputed. The current AHA/ASA guidelines accept intravenous alteplase treatment for patients treated within 3 hours of onset with an INR ≤1.7,²⁴ whereas the European license indicates that it is contraindicated if a patient takes OACs regardless of INR.¹⁷⁸ The current FDA label lists OACs as a warning. Two relatively small multicenter registries and several single-center case series have shown widely varied rates of sICH (0%–36%) in patients taking warfarin with subtherapeutic INR at the time of thrombolysis.^{157,177,179–186} In 2 meta-analyses, the larger of which included 284 patients, the OR for sICH was increased for warfarin-treated patients (OR, 2.6; 95% CI, 1.1–5.9; and aOR, 4.1; 95% CI, 1–16.1), but both of these analyses were not adjusted for potential confounders.^{184,187} Data from 2 large registries (GWTG and Safe Implementation of Thrombolysis in Stroke–International Stroke Thrombolysis Register [SITS-ISTR]) indicate that although patients on warfarin do have higher crude rates of sICH than those not taking warfarin, when confounders such as stroke severity, older age, and comorbidities are considered, warfarin treatment with subtherapeutic INR does not independently increase the risk of sICH.^{111,161}

Low-Molecular-Weight Heparins

Low-molecular-weight heparins (LMWHs) are commonly prescribed for the treatment and prevention of venous thromboembolism. Compared with unfractionated heparin, LMWHs typically do not prolong the pTT, have greater bioavailability, and are longer-acting. These features permit safe administration in the outpatient setting. Currently, intravenous alteplase for stroke is contraindicated if the patient is taking therapeutic

doses of LMWH because of the presumed high risk of hemorrhagic complications.²⁴

Evidence of intravenous alteplase use in this situation is scarce, and patients are scattered in small numbers in more general studies of off-label or off-license alteplase. One study of 5 Spanish hospitals included 98 patients taking anticoagulants who received intravenous alteplase.¹⁸⁸ Of these, 21 patients were receiving subcutaneous LMWH, 18 of whom had been administered a dose within the preceding 24 hours. Only 5 were taking therapeutic doses, whereas 16 were taking prophylactic doses, and all had normal coagulation values. In the patients taking LMWH, 8 (38%) had ICH (3 symptomatic), 7 (33%) had favorable outcome (mRS score, 0–2), and 6 (29%) died. Patients taking LMWH had 8.4 higher odds of sICH (95% CI, 2.2–32.2), 5.3 higher odds of mortality (95% CI, 1.8–15.5), and 68% lower probability of independence at 3 months compared with those on no anticoagulants.¹⁸⁸ It should be noted that most of these patients were hospitalized at the time of stroke and may have had comorbidities that were not accounted for. Other cases of very small numbers of patients on LMWH receiving thrombolysis are reported as parts of larger studies in which there were no instances of ICH.¹⁵⁶

Direct Thrombin Inhibitor (Dabigatran and Argatroban)

Newer OACs are rapidly emerging, and the evidence indicates that they are as effective in preventing stroke in patients with atrial fibrillation as, if not more effective than, warfarin.^{189–191} Dabigatran and argatroban directly inhibit thrombin, preventing the formation of fibrin from fibrinogen.¹⁹² Although the attractiveness of direct thrombin inhibitors is bolstered by more predictable pharmacokinetics, lack of requirement for routine laboratory monitoring, fewer drug-drug interactions, and possibly increased cost-effectiveness compared with warfarin,¹⁹³ the safety and efficacy of intravenous alteplase in patients who have been taking dabigatran are not well studied. Furthermore, if hemorrhages occur, management strategies and reversal of anticoagulation are still controversial. The elimination half-life of direct thrombin inhibitors is increased in patients with renal failure.

Currently, the literature on intravenous alteplase administration in stroke patients taking dabigatran is limited to only case reports^{188,194–198} (Table 15). In these, 1 intracranial hemorrhage was reported, which was fatal.¹⁹⁵ Even beyond the question of administering intravenous alteplase to a patient prescribed these medications as an outpatient, direct thrombin inhibitors have been studied as augmentation of intravenous alteplase therapy. In a recent pilot study of 65 patients with acute stroke, argatroban and intravenous alteplase were administered concurrently.¹⁹⁹ The rate of sICH was 4.6% (3 of 65), and 10.8% (7 of 65) died within 7 days. Of patients with transcranial Doppler performed (n=47), partial or complete recanalization was documented in 61%. The cumulative data on direct thrombin inhibitors and alteplase are quite limited and based primarily on case reports. Thus, the safety and efficacy of thrombolysis in patients taking direct thrombin inhibitors are not known. Although the INR and pTT are not adequately reliable indicators of the anticoagulation effect of

dabigatran, the thrombin time is sensitive to the presence of dabigatran activity.²⁰⁰ On the basis of our current understanding of pharmacokinetics, intravenous alteplase may be reasonable in patients with normal thrombin time, aPTT, and PT, but this is not well studied and should be a subject of future research.

Oral Factor Xa Inhibitors (Apixaban and Rivaroxaban)

Clinicians may expect to see an increasing number of patients who are anticoagulated with the oral factor Xa inhibitors apixaban and rivaroxaban. These agents have been shown to be either superior (apixaban) or noninferior (rivaroxaban) to warfarin in the prevention of secondary stroke and systemic embolization caused by nonvalvular atrial fibrillation and have reduced rates of bleeding complications.^{190,191} Direct factor Xa inhibitors may prolong the PT and aPTT, but these responses are not reliable enough to estimate the effects of these agents. Further research is needed to assess the safety and efficacy of administering intravenous alteplase to patients taking direct factor Xa inhibitors. In some cases, cautious treatment may be pursued according to the elimination half-life of the medication, but until a reliable, fast method to measure their anticoagulant effect is available, it should be assumed that patients taking these medications are at higher than ordinary risk. The elimination half-life of factor Xa inhibitors is increased in patients with renal failure.

Anticoagulant Use: Recommendations

1. **Intravenous alteplase may be reasonable in patients who have a history of warfarin use and an INR ≤ 1.7 (Class IIb; Level of Evidence B).**
2. **Intravenous alteplase in patients who have a history of warfarin use and an INR >1.7 is not recommended (Class III; Level of Evidence B).**
3. **Intravenous alteplase in patients who have received a dose of LMWH within the previous 24 hours is not recommended. This applies to both prophylactic doses and treatment doses (Class III; Level of Evidence B).**
4. **The use of intravenous alteplase in patients taking direct thrombin inhibitors or direct factor Xa inhibitors has not been firmly established but may be harmful (Class III; Level of Evidence C). The use of intravenous alteplase in patients taking direct thrombin inhibitors or direct factor Xa inhibitors is not recommended unless laboratory tests such as aPTT, INR, platelet count, ecarin clotting time, thrombin time, or appropriate direct factor Xa activity assays are normal or the patient has not received a dose of these agents for >48 hours (assuming normal renal metabolizing function).**

Major Surgery Within 14 Days

The label lists recent major surgery (eg, coronary artery bypass graft, obstetrical delivery, or organ biopsy) as a warning for use of alteplase, whereas the 2013 AHA/ASA guidelines²⁴ list major surgery within previous 14 days as a relative exclusion criterion. Recent intracranial and intraspinal surgery

Table 15. Characteristics of Patients Taking Dabigatran Who Were Treated With Thrombolysis

Study	Age, y/Sex	NIHSS Score	Dabigatran Dose, mg	Last Dose, h	PTT/INR	ICH	Outcome
de Smedt et al ¹⁹⁴	46/F	19	NA	7	34.8/1.2	N	Improved (NIHSS score 12)
Naranjo et al ¹⁹⁵	62/M	18	110 twice daily	3	37.1/1.3	Y	Died
Matute et al ¹⁸⁸	76/F	4	220 daily	15	30.6/1	N	Full recovery
Lee et al ¹⁹⁶	64/M	8	150 twice daily	NA	37.6/1.1	N	NA
Marrone and Marrone ¹⁹⁷	73/M	14	110 twice daily	9	38/1.1	N	Improved (NIHSS score 7)
Sangha et al ¹⁹⁸	51/M	6	150 twice daily	18	30.7/1.1	N	mRS score of 1 at 6 mo

F indicates female; ICH, intracerebral hemorrhage; INR, international normalized ratio; M, male; mRS, modified Rankin Scale; N, no; NA, not applicable; NIHSS, National Institutes of Health Stroke Scale; PTT, partial thromboplastin time; and Y, yes.

is addressed separately in this statement. As highlighted by Fugate and Rabinstein²⁰¹ in their recent review of intravenous alteplase contraindications, the terms recent and major introduce discretion and uncertainty into intravenous alteplase administration for this patient subset. Moreover, time frames for surgical patient exclusion range from 14 days in the 2 NINDS trials to 3 months in the ECASS trials.

Although the rationale behind this contraindication centers on the potential for surgical site or systemic hemorrhage, no Level A or B evidence currently supports this exclusion.

In their retrospective case-control trial of on-label versus off-label intravenous alteplase administration within 4.5 hours of an acute stroke, Guilan et al²⁰² included 13 patients with surgery or trauma in the preceding 3 months. Notably, 2 patients, a patient with perianal surgery patient and a patient with pacemaker implantation, suffered systemic hemorrhages requiring transfusion. A third patient with a history of a hip fracture secondary to trauma suffered a hemorrhage. None of these patients suffered neurological worsening or long-term consequences from their hemorrhages and subsequent resuscitation.

Similarly, De Keyser et al²⁰³ described a surgical-site hemorrhage in a patient with blepharoplasty who received alteplase. The patient required surgical evacuation but suffered no long-term consequences. Meretoja et al¹⁵⁷ offered insights from the Helsinki Stroke Registry, a retrospective review examining a single hospital from 1995 to 2008 and 1104 alteplase patients. Eight patients had undergone surgery within the preceding 3 months, and none had significant extracranial hemorrhages. Surgeries included inguinal hernia repair, gynecological tumor resection, coronary artery bypass graft surgery, femoral-popliteal bypass, ankle fracture surgery, colon resection with splenectomy, uvulectomy with functional endoscopic sinus surgery, and pyelostomy revision.

Ultimately, the current review affirms the paucity of data supporting major surgery as an absolute contraindication to intravenous alteplase administration. Another section of this statement details specific literature on cranial and spinal surgery. These procedures carry the additional risk of acute neural element compression beyond the hemodynamic instability otherwise associated with systemic hemorrhage.

Clinicians must therefore weigh the potential salutary benefit of intravenous alteplase in the individual stroke patient against the possibility of surgical-site hemorrhage. Provided that clinical services are available to manage potential surgical-site hemorrhages, intravenous alteplase remains reasonable in select stroke patients.

Major Surgery Within 14 Days: Recommendation

1. **Use of intravenous alteplase in carefully selected patients presenting with acute ischemic stroke who have undergone a major surgery in the preceding 14 days may be considered, but the potential increased risk of surgical-site hemorrhage should be weighed against the anticipated benefits of reduced stroke-related neurological deficits (Class IIb; Level of Evidence C).**

Major Trauma Within 14 Days and Serious Head Trauma Within 3 Months

According to the original FDA label, recent intracranial or intraspinal trauma is a contraindication to alteplase, whereas recent extracranial and extraspinal trauma is a warning. On the updated label, “recent (within three months) serious head trauma” is listed as a contraindication.

According the 2013 AHA/ASA guidelines,²⁴ significant head trauma (within previous 3 months) is an exclusion criterion, whereas serious trauma in general (within previous 14 days) is listed as a relative exclusion to treatment with intravenous alteplase.

Limited data are available on the use intravenous alteplase after major trauma or serious head trauma. In a 2007 review of off-label use of alteplase, only 1 of 273 patients in the published literature received intravenous alteplase after serious head trauma.²⁰⁴ In a more recent report, 1 of 236 treated patients had recent head trauma as the contraindication to alteplase.²⁰² In a European study, trauma, head trauma, or major surgery was the contraindication for intravenous alteplase in 20 treated patients.¹⁶⁰ Although age >80 years was the only off-label criterion associated with poorer outcome in that report, no details specific to the 20 patients for whom surgery or trauma was the contraindication were reported.¹⁶⁰

Posttraumatic infarction, defined as an ischemic stroke in an arterial distribution, is reported to occur in 2% to 10% of patients during the acute in-hospital phase of severe head trauma.^{205,206} Mechanisms of such infarcts include mass effect and compression of intracranial arteries resulting from cerebral edema and increased intracranial pressure and dissection of craniocervical arteries.

After major or minor trauma, dissection of the cervical vessels may cause ischemic stroke. In otherwise eligible patients with cervical artery dissection strokes, a meta-analysis of retrospective studies and case reports that involved 121 patients

(31 with preceding trauma) treated with intravenous alteplase found no safety concerns.²⁰⁷ Furthermore, cervical artery dissection outside of major trauma is not a contraindication to intravenous alteplase and is discussed below.²⁴ However, no data are available on the treatment of posttraumatic infarction with intravenous alteplase.

Major Trauma Within 14 days and Severe Head Trauma Within 3 Months: Recommendations

1. **In acute ischemic stroke patients with recent major trauma (within 14 days), intravenous alteplase may be carefully considered, with the risks of bleeding from injuries related to the trauma weighed against the severity and potential disability from the ischemic stroke (Class IIb; Level of Evidence C).**
2. **In acute ischemic stroke patients with recent severe head trauma (within 3 months), intravenous alteplase is contraindicated (Class III; Level of Evidence C).**
3. **Given the possibility of bleeding complications from the underlying severe head trauma, intravenous alteplase is not recommended in posttraumatic infarction that occurs during the acute in-hospital phase (Class III; Level of Evidence C).**

Cardiac Conditions

History of Recent Acute MI

Acute MI, occurring simultaneously with the presenting acute ischemic stroke, was an exclusion criterion for the 2 NINDS alteplase trials, which did not enroll patients with “clinical presentation consistent with acute myocardial infarction.”²¹ However, a recent acute MI (within previous 3 months) is not a contraindication or warning in the current FDA label and is only a relative exclusion criterion in the current 2013 AHA/ASA guidelines.²⁴

Using intravenous alteplase as a definitive simultaneous treatment for acute cerebral and coronary occlusion is not possible because of different dose requirements in the 2 vascular beds. Alteplase is administered at a higher dose when used to treat MI than when used to treat acute ischemic stroke. (For example, for a 7-kg patient, the MI dose is 100 mg and the acute ischemic stroke dose is 63 mg.) Giving alteplase at doses >0.9 mg/kg in acute ischemic stroke may be associated with increased risk of cerebral hemorrhagic transformation. Conversely, the lower stroke dose is of unknown efficacy for acute coronary occlusions, and in any case, primary angioplasty and stenting are preferred over intravenous alteplase as first-line treatment for acute MI.²⁰⁸ Different forms of tissue-type plasminogen activator such as tenecteplase and reteplase are not labeled for use in acute ischemic stroke.

However, a feasible option is to administer the stroke dose of alteplase to treat the acute ischemic stroke and then to proceed to percutaneous transluminal coronary angioplasty and stenting, if indicated, for the acute coronary event. Pretreatment with intravenous alteplase does not decrease the coronary benefit of percutaneous transluminal coronary angioplasty and stenting.^{209,210}

The major concerns about giving intravenous alteplase to patients with recently completed MIs are that they may be harboring ventricular thrombi that can be caused to embolize by lytics, post-MI pericarditis that may be transformed to pericardial hemorrhage by lytics, and cardiac rupture cause by lysis of fibrin clot within necrotic myocardial wall.

The frequency of left ventricular thrombus after MI has declined substantially in the modern era. Causes of left ventricular thrombus include segmental dysfunction of the infarcted myocardium resulting in stasis, endocardial tissue inflammation providing a thrombogenic surface, and a hypercoagulable state. Left ventricular thrombi usually develop within a few days after an acute MI. Left ventricular thrombi are most common after a large, anterior wall ST-segment-elevation MI (STEMI), are uncommon after an inferior wall STEMI, and are vanishingly rare after non-STEMI. In the modern era of percutaneous transluminal coronary angioplasty and stenting, the incidence of left ventricular thrombi after STEMI in several large series has been reported to be 2% to 8%.^{211–215} Anterior wall location and size of myocardial damage are the most consistent predictors of thrombus development.

Similarly, the frequency of pericarditis after MI appears to have declined in the percutaneous transluminal coronary angioplasty and stenting era, although incidence estimates vary widely on the basis of definition and ascertainment method. Auscultation of a friction rub is a specific, noninvasive sign of pericarditis but likely underestimates frequency, whereas diagnosis based on the presence of positional chest pain is more sensitive but likely overestimates frequency. Pericarditis frequencies of 7% to 25% after acute STEMI have been reported. Postinfarct pericarditis occurs more frequently in the setting of transmural infarction, anterior wall involvement, and depressed ejection fraction.^{216–218}

The published literature on treating acute ischemic stroke patients with recent MI with intravenous alteplase is limited in scope. There is at least 1 report of individual patients treated without complication.²¹⁹ Although there are at least 3 reports of 5 patients who developed hemopericardium after receiving intravenous alteplase for acute ischemic stroke, only 1 of these patients had clinical evidence of recent MI before treatment.^{220–222}

Acute MI or History of Recent MI (Preceding 3 Months): Recommendations

1. **For patients presenting with concurrent acute ischemic stroke and acute MI, treatment with intravenous alteplase at the dose appropriate for cerebral ischemia, followed by percutaneous coronary angioplasty and stenting if indicated, is reasonable (Class IIa; Level of Evidence C).**
2. **For patients presenting with acute ischemic stroke and a history of recent MI in the past 3 months, treating the ischemic stroke with intravenous alteplase is reasonable if the recent MI was non-STEMI (Class IIa; Level of Evidence C), is reasonable if the recent MI was STEMI involving the right or inferior myocardium (Class IIa; Level of Evidence C), and may be reasonable if the recent MI was STEMI involving**

the left anterior myocardium (*Class IIb; Level of Evidence C*).

Pericarditis

“Clinical presentation suggesting post-MI pericarditis” was an exclusion criterion in the 2 NINDS trials, and acute pericarditis is listed as a warning in the current FDA label.¹ Pericarditis is not listed as an exclusion criterion in the current 2013 AHA/ASA guidelines.²⁴

Pericarditis is inflammation of the fibroelastic pericardial sac. Acute pericarditis has been observed in $\approx 0.1\%$ of hospitalized patients and 5% of patients admitted to the emergency department for nonacute MI chest pain.²²³ In a population-based study, the incidence of acute pericarditis was 27.7 cases per 100 000 people per year.²²⁴ In Western countries, most cases of pericarditis in immunocompetent patients are attributable to viral infection or are idiopathic, with additional cases resulting from metabolic disorders (eg, renal failure), autoimmune disorders, neoplastic origin, and cardiovascular disorders, including acute MI and aortic dissection. Regional pericarditis is a common cause of chest pain after initial acute MI.²¹⁸ Acute pericarditis is diagnosed by the presence of at least 2 of 4 criteria: characteristic chest pain, sharp and pleuritic, improved by sitting up and leaning forward; pericardial friction rub; suggestive electrocardiogram changes, typically widespread ST-segment elevation; and new or worsening pericardial effusion.

Pathological examination in myopericarditis often shows focal myocardial hemorrhage, and the chronic inflammation can lead to abnormal hemostatic function. Pericarditis caused by recent transmural MI is much different from pericarditis resulting from other causes. The cardiac wall damage increases the risk of hemopericardium, which is potentially fatal. As a result, pericarditis has been treated as a relative contraindication to intravenous alteplase. However, clinical data documenting an increased risk are sparse. In the acute cardiac literature, although individual case reports describe episodes of hemopericardium after intravenous thrombolysis,^{225–227} other case reports and small series have reported administration without complication.^{228–230} We were not able to identify any reports of intravenous alteplase for acute ischemic stroke in patients with known pericarditis. The stroke thrombolysis recommendations below are in reference to pericarditis resulting from causes other than an acute MI. For stroke thrombolysis recommendations concerning an acute or recent MI, refer to the section above.

Pericarditis: Recommendations

1. For patients with major acute ischemic stroke likely to produce severe disability and acute pericarditis, treatment with intravenous alteplase may be reasonable (*Class IIb; Level of Evidence C*); urgent consultation with a cardiologist is recommended in this situation.
2. For patients presenting with moderate acute ischemic stroke likely to produce mild disability and acute pericarditis, treatment with intravenous alteplase is of uncertain net benefit (*Class IIb; Level of Evidence C*).

Left-Sided Heart Thrombus

The presence of a “high likelihood of left heart thrombus, e.g. mitral stenosis with atrial fibrillation” is a warning in the current FDA label. The presence of left-sided heart thrombus was not an exclusion criterion in the original 2 NINDS trials and is not an exclusion in the 2013 AHA/ASA guidelines.^{1,24}

Fibrinolytic treatment can cause fragmentation, mobilization, and embolization of preexisting thrombi in the myocardium. Among patients treated with fibrinolytics for acute myocardial ischemia, thromboembolic complications attributed to disintegration of left heart thrombi were observed in 1.5%.²³¹ Few data in patients treated for acute ischemic stroke are available. In 1 series of 5 patients with cardiac thrombi (2 atrial, 3 ventricular) treated with systemic alteplase for acute stroke, no early cerebral or systemic embolization occurred.²³² However, other individual case reports have described cerebral embolism, embolic MI, and lower-limb embolism.^{233–235} In a series of 228 consecutive patients treated with intravenous alteplase, early recurrent cerebral ischemic events occurred in 6 (2.6%), 5 of whom had atrial fibrillation. In 4 of the 6 patients, the early recurrent ischemia occurred during or shortly after the intravenous alteplase infusion and occurred 3 days later in the other 2 patients.²³⁶

Left-Sided Heart Thrombus: Recommendations

1. For patients with major acute ischemic stroke likely to produce severe disability and known left atrial or ventricular thrombus, treatment with intravenous alteplase may be reasonable (*Class IIb; Level of Evidence C*).
2. For patients presenting with moderate acute ischemic stroke likely to produce mild disability and known left atrial or ventricular thrombus, treatment with intravenous alteplase is of uncertain net benefit (*Class IIb; Level of Evidence C*).

Infective Endocarditis

“Subacute bacterial endocarditis” is a warning in the current FDA label. Endocarditis was not an exclusion in the original 2 NINDS trials and is not an exclusion in the 2013 AHA/ASA guidelines.^{1,24}

Cerebral embolic stroke is a frequent complication of infective endocarditis. Histopathological examination shows that vegetations are composed of not only micro-organisms and inflammatory cells but also platelets and fibrin, suggesting that fibrinolysis might promote reperfusion through cerebral vessels occluded by septic emboli.²³⁷ However, histopathological studies also suggest that cerebral infarcts caused by septic emboli are particularly prone to hemorrhagic transformation as a result of septic arteritis with erosion of the arterial wall in the recipient vessel, with or without the formation of mycotic aneurysms.²³⁸ Among 8 cases of acute ischemic stroke in infective endocarditis treated with intravenous alteplase alone described in 5 reports, a radiological hemorrhagic conversion was noted in 7.^{239–243} Recanalization was achieved in 2 of 3 patients investigated with follow-up vessel imaging.

Endocarditis: Recommendation

1. **For patients with acute ischemic stroke and symptoms consistent with infective endocarditis, treatment with intravenous alteplase is not recommended because of the increased risk of intracranial hemorrhage (Class III; Level of Evidence C).**

History of Intracranial/Spinal Surgery Within 3 Months

Recent (within 3 months) intracranial and intraspinal surgery is listed in the FDA label as a contraindication and in the 2013 AHA/ASA guidelines²⁴ as an exclusion criterion. As referenced in an earlier section of this statement, the potential for surgical-site hemorrhage involving the neural axis carries a secondary risk of neurological compromise for mass effect or compression. Recent intracranial or spinal surgery within 3 months is broadly considered a contraindication to intravenous alteplase. The following literature review explored the data supporting the hypothesized increased risk of intravenous alteplase in this patient cohort.

Beyond studies referenced in an earlier section of this statement on consideration of major surgery, few data exist on the risk profile of intravenous alteplase in neurosurgical patients. Breuer et al¹⁶⁰ considered 422 off-label alteplase administrations at a single German center. Their retrospective analysis included only 20 patients with recent major surgery or trauma; the head trauma patients provide the only proxy for intracranial surgery in this study. Their analysis of mild stroke patients uncovered no significant overall difference in symptomatic intracranial hemorrhage rates.

Therefore, no meaningful Level A or B evidence exists in the literature to support the prohibition of intravenous alteplase administration because of 3-month cranial or spinal surgery history. However, surgical-site bleeding carries the potential threat of neurological insult in this subset of stroke patients and may therefore attenuate the neurological benefit associated with intravenous alteplase. Similar to major surgery patients, the scale of the operation, relationship to critical neurological structures, and availability of neurosurgical support to manage potential bleeding complications should be considered in potential intravenous alteplase administration. Additionally, mechanical thrombectomy remains a strong option in patients harboring a large-vessel occlusion in the setting of recent cranial or spinal surgery.

Although the literature offers no definitive evidence to support a recommendation, the threshold for intravenous alteplase administration should remain higher in neurosurgical patients than in the general surgery subset.

History of Intracranial/Spinal Surgery Within 3 Months: Recommendation

1. **For patients with acute ischemic stroke and a history of intracranial/spinal surgery within the prior 3 months, intravenous alteplase is potentially harmful (Class III; Level of Evidence C).**

History of Ischemic Stroke Within 3 Months

Any previous ischemic stroke within 3 months before the consideration of intravenous alteplase eligibility was listed as a contraindication and exclusion in the original FDA label and 2013 AHA/ASA guidelines, respectively; however, it has now been completely removed from the updated FDA label.^{24,244,245} The recommendation to exclude these patients appears to have been drawn from trials of thrombolysis in patients with acute MI. Direct information on the presumed higher risk of intracerebral bleeding in patients with acute ischemic stroke treated with intravenous alteplase with a recent stroke in the past 3 months was largely lacking. European United License and Guidelines, European License, and Canadian License and Guidelines post prior stroke within the last 3 months as a contraindication for the use of intravenous alteplase in patients with acute stroke.²⁰³

Karliński et al²⁴⁶ analyzed patient data from Polish centers that contributed to SITS and evaluated the safety and effectiveness of intravenous alteplase in patients who were treated without adherence to the original European drug license compared with those who were strictly treated on-label. Off-label thrombolysis was administered in 224 of 946 patients (23.7%) with acute ischemic stroke. Previous stroke within the past 3 months was a criterion violated in 14 of 942 cases (1.5%). Both groups, on- and off-label, had similar proportions of sICH according to SITS (1.9% versus 1.4%), ECASS (6.7% versus 5.4%), and NINDS (10.6% versus 8.7%) definitions overall. Multivariate analyses adjusted for independent outcome predictors also did not reveal increased odds for sICH in off-label patients overall. There were no differences in 3-month mortality (21.8% versus 18.6%) and favorable outcome (49.4% versus 53.6%) overall. Although the investigators did not uncover a significant association between off-label intravenous alteplase administration and the risk of death or death and dependency at 3 months in the study population as a whole, they did observe a trend toward higher mortality (OR, 3.48; 95% CI, 0.96–12.7) and a trend toward increased death and dependency (OR, 4.07; 95% CI, 0.97–17.1) in patients with a history of previous stroke within 3 months, which did not reach statistical significance in the primary or secondary adjusted analyses.²⁴⁶

Karliński et al¹⁷⁶ expanded the study by analyzing the data contributed to the SITS registry from 9 countries between 2003 and 2010. Of 5594 consecutive patients, 1919 (34.3%) did not fully adhere to the license. Patients treated with previous stroke <3 months constituted 146 of 5497 (2.7%). Patients in the off-label group were significantly older and had a higher proportion of all stroke relevant comorbidities and prestroke disability. Their median delay from onset to treatment was significantly longer, but there were no differences in stroke severity. In patients treated off-label, there was a trend for a higher incidence of sICH according to the SITS definition (2.2% versus 1.5%; $P=0.111$) and a significant difference in sICH according to the ECASS definition (7.1% versus 5.3%; $P=0.010$). Neither was confirmed in multivariate analyses. For the off-label subgroup of stroke <3 months, in particular, the sICH after intravenous alteplase was not significantly different from that for on-label treatment group (OR of sICH [ECASS definition], 1.20; 95% CI, 0.43–3.34; $P=0.724$).¹⁷⁶

The existing evidence on intravenous alteplase in patients who have had a stroke within 3 months is limited and overlaps the evidence concerning intravenous alteplase for patients with a past history of stroke and concomitant diabetes mellitus.

There is evidence derived from the cardiorespiratory literature that repeated administration of systemic thrombolysis is effective and safe.^{247–249} However, repeated administration of intravenous alteplase for acute ischemic stroke after early recurrence has been reported only infrequently. There are a minimum of 2 published case reports, within 40 and 90 hours, without sICH complications.^{250–252} Some studies suggest that intravenous alteplase can be readministered safely in early recurrent strokes, provided that the initial event caused only a limited volume of parenchymal injury.^{251,252}

Further Study

What remains unknown is how soon after ischemic stroke it is relatively safe to administer intravenous alteplase for a recurrent acute ischemic stroke (1 day, 1 week, 1 month, or 3 months) and how best to quantitatively and qualitatively estimate the potential of increased risk of sICH on the basis of duration of time since prior stroke, the volume of parenchymal injury, and the severity and location of prior stroke. Theoretically, the thrombolysis-induced risk of hemorrhagic transformation of a recent ischemic stroke would decrease with the passage of time from prior incident ischemic stroke (ie, <1 month associated with higher risk versus 2 months associated with moderate risk versus 3 months associated with lower risk). Further research on risk stratification based on size, severity, location, and time would help inform clinicians before recommendations can be adjusted.

History of Ischemic Stroke Within 3 Months: Recommendations

1. **Use of intravenous alteplase in patients presenting with acute ischemic stroke who have had a prior ischemic stroke within 3 months may be harmful (Class III; Level of Evidence B).**
2. **The potential for increased risk of sICH and associated morbidity and mortality exists but is not well established (Class IIb; Level of Evidence B).**
3. **The potential risks should be discussed during thrombolysis eligibility deliberation and weighed against the anticipated benefits during decision making (Class I; Level of Evidence C).**

Active Internal Bleeding or History of Gastrointestinal and Genitourinary Bleeding Within 21 Days

Active internal bleeding or history of gastrointestinal or urinary tract bleeding within 21 days represents an alteplase exclusion criterion in the 2013 AHA/ASA guidelines,²⁴ the original FDA label, and the NINDS and ECASS 2 trials. However, the label separates active internal bleeding (a contraindication) from recent gastrointestinal or genitourinary bleeding (a warning). The revised PI still lists gastrointestinal or genitourinary bleeding as a warning but no longer specifies a time period since

the last bleeding instance. The European guidelines, ECASS I, ECASS III, and Safe Implementation of Thrombolysis in Stroke–Monitoring Study (SITS-MOST) permit systemic thrombolysis in this patient subset.²⁰¹ Notably, searches yielded no Level A or B evidence to support alteplase contraindication.

Despite a robust selection of surveyed literature, none pertained directly to the population of interest on secondary abstract and manuscript review. Interestingly, experience with intra-arterial administration of alteplase for mesenteric ischemia dominated literature results and appeared to carry a relatively safe hemorrhagic profile, but this has limited application to the setting of using intravenous alteplase for acute brain ischemia. Broad, retrospective studies performed by Guillan et al²⁰² and Meretoja et al¹⁵⁷ of “off-label” alteplase offer the greatest insights into this topic.

Guillan et al²⁰² discovered no significant sICH or 3-month mortality in a single-center, retrospective review of 269 on-label versus 236 off-label alteplase administrations. Seven of the off-label cases had “systemic disease with risk of bleeding.” Three of those cases involved disseminated breast tumor, 2 gastric tumors, 1 chronic liver disease, and 1 colon tumor. No patients suffered major hemorrhagic complications.

Similarly, the Meretoja et al¹⁵⁷ single-center, retrospective analysis of off-label alteplase administration included a patient with a 1-week history of hematuria and a second patient with active hepatitis. Neither patient suffered an sICH, and they had 90-day mRS scores of 1 and 3.

Existing literature is extremely sparse. Although intravenous alteplase was well tolerated in the few reported patients with recent gastrointestinal or genitourinary hemorrhagic events, further evidence is needed. For clinical purposes, it may be worthwhile to distinguish patients with a known source or structural lesion from those with an occult source of gastrointestinal or genitourinary bleeding. Patients with solid malignancies or defined ulcers or varices may harbor therapeutic targets for sclerotherapy or embolization in the event of systemic hemorrhage. Importantly, few data exist to support the increased hemorrhagic risk in these patients. Conversely, patients with an occult source for their previous gastrointestinal or genitourinary bleed may carry a less well-characterized risk profile with systemic thrombolysis.

Ultimately, the safety of administering intravenous alteplase to patients with acute stroke with recent gastrointestinal or genitourinary bleeding is uncertain; patients who suffered their hemorrhagic event >7 days preceding their acute stroke presentation may carry a lower bleeding risk.

Active Internal Bleeding or History of Gastrointestinal/Genitourinary Bleeding Within 21 Days: Recommendations

1. **Reported literature details a low bleeding risk with intravenous alteplase administration in the setting of past gastrointestinal/genitourinary bleeding. Administration of intravenous alteplase in this patient population may be reasonable (Class IIb; Level of Evidence C).**
2. **Patients with a structural gastrointestinal malignancy or recent bleeding event within 21 days of**

their stroke event should be considered high risk, and intravenous alteplase administration is potentially harmful (Class III; Level of Evidence C).

Arterial Puncture of Noncompressible Vessels in the Preceding 7 Days

The FDA label lists previous puncture of a noncompressible vessel as a warning for alteplase use, whereas the 2013 AHA/ASA guidelines²⁴ describe arterial puncture at a noncompressible site within 7 days as an exclusion.

On the basis of expert consensus, arterial puncture of a noncompressible vessel within the week preceding acute stroke symptoms is a contraindication to administering intravenous alteplase to patients with acute stroke.²⁴ The most likely scenario in which this problem would arise is after catheterization of the subclavian or internal jugular vein in critically ill patients, procedures that are complicated by inadvertent adjacent arterial puncture in up to 8% of cases.²⁵³ In addition to placement of central venous catheters for the resuscitation of critically ill patients, noncompressible veins may be accessed during medical care for placement of pacing or defibrillation leads, dialysis catheters, pulmonary artery catheters, or transcatheter heart valve placements. Notably, a patient undergoing one of these procedures may be less functional and more ill than the general population in which intravenous alteplase has been studied to date, and the ratio of risks to potential benefits in this subgroup may be substantially different.

The subclavian and axillary arteries are not easily accessible to manual compression, whereas compression of the carotid artery may result in major complications, including brain ischemia, hemorrhage, or death.²⁵³ The common clinical observation of increased bleeding in anticoagulated patients who have central venous catheters placed and the potential consequence of uncontrollable and life-threatening hemorrhage from a noncompressible vessel likely justify this exclusion criterion, although there is no existing literature to support or oppose this recommendation. Although there are treatments available, that is, surgical procedures or endovascular intervention (eg, percutaneous arterial closure device placement, balloon tamponade, or use of covered stents),²⁵⁴ they are not solutions to the problem because these procedures would confer significant bleeding risks to patients who receive thrombolysis.

Arterial Puncture of Noncompressible Vessels in the Preceding 7 Days: Recommendation

1. The safety and efficacy of administering intravenous alteplase to acute stroke patients who have had an arterial puncture of a noncompressible blood vessel in the 7 days preceding stroke symptoms are uncertain (Class IIb; Level of Evidence C).

Uncontrolled Hypertension, Severe Hypertension, Repeated Blood Pressure, or Requiring Aggressive Treatment

According to the 2013 AHA/ASA guidelines²⁴ and the original FDA label, elevated or uncontrolled blood pressure (systolic

>185 mmHg or diastolic >110 mmHg) is an exclusion criteria or contraindication, respectively. The updated FDA label lists “current severe uncontrolled hypertension” without any specific numeric thresholds. Uncontrolled or severe hypertension (>185 mmHg systolic or 110 mmHg diastolic on ≥ 2 consecutive measurements) has been a common reason to exclude a patient from intravenous alteplase in real-world practice, especially if not quickly brought under control with blood pressure treatment.^{12,255} High blood pressure at presentation has been associated with an elevated risk of sICH with intravenous alteplase in the SITS and GWTG phase 4 registries.^{110,256} The higher the blood pressure is, the greater the risk is. The only thrombolytic trial that did not exclude subjects with systolic blood pressure >185 mmHg was the Australian Streptokinase (ASK) trial. A correlation was seen between very high blood pressure and very high risk of major hemorrhage in the ASK trial.²⁵⁷ On the basis of these phase 4 studies and the ASK trial, intravenous alteplase treatment should not be administered if systolic blood pressure cannot be controlled at or below 185 mmHg systolic. A lower threshold for blood pressure control cannot be advocated without further randomized trials. The Enhanced Control of Hypertension and Thrombolysis Stroke Study (ENCHANTED) trial plans to randomize subjects treated with intravenous alteplase to 2 blood pressure regimens (standard, <185 mmHg; or aggressive, 140–150 mmHg).

There is limited literature to guide decision making on how much lowering of blood pressure is safe.²⁵⁸ Acute blood pressure reduction producing large drops in blood pressure over the first 24 hours could result in a higher incidence of adverse effects such as stroke progression.²⁵⁹ However, there are no studies supporting a relationship between worse outcome and blood pressure reduction before intravenous alteplase.²⁶⁰ As long as systolic blood pressure can be reduced to 185 mmHg or lower and diastolic blood pressure can be reduced to 110 mmHg or lower by whatever means necessary, the patient remains suitable for thrombolysis with intravenous alteplase.

Uncontrolled Hypertension, Severe Hypertension, Repeated Blood Pressure, or Requiring Aggressive Treatment: Recommendations

1. Intravenous alteplase is recommended in patients whose blood pressure can be lowered safely (to <185/110 mmHg) with antihypertensive agents, with the physician assessing the stability of the blood pressure before starting intravenous alteplase (Class I; Level of Evidence B).
2. If medications are given to lower blood pressure, the clinician should be sure that the blood pressure is stabilized at the lower level before beginning treatment with intravenous alteplase and maintained below 180/105 mmHg for at least the first 24 hours after intravenous alteplase treatment (Class I; Level of Evidence B).

History of Intracranial Hemorrhage

Patient history of ICH represents an additional contraindication or exclusion for intravenous alteplase for stroke

according to the original FDA label and the 2013 AHA/ASA guidelines.²⁴ The recently updated label only lists recent ICH as a warning and removed a history of ICH as a contraindication. Similar to earlier reviews of intravenous alteplase exclusion criteria, the literature offers only a handful of cases in the context of larger retrospective reviews. The lack of any data on this issue is possibly the reason the revised FDA label removed any history of ICH as a contraindication and added a warning against recent ICH only. It remains unclear how the FDA would define recent in such a setting. Interestingly, studies examining the presence of cerebral microbleeds (CMBs) before intravenous alteplase administration by MRI may provide larger insights into this subset of stroke patients. From a pathophysiological perspective, the cause of these microbleeds remains unclear and may reflect a form of reperfusion injury or disrupted cerebral autoregulation. The presence of these lesions after alteplase administration may thus be unrelated and artifactual.

Kvistad et al¹⁵⁶ found comparable ICH rates in a study of 130 on-label versus 135 off-label intravenous alteplase administrations. However, the lone patient with prior ICH suffered an sICH after alteplase administration. Meretoja et al¹⁵⁷ administered intravenous alteplase to a single prior ICH patient and 2 patients with prior SAH who had not received surgery; none of these 3 patients suffered an ICH with alteplase administration.

Both Aleu et al²⁰⁴ and Matz and Brainin²⁶¹ performed recent literature reviews on off-label thrombolysis for stroke; neither found reports of intravenous alteplase administration in the setting of prior ICH. In a Medline and Google Scholar search from December 1995 through March 2006, Aleu et al found 24 patients with microbleeds before alteplase by MRI. Five patients received intra-arterial alteplase and 19 received conventional intravenous alteplase; only 1 patient in each group suffered an sICH. Matz and Brainin similarly found “no published data on patients with a history of intracerebral or intracranial bleeding and outcome after thrombolysis.”

The Bleeding Risk Analysis in Stroke Imaging Before Thrombolysis (BRASIL) study used MRI within 6 hours of stroke onset to examine the presence and number of CMBs. Two hundred forty-two CMBs were detected in 510 stroke patients. A Fisher exact test ($P=0.17$) demonstrated no statistical difference in sICH rate with alteplase administration between the CMB and non-CMB groups. Additionally, an increased number of CMBs in an individual patient (ie, >5) did not comport with an increased sICH risk. The absolute sICH risk in this study with intravenous alteplase administration was 3.1%.²⁶²

Overall, the risk of sICH likely corresponds to the volume of encephalomalacia from the previous ICH, whether the previous ICH occurred in the same vascular territory as the acute stroke presentation, and how recently the ICH took place. In the absence of supporting data, the treating clinician should use these factors to stratify the sICH risk for intravenous alteplase administration in this patient subset. Given the low overall ICH rate in patients with acute CMBs, it remains unlikely that the sICH rate would swamp the benefits of intravenous alteplase in patients with more remote ICH. Intravenous alteplase administration may be reasonable in this patient subset with due consideration of the above factors and

a diagnostic parsing of stroke mimics (SMs) in these patients with preexisting intracranial disease.

History of Intracranial Hemorrhage: Recommendations

1. **Intravenous alteplase has not been shown to increase sICH rates in patients with CMBs. Intravenous alteplase administration in these patients is therefore reasonable (Class IIa; Level of Evidence B).**
2. **Intravenous alteplase administration in patients who have a history of intracranial hemorrhage is potentially harmful (Class III; Level of Evidence C).**

Unruptured Intracranial Aneurysm

The 2013 AHA/ASA guidelines²⁴ list an intracranial aneurysm as a contraindication or an exclusion criterion for intravenous alteplase for stroke; it is listed as a warning in the FDA label.²⁴

A systematic review and meta-analysis show that unruptured intracranial aneurysms occur in 2% to 3% of the general population.^{263,264} Data on the safety of intravenous alteplase in patients with incidental unruptured intracranial aneurysms are derived from case reports and series. With the increased utility of noninvasive imaging such as CT or magnetic resonance angiography, in patients with acute stroke evaluated for consideration of intravenous alteplase therapy, the diagnosis of incidental aneurysms will continue to gain clinical significance. The largest case series included 22 unruptured aneurysms; of those, 73% were in the anterior circulation and 27% were ≥ 5 mm.²⁶⁵ The rates of ICH were similar for patients with and without aneurysms. Other series also indicate no significant increase in ICH risk among patients with unruptured aneurysms undergoing treatment with intravenous alteplase compared with those without aneurysms.^{266–269} Although limited by selection bias, these series suggest that intravenous alteplase can be safely administered in patients with incidental intracranial aneurysms. No data are available to evaluate the safety of intravenous alteplase in patients with unruptured large or giant aneurysms, which might carry a higher risk for ICH.

Unruptured Intracranial Aneurysm: Recommendations

1. **For patients presenting with acute ischemic stroke who are known to harbor a small or moderate-sized (<10 mm) unruptured and unsecured intracranial aneurysm, administration of intravenous alteplase is reasonable and probably recommended (Class IIa; Level of Evidence C).**
2. **Usefulness and risk of intravenous alteplase in patients with acute ischemic stroke who harbor a giant unruptured and unsecured intracranial aneurysm are not well established (Class IIb; Level of Evidence C).**

Intracranial Vascular Malformation

The 2013 AHA/ASA guidelines²⁴ list an intracranial arteriovenous malformation as a contraindication or an exclusion

criterion for intravenous alteplase for stroke; it is listed as a warning within the FDA label.

Intracranial vascular malformations include cavernous angiomas, capillary telangiectasias, development venous anomalies, and arteriovenous malformations and fistulas. The associated risk of spontaneous hemorrhage varies significantly, depending on the specific type of lesion and its structure. Very limited data exist on the safety of intravenous alteplase in patients with vascular malformations. Safe administration of intravenous alteplase in patients with cerebral arteriovenous malformation, cavernous malformation, and dural arteriovenous fistula has been described in single case reports.^{270–272} Given the increased risk of hemorrhage in patients with intracranial malformations and limited experience with the use of intravenous alteplase in this group of patients, no solid conclusions can be made on the safety of thrombolysis in stroke patients with known or incidental malformations.

Intracranial Vascular Malformation: Recommendations

1. **For patients presenting with acute ischemic stroke who are known to harbor an unruptured and untreated intracranial vascular malformation, the usefulness and risks of administration of intravenous alteplase are not well established (Class IIb; Level of Evidence C).**
2. **Because of the increased risk of ICH in this population of patients, intravenous alteplase may be considered in patients with stroke with severe neurologic deficits and a high likelihood of morbidity and mortality to outweigh the anticipated risk of ICH secondary to thrombolysis (Class IIb; Level of Evidence C).**

Intracranial Neoplasms

The 2013 AHA/ASA guidelines²⁴ list an intracranial neoplasm as a contraindication or an exclusion criterion for intravenous alteplase for stroke; it is listed as a warning within the current FDA label.

Intracranial neoplasms are divided into extra-axial and intra-axial tumors. Consideration of intravenous alteplase risk on the basis of anatomic and histological factors may inform systemic thrombolysis in this patient cohort. Importantly, glioblastoma multiforme (GBM) represents a notable stroke imaging mimic; several case reports detail sICH events with intravenous alteplase administration in GBM patients.

Neil and Oviagele²⁷³ reported intravenous alteplase administration in 2 patients with a presumed acoustic neuroma in the cerebellopontine angle and an occipital falcine meningioma. Neither patient suffered a symptomatic intracranial hemorrhage. The large, retrospective review by Guillan et al²⁰² included alteplase administration in 3 patients with meningioma, 1 patient with cholesteatoma, and 1 patient with paranasal tumor. None of these patients suffered an sICH with intravenous alteplase. Hsieh and Chen²⁷⁴ similarly reported the safe administration of intravenous alteplase in the setting of a meningioma. Etgen et al²⁷⁵ performed a literature

review of intravenous alteplase administration in the setting of brain tumors that included a 12th meningioma case; this review uncovered only a single sICH that occurred in a patient with GBM. Thus, no case of sICH referable to extra-axial neoplasms exists in the literature.

GBM and intrinsic glial tumors may carry a different sICH rate with intravenous alteplase administration. Garcia et al²⁷⁶ described the safe administration of intravenous alteplase in a patient thought to be having an acute stroke that later declared itself a GBM. Guillan et al²⁰² described 2 patients with SM in their series. One patient had a GBM and the other had gliomatosis cerebri; neither suffered an sICH with intravenous alteplase administration. Grimm and DeAngelis²⁷⁷ reported the only sICH from intravenous alteplase administration in the setting of a GBM; the intratumoral hemorrhage occurred 20 days after administration and may not have been due strictly to thrombolysis. For a more detailed assessment of intravenous alteplase in scenarios of SM, refer to discussion in a following section.

Systemic thrombolysis in the setting of intracranial neoplasms occurs for indications beyond stroke and may inform additional sICH risk. Rubinshtein et al²⁷⁸ described intravenous alteplase and streptokinase administration for 2 patients with MI in the setting of a pituitary adenoma; neither suffered an sICH. Han et al²⁷⁹ similarly reported safe intravenous alteplase administration for massive pulmonary embolism in the setting of a GBM without an sICH.

Although data on intravenous alteplase in the setting of intracranial neoplasms are confined to case reports, systemic thrombolysis appears safe in extra-axial, intracranial neoplasms. Although GBMs may carry a slightly increased risk of sICH, their acute recognition may prove challenging; literature concerning intravenous alteplase in this administration highlights GBM as an SM. Thus, the presence of an intracranial neoplasm should not absolutely contraindicate intravenous alteplase administration. The data surrounding the sICH rate in intracranial metastases, most notably hemorrhagic metastases including renal cell, cholangiocarcinoma, and melanoma, are less available. Ultimately, the histology, location, and baseline bleeding risk of the tumor can inform reasonable intravenous alteplase administration in these patients.

Intracranial Neoplasms: Recommendations

1. **Intravenous alteplase treatment is probably recommended for patients with acute ischemic stroke who harbor an extra-axial intracranial neoplasm (Class IIa; Level of Evidence C).**
2. **Intravenous alteplase treatment for patients with acute ischemic stroke who harbor an intra-axial intracranial neoplasm is potentially harmful (Class III; Level of Evidence C).**

Serious Medical Comorbid Illnesses

The FDA label warns against the use of intravenous alteplase in patients with hemostatic defects, including those secondary to significant hepatic dysfunction, renal disease, or any other comorbid condition in which bleeding

might constitute a significant hazard, but the 2013 AHA/ASA guidelines²⁴ do not.

Significant comorbidity was cited as the main exclusion criterion for alteplase in 8.3% to 14% of eligible stroke patients in prior studies.^{120,280} Another study found that 9 of 73 patients (12.3%) were excluded on basis of poor prognosis (8 of whom had preexisting dementia).²⁸¹ Several comorbid conditions bear discussion, including severe renal or hepatic disease (discussed above), dementia, recrudescence, and active malignancy.

Preexisting Dementia

Neither the FDA label nor the 2013 AHA/ASA guidelines²⁴ specifically contraindicate intravenous alteplase in patients with preexisting dementia who have an acute ischemic stroke.

Patients with preexisting dementia are less likely to receive alteplase for acute stroke.^{282,283} Baseline dementia is associated with worse outcomes after stroke, including those who undergo reperfusion therapy.^{284,285} However, whether dementia carries inherent risks of complications after thrombolysis, perhaps because of concomitant amyloid angiopathy and/or microbleeds, is less certain. In a case-control study using the Nationwide Inpatient Sample to identify thrombolized stroke patients with dementia compared with those without dementia, risks of ICH (5.8% versus 4.5%; $P=0.45$) and mortality (17.4% versus 14.5%; $P=0.31$) were not different. However, the risks of ICH (OR, 2.80; 95% CI, 1.82–4.32) and mortality (OR, 2.13; 95% CI, 1.43–3.17) were higher among dementia patients treated with intravenous alteplase compared with those who did not receive it. Furthermore, dementia was an independent predictor of death among patients receiving intravenous alteplase.²⁸² Using the Registry Canadian Stroke Network, a propensity score-matched (1:1) study of stroke patients with preexisting dementia compared with those without found that in the subgroup of patients who received intravenous alteplase ($n=198$), there were no differences in the risk of ICH (relative risk [RR], 1.27; 95% CI, 0.69–2.35), sICH (RR, 1.00; 95% CI, 0.47–2.13), or 30-day mortality (RR, 1.27; 95% CI, 0.60–1.55). There was a trend toward greater disability at discharge among patients with dementia (RR, 1.22; 95% CI, 0.98–1.52).²⁸³

Malignancy

Neither the FDA label nor the 2013 AHA/ASA guidelines²⁴ specifically contraindicate intravenous alteplase in patients with preexisting malignancy who have an acute ischemic stroke.

Cancer is an independent predictor of poor outcome after an ischemic stroke.^{286,287} Some risk scores have incorporated preexisting cancer to weight the risk of death or disability.^{286,287} Given their life expectancy, patients with known cancer have been excluded from prior thrombolytic trials and subsequent observational studies. As a result of the low life expectancy in patients with malignancy, the benefits of intravenous alteplase for stroke may also be limited. Only small case series of intravenous alteplase for stroke in patients with current malignancy in clinical practice have been published.^{172–174,288} These 4 studies included a combined 38 patients with active malignancy

(without brain metastases) and suggest no increased risk of intracranial systemic hemorrhage after intravenous alteplase administration. Thrombolysis in patients with intracranial neoplasm and intracardiac tumors is discussed in other sections of this statement.

Recrudescence

Treatment of SMs is covered in another section, but it bears mention here that medical conditions such as acute kidney disease, glucose derangements, acute systemic infections, and medications can produce re-emergence, recrudescence, or worsening of neurological deficits in patients with prior stroke. A study of the prevalence of SM in stroke code alerts found that reemergence of prior deficits accounted for 11 of 104 SM presentations (10.6%).²⁸⁹ Patients with SMs are more likely to have history of prior stroke or transient ischemic attack or baseline cognitive impairment and present with different clinical patterns such as global aphasia without hemiparesis, acute confusion, or decreased level of consciousness than patients with true stroke.^{290–294}

Serious Medical Comorbid Illnesses: Recommendations

1. **In patients with end-stage renal disease on hemodialysis and normal aPTT, intravenous alteplase is recommended (Class I; Level of Evidence C). However, those with elevated aPTT may have elevated risk for hemorrhagic complications.**
2. **Patients with preexisting dementia may benefit from intravenous alteplase (Class IIb; Level of Evidence B). Individual considerations such as life expectancy and premorbid level of function are important to determine whether alteplase may offer a clinically meaningful benefit.**
3. **The safety and efficacy of alteplase in patients with current malignancy are not well established (Class IIb; Level of Evidence C). Patients with systemic malignancy and reasonable (>6 months) life expectancy may benefit from intravenous alteplase if other contraindications such as coagulation abnormalities, recent surgery, or systemic bleeding do not coexist.**

Preexisting Disability

Neither the FDA label nor the 2013 AHA/ASA guidelines²⁴ specifically contraindicate intravenous alteplase in patients with preexisting disability who have an acute ischemic stroke.

Preexisting disability is one of the considerations in the decision-making process of intravenous alteplase for stroke. With the aging of the population, the longer life expectancy, and the increasing prevalence of comorbidities with age, clinicians will likely be assessing more acute stroke patients with preexisting disability or arriving from nursing homes.^{295,296} Preexisting disability, usually defined as an mRS score ≥ 2 , is an independent predictor of stroke outcomes^{287,297–300} and longer length of hospitalization.³⁰¹ The prevalence of prestroke disability varies by age group and country. For example, a cohort study from Brazil ($n=2407$; mean age, 67.7 years)

reported prestroke disability (mRS score ≥ 3) in 32.6% of patients.³⁰² A recent study of intravenous alteplase therapy from England (n=37151) revealed that the prevalence of preexisting disability in the stroke population increased with age (3.8%–8.6% for those ≤ 60 years of age versus 33.7%–46.9% among those ≥ 90 years of age). Moreover, patients receiving alteplase were more likely to be independent (pre-stroke mRS score ≤ 1).⁶¹ Similar results were observed in a cohort study including 12686 stroke patients from Canada (alteplase, 88.7% versus no alteplase, 77.5%; $P < 0.001$).¹¹³ In the Swedish Stroke Registry, only 0.6% (n=25) of patients dependent for activities of daily living received alteplase compared with 3.8% (n=2505) who were independent.³⁰³ Being independent for activities of daily living was associated with 5-fold higher chance of receiving alteplase (OR, 5.11; 95% CI, 3.29–7.92).³⁰³

Observational studies suggest that each 1-point increase in mRS is similar to being ≈ 5 years older.²⁹⁹ Other studies evaluating the efficacy of alteplase revealed that age and NIHSS are independent predictors of discharge home or to the same place or residence as before stroke.^{41,304,305} A study from Australia including 566 stroke patients revealed that prestroke residential status, ability to walk (measured with the Motor Assessment Scale), and age correctly predicted 99% of stroke patients discharged home with an accuracy of 87.3%. For every 1-point increase in Motor Assessment Scale-5 (gait), stroke patients were 1.66 times more likely to go home (95% CI, 1.28–2.27; $P < 0.001$).³⁰⁶ Additional factors influencing discharge destination include the functional independent measure, marital status, and socioeconomic status.^{307–310}

Interestingly, patients with preexisting disability were largely excluded from most RCTs.^{42–45} In the 2 NINDS trials, of the 48 patients (7.7%) with preexisting disability, 24 received alteplase and 24 received placebo. Older age, higher baseline NIHSS score, history of diabetes mellitus, and preexisting disability were all associated with a decreased likelihood of having a favorable clinical outcome at 3 months.³¹¹ Stroke patients with preexisting disability receiving alteplase had a lower probability of achieving a favorable outcome at 3 months compared with those without disability receiving alteplase (25.0% versus 52.4%; OR, 0.20; 95% CI, 0.07–0.62 after adjustment for age and baseline NIHSS score). However, there was a trend toward benefit with alteplase at 3 months for patients with preexisting disability (25% versus 12.5%; OR, 2.33; 95% CI, 0.51–10.7) compared with placebo, although wide CIs make this difficult to interpret.³¹¹ Foell and colleagues³¹² analyzed 3-month outcomes of patients with and without preexisting disability among patients receiving alteplase. They also compared their results with those obtained in the NINDS trial part II. Patients with preexisting disability had a higher mortality rate (33% versus 14%) and greater functional disability, as measured by the mRS, than patients without a preexisting disability.

The analysis of dichotomous outcomes (eg, mRS) has several limitations. Of particular concern is outcome definition of independence (mRS score, 0–2) or no disability (mRS score, 0–1) for patients with preexisting disability (mRS score ≥ 2). To overcome this issue, a shift analysis has emerged as an

analytical approach to determine the extent to which subjects shifted toward good functional outcomes accounting for the pre-stroke mRS status.^{313,314} The analysis of the 2 NINDS trials and the ECASS II trial indicate that patients treated with alteplase up to 6 hours after stroke onset shifted in a favorable direction toward a better health state compared with the placebo-treated patients (NINDS trials: OR, 1.60; 95% CI, 1.21–2.11; ECASS II: OR, 1.32; 95% CI, 1.02–1.71). However, disparities across baseline severity strata undermine the efficiency of the shift analysis, explaining why it does not markedly outperform the binary outcome tests.³¹⁵ Karlinski et al³¹⁶ analyzed the data of 7250 stroke patients in the Safe Implementation of Treatments in Stroke–Eastern Europe (SITS-EAST) registry with the aim of evaluating the impact of different levels of prestroke disability on patients' profile and outcome after intravenous alteplase. Of all 7250 patients, 5995 (82%) had a prestroke mRS score of 0, 791 (11%) had an mRS score of 1, 293 (4%) had an mRS score of 2, and 171 (2%) had an mRS score of ≥ 3 . Compared with patients with an mRS score of 0, all other groups were older and had more comorbidities and more severe neurological deficit on admission. There was no clear association between preexisting disability and the risk of sICH. Prestroke mRS scores of 1, 2, and ≥ 3 were associated with an increased risk of death at 3 months (OR, 1.3, 2.0, and 2.6, respectively) and a lower chance of achieving favorable outcome (achieving an mRS score of 0–2 or returning to prestroke mRS: OR, 0.80, 0.41, and 0.59, respectively). Patients with mRS scores of ≥ 3 and 2 had similar favorable outcomes (34% versus 29%) despite higher mortality (48% versus 39%).

The analysis of disability-adjusted life-year applied to the NINDS alteplase trials adjusted by preexisting disability suggests that on average patients receiving intravenous alteplase experienced >1 year 3 months of additional healthy life. For all patients achieving a benefit (nearly one third of patients), alteplase conferred an average of 4 years 5 months of healthy life.³¹⁷

Nursing Homes, Life Expectancy, and Other Confounders

Other factors associated with decreased quality of life or dependency relate to the place of residence and life expectancy before stroke. The decision for thrombolysis among patients from long-term care facilities or nursing homes is controversial. Scarce evidence is available because patients in long-term care facilities or nursing homes have some degree of dependency for activities of daily living, a condition that limited recruitment in most RCTs. Observational studies suggests a lower frequency of intravenous alteplase treatment among patients arriving from nursing homes or dependent for activities of daily living. For example, in the Swedish Stroke Register including 70705 patients, only 1% (n=30) of individuals living in an institution received intravenous alteplase compared with 3.7% (n=2498) of noninstitutionalized individuals ($P < 0.001$).³⁰³

Life expectancy <12 months is regarded as a relative contraindication for intravenous alteplase according to The Joint Commission.³¹⁸ Most patients with lower life expectancy may have an underlying malignancy or metastatic cancer, as described in a previous section.

Patients with preexisting neurological and psychiatric disorders or conditions may present to the emergency department with syndromes mimicking stroke, which is addressed more completely below.³¹⁹

Preexisting Disability: Recommendation

- 1. Preexisting disability does not seem to independently increase the risk of sICH after intravenous alteplase, but it may be associated with less neurological improvement and higher mortality. Thrombolytic therapy with intravenous alteplase for acute stroke patients with preexisting disability (mRS score ≥ 2) may be reasonable, but decisions should take into account relevant factors other than mRS (including quality of life, social support, place of residence, need for a caregiver after alteplase administration, patients' and families' preferences, and goals of care) (Class IIb; Level of Evidence B).**

Blood Glucose

In the 2013 AHA/ASA guidelines, determination of blood glucose remains a prerequisite for alteplase eligibility and administration.²⁴ Levels between 50 and 400 mg/dL had previously been recommended for alteplase eligibility because of their inclusion in the 2 NINDS trials,¹ although the most recent AHA/ASA guideline mentions excluding only patients with glucose <50 mg/dL.²⁴ The original FDA label for alteplase reiterated the NINDS criteria and further stated that "... special diligence is required in making this diagnosis in patients whose blood glucose values are <50 mg/dL (2.7 mmol/L) or >400 mg/dL (22.2 mmol/L)." Thus, the rationale for its inclusion in the eligibility criteria derives mostly from a concern that hypoglycemia and hyperglycemia are known to produce acute focal neurological deficits that can mimic those from acute brain ischemia. In practice, glucose levels account for $<1\%$ of alteplase contraindications in the GWTG-Stroke registry. This warning has now been removed from the most updated FDA label.

Focal neurological deficits resulting from hypoglycemia are rare but known to occur³²⁰ and may be attributable to the ischemic vulnerability to low levels of circulating glucose required for aerobic metabolism in highly metabolically active brain regions. In an imaging-based meta-analysis, $\approx 20\%$ of hypoglycemic attacks have restricted diffusion on imaging, causing further conflation of ischemic stroke and hypoglycemia.³²¹ However, it rarely produces stroke-like deficits in the absence of other more typical symptoms such as altered consciousness, seizures, and diaphoresis. Prior studies suggest that mimics resulting from hypoglycemia occurred in $<1\%$ of suspected stroke presentations.^{289,320,322} Hyperglycemia may also mimic stroke and was reported in 4 of 1460 patients (0.3%) in 1 large study.³²⁰ Other studies have noted that toxic-metabolic disturbances, of which glucose derangements may be the most common, account for 2.9% of acute stroke presentations.^{291,293} The topic of SMs is addressed in greater detail below.

In addition to the desire to avoid including patients with SM for randomization in the 2 NINDS trials, the risk of poor

outcomes, including sICH, as a result of hyperglycemia was major concern.^{323–328} Furthermore, hyperglycemia may accelerate tissue infarction after ischemia and decreases the chances of successful recanalization.^{329,330} It is worth noting, however, that persistent hyperglycemia, rather than baseline hyperglycemia alone, may be more important in predicting these adverse outcomes.³³¹ The safety of intravenous alteplase in patients with extreme glucose levels suggests increased risk of sICH, particularly with hyperglycemia. In the SITS-EAST study, 14 of 5461 participants (0.2%) had glucose levels >400 mg/dL and 1 had glucose <50 mg/dL; together, those with hypoglycemia or hyperglycemia and treated with alteplase were at increased risk of sICH (unadjusted OR, 5.91; $P=0.030$) and unfavorable outcome (aOR, 8.59; $P=0.064$).¹⁷⁶ In the VISTA study, which included 6 patients treated with alteplase despite baseline glucose >400 mg/dL and 5 despite glucose <50 mg/dL, no clear association with hemorrhagic risk or outcome was observed compared with control subjects.⁵²

On the basis of the low rate of glycemic abnormalities mimicking stroke on acute presentations, the safety of alteplase among SM patients, the relatively greater impact of persistent rather than initial hyperglycemia on poor outcomes, and the frequent possibility that ischemic strokes may occur simultaneously in diabetic patients also presenting with hypoglycemia or hyperglycemia, it is reasonable to consider intravenous alteplase in suspected stroke patients with initial blood glucose levels <50 or >400 mg/dL after appropriate glycemic management (ie, dextrose or insulin, respectively) and neurological re-examination within a short time frame (ie, 15 minutes). If the significant neurological deficits persist with normalization of glucose levels, intravenous alteplase may be optional in such patients. However, data on this practice are lacking.

Blood Glucose: Recommendations

- 1. Intravenous alteplase is recommended in otherwise eligible patients within initial glucose levels >50 mg/dL (Class I; Level of Evidence A).**
- 2. Treating clinicians should be aware that hypoglycemia and hyperglycemia may mimic acute stroke presentations and check blood glucose levels before intravenous initiation. Intravenous alteplase is not indicated for nonvascular conditions (Class III; Level of Evidence B).**
- 3. Treatment with intravenous alteplase in patients with acute ischemic stroke who present with initial glucose levels >400 mg/dL that are subsequently normalized and who are otherwise eligible may be reasonable (Class IIb; Level of Evidence C).**

Seizure at Stroke Onset Syndrome

The original FDA label listed seizure at the onset of stroke as a contraindication to intravenous alteplase, whereas the 2013 AHA/ASA guidelines²⁴ list seizure at onset with post-ictal residual neurological impairments as a relative exclusion criterion. The most updated FDA label, however, has removed any reference to seizure from the warnings and contraindications sections.

A clinical suspicion of seizure at onset of stroke syndrome was traditionally considered a contraindication to administering intravenous alteplase to stroke patients. This was based on the rationale that a focal neurological deficit in this setting is more likely attributable to a SM, that is, postictal Todd paralysis, than to acute cerebral ischemia. These entities are not mutually exclusive, however, because seizures can rarely occur at the onset of acute ischemic stroke.³³² Notably, the risk of sICH after thrombolysis of SMs is exceedingly low.^{319,333,334} Furthermore, historical features of seizure activity at onset might be misleading. In 1 retrospective study of 326 stroke patients, a concern for witnessed seizure at onset occurred in 9 patients, 5 of whom ultimately had ischemic infarctions caused by intracranial arterial occlusions.³³⁵

The evidence for intravenous alteplase use in patients with seizures at symptom onset is made up predominantly of retrospective reviews of prospectively collected stroke patients from registries (Table 16).

In total, there are almost 300 patients with seizure at onset who received intravenous alteplase for stroke-like symptoms described in the English literature.^{294,319,333,334,336–341} Of these, sICH has been reported in only 2 patients, and 1 of these patients had a remote history of surgical removal of a brain tumor that may have served as a nidus for the development of ICH. If true clinical uncertainty remains in the evaluation of a patient with seizure at onset of a focal neurological symptom, CT or magnetic resonance perfusion studies could theoretically be useful in selecting patients for treatment, but this has not been systematically studied, and intravenous alteplase should not be delayed to await results of these studies in most cases.

In summary, evidence derived mostly from prospective stroke registries suggests that a seizure at onset of symptoms should not be considered an absolute contraindication to administering intravenous alteplase to acute stroke patients.

Seizure at Stroke Onset Syndrome: Recommendation

- Intravenous alteplase is reasonable in patients with a seizure at the time of onset of acute stroke if evidence suggests that residual impairments are secondary to stroke and not a postictal phenomenon (Class IIa; Level of Evidence C).**

Major Early Infarct Size, Large Areas of Ischemic Stroke, Early Ischemic Changes as Measured by ASPECTS, and the One-Third Rule

The FDA label has now removed any mention of major early infarct signs on a cranial CT scan (eg, substantial edema, mass effect, or midline shift). Previously, the label warned that the risks of intravenous alteplase therapy may be increased in these patients. In the 2013 AHA/ASA guidelines,²⁴ intravenous alteplase is recommended in the setting of early ischemic changes (EICs) on CT, regardless of their extent, but the guidelines caution that frank hypodensity on CT may increase the risk of hemorrhage. If frank hypodensity involves more than one third of the MCA territory, intravenous alteplase is contraindicated and should be withheld.

One of the most challenging exclusion criteria with intravenous alteplase is the presence and extent of EICs on non-contrast CT. EICs on cerebral noncontrast CT is defined as parenchymal hypoattenuation (gray-white indistinction or decreased density of brain tissue relative to attenuation of other parts of the same structure or of the contralateral hemisphere) or focal swelling or mass effect (any focal narrowing of the cerebrospinal fluid spaces as a result of compression by adjacent structures). Isolated cortical swelling has subsequently been shown to represent actual penumbral tissue that may fully reverse with reperfusion.^{342,343} EICs reflect primarily a decrease in x-ray attenuation, which is inversely correlated with tissue net water uptake and may be a marker of irreversibly damaged ischemic brain tissue.³⁴⁴ Controversy remains as to the degree of x-ray hypoattenuation required for irreversible injury. ECASS I pioneered the assessment of EIC by introducing the rule of EICs in more than one third of the MCA territory.⁴⁷ A post hoc analysis of ECASS I suggested that the extent of EIC was an important predictor of the response to intravenous alteplase.³⁴⁵ In patients with a small (less than one third of the MCA territory) hypoattenuating area, intravenous alteplase increased the odds of good functional outcome (OR, 3.43; 95% CI, 1.61–7.33). The benefit was less clear for patients without EICs (OR, 1.27; 95% CI, 0.82–1.95) or hypoattenuation involving more than one third of the MCA territory (OR, 0.41; 95% CI, 0.06–2.70). Increased risk for sICH was seen in ECASS I and confirmed in secondary analysis of the ECASS II CT scans when EIC in more than one

Table 16. Summary of Studies Including ≥5 Patients Treated With Intravenous rtPA Who Had Seizures at Symptom Onset

Study	Study Design	Seizure/Total SMs, n	Average Initial		sICH, n	mRS Score of 0–1, %
			NIHSS Score	Any ICH, n		
Winkler et al ³¹⁹	Retrospective of prospective registry	6/7	10*	0	0	86
Chernyshev et al ³³⁴	Retrospective of prospective registry	26/69	7	0	0	87
Zinkstok et al ²⁹⁴	Multicenter, observational cohort	81/100	6	NA	2	75
Tsivgoulis et al ³³⁶	Retrospective of prospective registry	11/56	6	NA	0	96
Förster et al ³³⁷	Retrospective of prospective registry	20/42	6.5	NA	0	NA
Chang et al ³³⁸	Retrospective	6/14	6*	0	0	NA†

ICH indicates intracerebral hemorrhage; mRS, modified Rankin Scale; NA, not applicable; NIHSS, National Institutes of Health Stroke Scale; rtPA, recombinant tissue-type plasminogen activator; sICH, symptomatic intracerebral hemorrhage; and SM, stroke mimic.

*Average indicates the median except where indicated by an asterisk (mean).

†In that trial, 97% had an mRS score of 0 to 2.

third of the MCA territory was involved.³⁴⁶ However, despite evidence that the EIC in more than one third of the MCA was a poor prognostic marker overall regardless of treatment arm, ECASS II did not demonstrate statistical evidence of treatment effect modification. In other words, there was no evidence that intravenous alteplase was less effective in patients with EICs in more than one third of the MCA territory. A further practical limitation of the more than one third of the MCA rule is that, in practice, it cannot be applied reliably.^{347,348}

In the NINDS alteplase stroke study, CT was used as a screening tool to exclude ICH before intravenous alteplase administration. The extent of EICs on the baseline CT scan did not influence patient eligibility.¹ The NINDS alteplase trial EIC definition was based on edema and mass effect. A total of 5.2% of patients had evidence of such findings. Their presence was associated with a higher risk of sICH; however, no treatment-modifying effect was demonstrated.¹⁰⁹ A more detailed rereview of the NINDS alteplase stroke study scans resulted in a higher prevalence of EICs (31%), largely as a result of a differing appreciation and definition of EIC.³⁴⁹ However, again, no EIC-by-treatment interaction was statistically observed even when the EIC involved more than one third of the MCA territory.

The Alberta Stroke Program Early CT Score (ASPECTS) was developed to provide a systematic and semiquantitative approach to assessing EICs on noncontrast CT.³⁵⁰ ASPECTS allots the MCA territory 10 regions of interest that are weighted on the basis of functional importance. Equal weighting is given to smaller structures (such as the internal capsule, basal ganglia, and caudate nucleus) and larger cortical areas. EIC contributing to ASPECTS is now defined as parenchymal hypoattenuation only.³⁵¹

In a post hoc analysis of the NINDS alteplase stroke study, ASPECTS on baseline noncontrast CT dichotomized into >7 versus ≤7 did not have a treatment-modifying effect on favorable functional outcome. However, higher ASPECTS values (ASPECTS >7) were associated with a trend toward reduced mortality. Mean final infarct volumes were also half as large in patients on alteplase compared with patients on placebo (7.8 versus 15.2 mL, respectively). In the low ASPECTS group (ASPECTS 0–2) with extensive EICs, patients in both treatment arms had very large mean final infarct volumes exceeding 200 mL, but this group represented only 16 of 608 patients (2.6%) in the 2 NINDS trials, thus limiting the clinical relevance of the group.³⁵²

On the basis of current literature, there remains no established extent or severity of EICs that should exclude patients from intravenous alteplase within the standard approved time window. Neither the more than one third of the MCA rule method nor an ASPECTS threshold has demonstrated a clear treatment interaction with intravenous alteplase, nor does either method identify a group of patients with uniformly dismal outcome despite intravenous alteplase. Baseline noncontrast CT scan EIC detection is not critical to intravenous alteplase decision making in the first 6 hours from acute stroke symptom onset. However, RCTs either have enrolled few patients with very extensive EICs (eg, ASPECTS 0–2) or have purposely excluded them (eg, the ECASS III trial); therefore, the safety and efficacy

of alteplase in this group with very extensive EICs remain poorly defined.

EICs on CT: Recommendations

1. **Intravenous alteplase administration is recommended in the setting of EICs of mild to moderate extent (other than frank hypodensity) (Class I; Level of Evidence A).**
2. **There remains insufficient evidence to identify a threshold of hypoattenuation severity or extent that affects treatment response to alteplase. However, administering intravenous alteplase to patients whose CT brain imaging exhibits extensive regions of clear hypoattenuation is not recommended. These patients have a poor prognosis despite intravenous alteplase, and severe hypoattenuation defined as obvious hypodensity represents irreversible injury (Class III; Level of Evidence A).**

Diabetic Hemorrhagic Retinopathy or Other Ophthalmological Conditions

Ocular hemorrhage as a complication of intravenous alteplase administration for any indication has only rarely been reported. However, there may be some concern that the ocular hemorrhagic risk may be higher in patients with diabetes mellitus in general and with diabetic retinopathy in particular. Diabetic retinopathy has been proposed as a contraindication to or warning for intravenous alteplase in the absence of strong evidence to support substantial risk or hazard.³⁵³

The bleeding section of the FDA label warning lists diabetic hemorrhagic retinopathy or other hemorrhagic ophthalmic conditions among a list of conditions for which the hemorrhagic risks of alteplase for approved indications, for example, acute ischemic stroke, may be increased and should be weighed against the anticipated benefits.³⁵⁴

In neither the updated AHA/ASA guidelines for the management of acute ischemic stroke²⁴ nor the American College of Cardiology/AHA guidelines for the management of patients with STEMI^{245,353} is diabetic hemorrhagic retinopathy or other hemorrhagic ophthalmic conditions among the absolute or relative contraindications to intravenous alteplase administration.

Diabetic hemorrhagic retinopathy was historically classified as an absolute contraindication to alteplase in patients with acute MI because of the potential risk of retinal hemorrhage.³⁵³ However, there appears to be no clear evidence that patients with diabetic retinopathy are at an increased risk for intraocular hemorrhage after systemic thrombolytic therapy. In temporal proximity to the dissemination of American College of Cardiology/AHA 1990 acute MI guidelines, there were only 2 published case reports of patients sustaining an intraocular hemorrhage after thrombolysis.^{355,356} One of these subjects had diabetes mellitus and the other did not.

Thereafter, only 3 additional reports were published. Chorich et al³⁵⁷ reported 3 patients with hemorrhagic ocular and orbital complications associated with systemic administration of intravenous alteplase or streptokinase for acute MI.

The study design was a retrospective small case series. The ocular hemorrhages were spontaneous suprachoroidal (n=1) periorbital eyelid (n=2) postoperative cataract surgery and external levator resection. Surgical procedures to reduce intraocular pressure or to relieve optic nerve compression were performed. Two of the 3 patients were reported to have some significant visual loss after 2 to 8 weeks of limited follow-up. Barsam et al³⁵⁸ reported a single case of spontaneous suprachoroidal hemorrhage in an 86-year-old diabetic who received intravenous alteplase for acute MI. Khawly et al³⁵⁹ described a 67-year-old man who was discovered to have sustained a hemorrhagic choroidal detachment 4 days after intravenous alteplase for acute MI, cardiac arrest, and successful resuscitation. Follow-up examination displayed resolution of ocular hemorrhage and no underlying choroidal pathology.

To better define the incidence and location of ocular hemorrhage in patients with and without diabetes mellitus treated with thrombolytic therapy for acute MI, Mahaffey et al³⁶⁰ analyzed patients with ocular hemorrhage in the Global Utilization of Streptokinase and Alteplase for Occluded Coronary Arteries (GUSTO)-I trial. All definite and suspected ocular hemorrhages from postthrombolysis hemorrhagic complications reported in GUSTO-I were identified. In GUSTO-I, the treatment regimens included intravenous streptokinase and alteplase administered in an accelerated regimen (15-mg IV bolus followed by 0.75 mg/kg body weight over 30 minutes and then 0.5 mg/kg over the next 60 minutes) or intravenous streptokinase and intravenous alteplase 1.0 mg/kg over 60 minutes, and the thrombolytic treatment was always coadministered with intravenous heparin and acetylsalicylic acid. There were 40 899 patients (99.7%) with data on diabetic history and ocular hemorrhage. Twelve patients (0.03%) sustained an ocular bleed. Of these 12, only 1 patient sustained an intraocular (1 subretinal; 0 vitreal) hemorrhage (after a fall). The remaining hemorrhages were extraocular (4 periorbital, 7 subconjunctival). Of the total study population, 6011 patients (15%) had a history of diabetes mellitus. There was no statistically significant difference in the rate of ocular hemorrhage in patients with and without diabetes mellitus. The upper 95% CI for the incidence of true intraocular hemorrhage in patients with diabetes mellitus was 0.05% and without diabetes mellitus was 0.006%. Mahaffey et al³⁶⁰ concluded that ocular hemorrhage overall and intraocular hemorrhage in particular after systemic thrombolysis for acute MI are extremely uncommon and proposed that diabetic retinopathy should not be considered a contraindication to thrombolysis.

Diabetic retinopathy is either proliferative or nonproliferative. In proliferative retinopathy, preretinal neovascularization but no preretinal hemorrhage is observed. In nonproliferative retinopathy, retinal microaneurysms and retinal blot hemorrhages are observed. In patients with diabetic retinopathy, vitreous hemorrhage may result from posterior vitreous detachment, which may cause traction and damage to adherent vessels.³⁶¹ Thrombolysis is unlikely to increase the risk of spontaneous detachment but may do so in instances of recent trauma with disruption of the structural integrity of the microvasculature.³⁶²

In the emergency department, the rapid diagnosis of retinopathy is often challenging in the setting of an acute

ischemic stroke. Patients may not be capable of cooperating with a complete fundoscopic examination because of an alteration in level of consciousness or aphasia. Although some patients may have had previous ophthalmological examinations, neither paper nor electronic medical records may be readily available at the time of diagnosis of acute stroke and thrombolysis decision making. Without a complete fundoscopic examination (including dilation of pupil) by a qualified and experienced provider, even significant diabetic retinopathy is regularly missed.^{363,364}

Ophthalmological outcome after intraocular hemorrhage associated with thrombolysis, whether for acute MI or ischemic stroke, is largely unknown.^{365–368}

Paradoxically, despite concerns over ocular hemorrhage after intravenous alteplase, intravitreal or subretinal alteplase injections, in conjunction with intravitreal gas and vitrectomy, are reportedly used to improve visual acuity in instances of acute submacular hemorrhage.³⁶⁹

A case report by Ahmad et al³⁷⁰ describing a 70-year-old man presenting to hospital with an acute ischemic stroke for whom intravenous alteplase was withheld because of vitreous hemorrhage, citing the label that lists hemorrhagic ophthalmic conditions as a relative contraindication, drew considerable attention in the form of published correspondence, comments, and opinions. Sethi et al³⁷¹ posed the sensible question, “Would you save this patient’s eye or his brain?” Moudgil³⁷² argued that treating the major cerebral infarction should take precedence over preventing worsening of vitreous hemorrhage; promoted the concept of shared decision making between patient, family, and physician; and reminded the medical community that an older vitreous hemorrhage is less likely to rebleed and that the presence of preexisting retinopathy may indicate poor visual acuity at baseline. Additionally, the authors of the comments suggested that to minimize the risk of vitreous rebleed, intra-arterial thrombolysis and mechanical thrombectomy are both considerations.^{370–372}

Conclusions

Ocular hemorrhage in general and intraocular hemorrhage in particular after intravenous alteplase therapy for approved indications, that is, acute ischemic stroke and acute MI, are extremely uncommon. Best estimates of incidence are 0% (95% CI, 0.0–0.05) for patients with diabetes mellitus and 0.003% (95% CI, 0.0–0.006) for patients without diabetes mellitus. The upper 95% CI limit of 0.05% for the incidence of intraocular hemorrhage in patients with diabetes mellitus is very small and quite negligible compared with the proven disability-preventing benefit of intravenous alteplase in patients with acute ischemic stroke. Diabetic retinopathy should not be considered an absolute contraindication to intravenous alteplase in patients with an acute ischemic stroke.

Diabetic Hemorrhagic Retinopathy or Other Hemorrhagic Ophthalmological Conditions: Recommendation

1. Use of intravenous alteplase in patients presenting with acute ischemic stroke who have a history of diabetic hemorrhagic retinopathy or other

hemorrhagic ophthalmic conditions is reasonable to recommend, but the potential increased risk of visual loss should be weighed against the anticipated benefits of reduced stroke-related neurological deficits (*Class IIa; Level of Evidence B*).

Suspicion of SAH on Pretreatment Evaluation

The original FDA label contraindicated use of alteplase in instances of suspicion of SAH on pretreatment evaluation, and similarly, the 2013 AHA/ASA guidelines²⁴ list symptoms suggesting SAH as an exclusion criterion. However, the updated FDA label now just lists SAH as an exclusion without reference to the clinician's suspicion or the clinical symptoms.

Suspicion of SAH usually involves a compelling clinical history such as a sudden severe or "thunderclap" headache or the presence of xanthochromia on lumbar puncture. The presence of frank SAH on prealteplase CT imaging would be an absolute contraindication for thrombolysis. SAH raises the concern for an unsecured, occult intracranial aneurysm.

Sheth et al²⁶⁸ demonstrated retrospectively that a significant percentage of patients with acute stroke harbor asymptomatic intracranial aneurysms. In their series, 5% of study patients had incidental aneurysms; these patients did not suffer a higher sICH rate with intravenous alteplase administration. The matter of intravenous alteplase and asymptomatic unruptured intracranial aneurysms, large and small, is discussed more fully above. Potentially ruptured aneurysms obviously represent more structurally unstable lesions than those reviewed by Sheth et al. Moreover, another section in this statement details the potential challenge of acute-phase lumbar puncture in the setting of potential alteplase administration. A lumbar puncture is generally advised as the next step after a negative head noncontrast CT in the evaluation of patients with thunderclap headache, followed by noninvasive angiographic imaging (CT angiography or magnetic resonance angiography of the head and neck) and brain MRI.³⁷³ Potentially for a unique scenario of an acute stroke syndrome presentation that includes thunderclap headache, a change in the sequence may be advisable, with a negative head noncontrast CT being followed by CT angiography or magnetic resonance angiography (of the head and neck) and brain MRI rather than immediately turning to a lumbar puncture.

Given the potential for other vascular lesions, including dural arteriovenous fistulas and arterial dissection, cerebral venous sinus thrombosis, and reversible cerebral vasoconstrictive syndrome, vascular imaging such as CT angiography or magnetic resonance angiography in the acute phase may inform alteplase administration. In the absence of a demonstrated vascular source, there are no data to suggest an increased risk of sICH from systemic thrombolysis. Thus, intravenous alteplase administration would be reasonable in this cohort. Structural vascular imaging would further rule out complex stroke causes and unsecured intracranial lesions. Clinicians administering intravenous alteplase in environments without available, acute arterial imaging should consider the burden of SAH and degree of stroke deficit in weighing the risks and benefits of intravenous alteplase administration.

Suspicion of SAH on Pretreatment Evaluation: Recommendation

1. Intravenous alteplase is contraindicated in patients presenting with symptoms and signs most consistent with an SAH (*Class III; Level of Evidence C*).

Examining the Individual Exclusions to an Extended Time Window From the ECASS III Trial

The FDA label emphasizes that intravenous alteplase should be initiated only within 3 hours after the onset of stroke symptoms, whereas the 2013 AHA/ASA guidelines²⁴ address administration within 3 to 4.5 hours. The AHA/ASA issued a scientific advisory statement recommending intravenous alteplase for eligible patients who meet ECASS III trial eligibility criteria in the extended 3- to 4.5-hour treatment window. In addition to the 0- to 3-hour exclusion criteria, the following are excluded in the 3- to 4.5-hour window: age >80 years, any OAC use regardless of initial INR, NIHSS score >25, CT hypodensity on more than one third of the MCA territory, and combined prior stroke and diabetes mellitus history.³⁷⁴ Despite the fact that the FDA has not approved alteplase use for the extended window in the United States, its application in clinical practice has spread.³⁷⁵ In a study from Cincinnati, 15 of 66 patients who presented in the 3- to 4.5-hour window were ineligible for alteplase on the basis of age >80 years alone, 3 on the basis of stroke and diabetes mellitus, 2 on the basis of OAC use, and 2 on the basis of an NIHSS score >25.¹³ Overall, only an additional 3.4% of patients with acute stroke arrived in the expanded time window; only 0.5% met the stricter 3- to 4.5-hour eligibility criteria for intravenous alteplase; and 0.7% met the more flexible 0- to 3-hour eligibility criteria. Several studies have reported the safety and efficacy of off-label alteplase use in the 0- to 3-hour window, but relatively few studies have reported the safety of treatment of patients within the 3- to 4.5-hour window.^{376,377}

Age

Prior studies have examined the safety of alteplase in different age groups. Eligibility based on age in the 0- to 3-hour window is covered above. In the pooled analysis of EPITHET and IST-3, 970 subjects >80 years of age were randomized to alteplase versus placebo in the 3- to 6-hour window. Compared with those ≤80 years of age, the likelihood for favorable outcome at 3 months in those treated with alteplase versus those treated with placebo was not different by age; however, the OR for good outcome compared with placebo was not significant (OR, 0.97; 95% CI, 0.73–1.30) and far less than the benefit in patients treated in the 0- to 3-hour window.⁴⁸ Data were not presented comparing outcomes by age strata in the 3- to 4.5-hour window alone. Only 2 other studies have evaluated age >80 years specifically in the 3- to 4.5-hour window. In the GWTG-Stroke database, among 1008 patients >80 years of age treated with intravenous alteplase in the extended window, sICH was observed in 8% (versus 6.7% among patients >80 years of age in the <3-hour window; $P=0.11$), 19.5% were ambulatory at hospital discharge (versus 17.7% in the <3-hour

group; $P=0.08$), and 21.2% were discharged home (versus 20.3% in the <3-hour group; $P=0.41$).³⁷⁷ In a smaller study that compared outcomes after intravenous alteplase in the extended window by age strata of 31 patients >80 years of age, there were 2 patients with sICH (6.5%) compared with 7 of 160 patients (4.4%) <80 years of age ($P=0.64$). Not surprisingly, however, in-hospital mortality was higher among those >80 years of age (16.1% versus 3.8%; $P=0.02$).³⁷⁶ In a study that examined the impact of removing specific exclusions for intravenous alteplase in stroke, if the upper age limit were removed for treatment in the 3- to 4.5-hour window, the percentage of eligible patients would increase from 26% to 29%.¹⁵

NIHSS Score

Limited data exist on the treatment of patients with NIHSS score >25 in the extended window. In the GTWG-Stroke analysis, of the 179 patients meeting this exclusion criterion and treated with alteplase, 8.4% had sICH (versus 10.0% in the <3-hour group; $P=0.50$), 7.8% were ambulatory (versus 10.0% in the <3-hour group; $P=0.60$), and 11.7% were discharged home (versus 11.5% in the <3-hour group; $P=0.05$).³⁷⁷

Warfarin Use

In the SITS-ISTR and GTWG-Stroke studies, warfarin use was not associated with increased risk of sICH or worse outcomes after alteplase.^{111,161} However, data are not reportedly separately on sICH risk in the subgroup of patients presenting in the 3- to 4.5-hour window and taking warfarin at baseline.¹¹¹ However, in a subsequent study from the GTWG-Stroke, 282 patients on an OAC with an INR <1.7 at baseline were treated with alteplase in the 3- to 4.5-hour window. Symptomatic hemorrhage was 5.7% compared with 6.8% in the <3-hour group ($P=0.49$); ambulation at discharge was noted in 26.6% versus 24.7% ($P=0.53$); and discharge home occurred in 30.5% versus 26.4% ($P=0.38$).³⁷⁷ In a smaller study by Cronin et al,³⁷⁶ 2 of 11 patients (18.2%) on warfarin had sICH compared with 3.9% of those not taking warfarin ($P=0.09$), but mortality was similar between groups ($P=0.49$).

Stroke and Diabetes Mellitus

Because it is not covered in the previous sections and it is a contraindication in the European license for alteplase use in the 0- to 3-hour and 3- to 4.5-hour windows, the risks of intravenous alteplase treatment among patients with stroke and diabetes mellitus is worth examining. Prior stroke and diabetes mellitus are strong predictors of poor outcome after treatment with alteplase.^{378,379} Poor response to thrombolytic therapy, concomitant use of antithrombotic therapy, and higher risk of stroke recurrence and complications are also cited in some studies.^{380,381} Given these concerns, patients with both conditions were excluded in the ECASS III trial. Subsequently, analyses from several registries have provided more evidence on the safety and efficacy of intravenous alteplase in this subset of patients. However, no placebo-controlled data exist.

In the Helsinki Stroke Registry of 1104 thrombolized stroke patients, 26 patients with stroke and diabetes mellitus were included.¹⁵⁷ In multivariable analysis, the combination was not associated with 3-month mRS score >2 or sICH. A

multicenter registry from Madrid that included 34 patients with prior stroke and diabetes mellitus also did not find an impact of the combination on risk of sICH or poor outcome after alteplase.³⁸¹ In the SITS-EAST analysis of patients treated outside the European license, 216 patients had prior stroke and diabetes mellitus. In multivariable analysis, the combination was not a predictor of sICH, unfavorable outcome, or mortality.¹⁷⁶ In VISTA, patients without diabetes mellitus and prior stroke had significantly better outcomes than those with both conditions. However, comparing thrombolized patients ($n=86$) to nonthrombolized patients ($n=405$) with diabetes mellitus and prior stroke showed a trend toward better outcomes (OR, 1.5; 95% CI, 0.98–2.3) after thrombolysis.³⁸⁰ A larger study compared patients receiving intravenous alteplase in the SITS-ISTR registry with nonthrombolized patients from VISTA. Of 29 500 patients, 1141 (5.5%) had both diabetes mellitus and prior stroke. In this subgroup, thrombolysis compared with no thrombolysis was associated with lower mRS score in ordinal analysis (aOR, 1.23; 95% CI, 1.00–1.52; $P=0.05$). No interaction between prior stroke/diabetes mellitus with intravenous alteplase treatment and 3-month outcome was found.³⁸² An updated analysis from VISTA using an ordinal shift analysis included 672 patients with stroke and diabetes mellitus (106 receiving alteplase and 566 control subjects) and estimated that alteplase was associated with increased odds of more favorable outcome at 3 months adjusted for age and baseline NIHSS score (OR, 1.5; 95% CI, 1.03–2.18).⁵²

Unfortunately, these data do not inform about the specific risks in patients treated in the 3- to 4.5-hour window. In the GTWG-Stroke registry, among 335 patients with prior stroke and diabetes mellitus treated with intravenous alteplase in the 3- to 4.5-hour window, 6.9% had sICH (versus 4.6% in the <3-hour group; $P=0.08$), 34.9% were ambulatory at discharge (versus 30.8% in the <3-hour group; $P=0.07$), and 40.3% were discharged home (versus 36.9%; $P=0.30$).³⁷⁷ In the single-center study, among 14 patients with stroke and diabetes mellitus, 1 sICH occurred (7.1%) compared with 8 (4.5%) in those without the combination ($P=0.50$).³⁷⁶ From these data, it does not seem warranted to exclude patients with stroke and diabetes mellitus from intravenous alteplase therapy, especially in the 0- to 3-hour window, for which there are far greater published data. In the extended 3- to 4.5-hour window, more data are needed.

Extended 3- to 4.5-Hour Window: Recommendations

1. Intravenous alteplase is recommended for carefully selected patients who meet ECASS III criteria and are treated in the 3- to 4.5-hour window (*Class I; Level of Evidence B*).
2. For patients >80 years of age presenting in the 3- to 4.5-hour window, intravenous alteplase treatment is safe and can be as effective as in younger patients (*Class IIa; Level of Evidence B*).
3. For patients taking warfarin and with an INR <1.7 who present in the 3- to 4.5-hour window, intravenous alteplase treatment appears safe and may be beneficial (*Class IIb; Level of Evidence B*).

4. **The benefit of intravenous alteplase administration for acute stroke patients with a baseline NIHSS score >25 and presenting in the 3- to 4.5-hour window is uncertain (Class IIb; Level of Evidence C).**
5. **In acute ischemic stroke patients with prior stroke and diabetes mellitus presenting in the 3- to 4.5-hour window, intravenous alteplase may be as effective as treatment in the 0- to 3-hour window and may be a reasonable option (Class IIb; Level of Evidence B).**

Miscellaneous Topics

Wake-Up/Unclear Onset Time Stroke

The FDA label contraindicates administration of intravenous alteplase beyond 3 hours after stroke symptom onset, whereas the 2013 AHA/ASA guidelines²⁴ draw attention to the possible role of CT and MRI perfusion imaging for patients beyond the time window for intravenous alteplase to inform clinical decision making.

Uncertain onset time accounts for 24% of the reasons why patients with ischemic stroke are deemed ineligible for treatment with alteplase.¹²¹ This group includes the estimated 14% to 30% of all ischemic strokes that are wake-up strokes.^{383,384} It has been proposed that a fluid-attenuated inversion recovery (FLAIR) sequence on MRI could estimate stroke within 4.5 hours in patients with wake-up/unclear onset time stroke.³⁸⁵ Particularly, hyperintensity of diffusion-weighted imaging (DWI) is thought to occur within minutes in acute ischemic stroke, whereas FLAIR changes are delayed. Thus, a DWI-FLAIR mismatch may distinguish hyperacute (<4.5 hours) from acute (>4.5 hours) ischemic stroke. In a retrospective study of 130 patients with known stroke onset times who underwent 1.5-T MRI within 12 hours of symptom onset, 63 patients underwent imaging within 3 hours of symptom onset and 67 had imaging after 3 hours.³⁸⁶ Signal intensities within the stroke and contralateral regions of interest were used to compute imaging ratios for DWI, FLAIR, and apparent diffusion coefficient. The FLAIR ratios had a sensitivity and specificity of >90% in differentiating stroke <3 hours from stroke >3 hours.³⁸⁶ However, the sensitivity and specificity have not been as robust in other studies.^{387–389}

In 94 patients with known stroke onset who underwent MRI within 12 hours of symptom onset, negative FLAIR imaging had 46% sensitivity and 79% specificity for identifying patients whose stroke onset was <4.5 hours, and there was no correlation between signal intensity and time from onset.³⁸⁹ In a multicenter, observational study of 543 acute stroke patients, DWI and FLAIR images were obtained within 12 hours of symptom onset.³⁸⁷ Ischemic lesions were present on DWI in 516 patients (95%) and on FLAIR in 271 patients (50%). DWI-FLAIR mismatch had 62% sensitivity and 78% specificity for identifying patients within 4.5 hours of symptom onset. Furthermore, interobserver agreement for identifying an ischemic lesion on FLAIR imaging was moderate ($\kappa=0.57$).³⁸⁷ Although limited studies have sought to use MRI and clinical criteria to select patients with wake-up stroke or unclear onset times for intravenous alteplase administration,³⁹⁰ the current available data remain inadequate.

Patients with wake-up stroke and unknown-onset ischemic stroke have been considered for intravenous alteplase on the basis of CT imaging. CT findings did not differ in 17 patients with wake-up stroke compared with 46 patients with known stroke onset, whereas patients with unknown onset tended to have more hypodensities.³⁹¹ In another study, the ASPECTS, in 28 patients who were last normal >4 hours before arrival and underwent head CT within 15 hours of the time last seen normal were compared with those of 68 patients with known stroke onset times who underwent CT within 4 hours of symptom onset. ASPECTS was 8 to 10 in 89% of the wake-up group and 96% in the control group ($P=0.35$).³⁹² In a prospective, observational study of 676 ischemic stroke patients imaged within 24 hours of symptom onset, lesion volumes were larger in the 125 patients with unclear onset time, but there was no difference in lesion volume, CT perfusion mismatch, and large-vessel intracranial occlusion in the 131 patients with wake-up stroke compared with 420 patients with known onset.³⁹³ From these reports, it has been suggested that wake-up strokes likely occur close to awakening and thus patients with wake-up strokes may be considered for intravenous alteplase if hospital arrival occurs shortly after awakening.

In a retrospective study, 28 wake-up stroke patients received intravenous alteplase alone, 4 received intravenous and intra-arterial alteplase, and 14 received intra-arterial alteplase alone. Two sICHs occurred (4.3%).

Although mortality was higher in the treated wake-up group compared with the nontreated wake-up stroke patients (15% versus 0%), when the treated wake-up stroke patients were compared with 174 intravenous alteplase patients treated within 3 hours of symptom onset, no significant difference in safety and clinical outcomes was observed.³⁹⁴ In a recent observational study, the criteria for selection of patients with wake-up stroke for alteplase treatment were (1) last seen normal <12 hours or >4.5 hours after symptom onset; (2) no neurological deficits when last seen awake and witnessed persistent deficits on awakening; (3) emergency presentation to hospital; (4) NIHSS score ≥ 5 on initial assessment; (5) no EICs or EICs of less than one third of the MCA territory on baseline CT scan; and (6) no absolute contraindications to alteplase use.^{395,396} Of 68 patients treated with alteplase, 2 experienced sICH, and the overall observed outcomes were similar to those of a comparator group not treated with alteplase.^{395,396}

In summary, the treatment of wake-up and unclear onset stroke patients with intravenous alteplase is an area of active investigation. Ongoing clinical trials such as the European stroke trial, “Efficacy and safety of MRI-based thrombolysis in wake-up stroke: a randomized, double-blind, placebo-controlled trial (WAKE-UP),”³⁹⁷ and the National Institutes of Health/NINDS-sponsored trial, “MR WITNESS: A Phase IIa Safety Study of Intravenous Thrombolysis with Alteplase in MRI-Selected Patients,”³⁹⁸ should further elucidate the safety and efficacy of treatment approaches in wake-up stroke.

Wake-Up/Unclear Onset Time Stroke: Recommendations

1. **Intravenous alteplase is not recommended in ischemic stroke patients who awoke with stroke with**

time last known to be at baseline state >3 or 4.5 hours (*Class III; Level of Evidence B*).

2. Intravenous alteplase is not recommended in ischemic stroke patients who have an unclear time and/or unwitnessed symptom onset and in whom the time last known to be at baseline state is >3 or 4.5 hours (*Class III; Level of Evidence B*).
3. Use of imaging criteria to select ischemic stroke patients who awoke with stroke or have unclear time of symptom onset for treatment with intravenous alteplase is not recommended outside a clinical trial (*Class III; Level of Evidence B*).

Menstruation and Menorrhagia

Neither the FDA label nor the 2013 AHA/ASA guidelines²⁴ address this risk specifically, but the label warns of internal bleeding, including that from the genitourinary tract. There are limited data on the safety of alteplase administration in women who are actively menstruating or who have a history of menorrhagia. Women with active menstruation were not excluded from the two 1995 NINDS alteplase trials; of 5 women who received alteplase and were actively menstruating, 1 woman with a history of dysfunctional vaginal bleeding had increased menstrual flow with mild hypotension and required transfusion with 3 U packed red blood cells.³⁹⁹ Additionally, there is a single case report of a 46-year-old woman without a history of menorrhagia who had increased menstrual flow and hypotension and required transfusion with 2 U packed red blood cells; normal menstrual flow resumed 12 hours after the start of the intravenous alteplase infusion.³⁹⁹ The authors of that case report reviewed 25 cases of menstruating women who received a thrombolytic agent for the treatment of MI or deep venous thrombosis and found reports of transfusion in only 2 patients who were receiving heparin in addition to thrombolysis.³⁹⁹

Menstruation and Menorrhagia: Recommendations

1. Intravenous alteplase is probably indicated in women who are menstruating who present with acute ischemic stroke and do not have a history of menorrhagia. However, women should be warned that alteplase treatment could increase the degree of menstrual flow (*Class IIa; Level of Evidence C*).
2. Because the potential benefits of intravenous alteplase probably outweigh the risks of serious bleeding in patients with recent or active history of menorrhagia without clinically significant anemia or hypotension, intravenous alteplase administration may be considered (*Class IIb; Level of Evidence C*).
3. When there is a history of recent or active vaginal bleeding causing clinically significant anemia, then emergent consultation with a gynecologist is probably indicated before a decision about intravenous alteplase is made (*Class IIa; Level of Evidence C*).
4. In patients who are menstruating or have active vaginal bleeding and are treated with alteplase, the degree of vaginal bleeding should be monitored for 24 hours after alteplase (*Class I; Level of Evidence C*).

Intracardiac Mass

Cardiac mass was not an exclusion criterion in the 2 NINDS alteplase stroke trials, is not an exclusion criterion in the current AHA/ASA guidelines, and is not a warning or contraindication in the current FDA label.^{1,24} The literature was reviewed to identify thrombolytic experience with 2 of the most common cardiac masses related to acute ischemic stroke: myxoma and fibroelastoma.

Myxomas are the most common primary cardiac neoplasm. The tumors originate from cells from a multipotent mesenchyme capable of neural and endothelial differentiation, and ≈80% arise in the left atrium. Systemic embolization occurs in more than one quarter of patients and frequently presents as ischemic stroke.^{400,401} Tumor emboli may also invade brain arteries, causing vessel rupture or aneurysm formation and initial presentation with intracerebral and SAH.⁴⁰² Although emboli are most often composed of myxomatous tissue, they may also arise from thrombus adherent to the tumor.⁴⁰³ Although tumoral emboli would not be expected to respond to fibrinolysis, thrombotic emboli would be responsive, as illustrated by case reports of recanalization in response to local, intra-arterial instillation of fibrinolytics.^{404,405} There have been at least 15 case reports of patients with atrial myxoma treated with intravenous fibrinolysis with alteplase.^{406–410} In 1 case, comparison of pretreatment magnetic resonance angiography and posttreatment transcranial Doppler and catheter angiography showed recanalization.⁴⁰⁶ Hemorrhagic transformation within the first 24 hours occurred in 2 of the 15 patients (13%).

Papillary fibroelastomas are the second most common benign cardiac neoplasm and typically appear as frond-like arms emanating from a stalked central core. More than 80% of fibroelastomas are found on the heart valves, usually atrial or mitral, with the remaining lesions scattered throughout the atria and ventricles. The most common clinical presentation is stroke or transient ischemic attack caused by cerebral embolization. Unlike myxoma, invasive destruction of the cerebral vasculature and presentation with cerebral hemorrhage do not routinely occur. Cerebral emboli may be of tumoral composition or arise from thrombus formed on the tumor. Intra-arterial fibrinolysis yielded partial recanalization in a single reported posterior circulation occlusion, indicating potential for some emboli to resolve with lytic treatment.⁴¹¹ At least 2 case reports have described treatment with intravenous alteplase without hemorrhagic complication.^{412,413}

Intracardiac Mass: Recommendations

1. For patients with major acute ischemic stroke likely to produce severe disability and cardiac myxoma, treatment with intravenous alteplase may be reasonable (*Class IIb; Level of Evidence C*).
2. For patients presenting with major acute ischemic stroke likely to produce severe disability and papillary fibroelastoma, treatment with intravenous alteplase may be reasonable (*Class IIb; Level of Evidence C*).

Aortic Arch Dissection and Cervicocephalic Arterial Dissection, Known or Suspected

The FDA label makes no reference to issues surrounding arterial dissections; however, the 2013 AHA/ASA guidelines²⁴

address the consideration of aortic dissection in the diagnostic study section.

Intravenous alteplase within 3 hours of the onset of acute ischemic stroke symptoms is the standard of care in the United States. However, it is feared that in patients with ascending aortic arch dissection, intravenous alteplase could induce rupture of the dissection. In some cases of acute aortic dissection, neurological deficits could be observed,⁴¹⁴ especially if the dissection extends into the cervical internal carotid artery. A paucity of cases reported in the literature deal with this issue; the majority favor avoiding the use intravenous alteplase in the setting of aortic dissection.^{415–417} When intravenous alteplase was administered in the setting of acute stroke, some patients developed symptoms such as flank pain,⁴¹⁴ chest and ear pain,⁴¹⁸ or a cold extremity with no palpable pulse.⁴¹⁹ Further imaging revealed aortic dissection in each case. The presence of aortic dissection precluded the use of intravenous alteplase in almost all reports. Thus, clinical clues such as chest pain radiating to the back, diaphoresis, or hypotension must be sought. If aortic dissection is clinically suspected, obtaining a chest x-ray for widened mediastinum or CT angiography (head and neck including an arch study) before the administration of alteplase is warranted.

The use of intravenous alteplase in the setting of strokes that are attributable to cervical artery dissection is less clear. The problem with cervical carotid dissection is not only occlusion/stenosis of the cervical internal carotid artery but also tandem distal emboli. In one of the largest studies on cervical internal carotid artery dissection and alteplase administration, the Swiss multicenter study,⁴²⁰ intravenous alteplase-treated patients with stroke attributable to cervical carotid dissection were compared with patients with stroke attributable to another cause (noncervical carotid dissection). Intravenous alteplase-treated patients with cervical carotid dissection had lower chances of recovering favorably than intravenous alteplase-treated patients without cervical carotid dissection. The lower recovery rate was not caused by different intracranial bleeding or recurrent stroke rates between the 2 groups. A meta-analysis of the safety of intravenous alteplase in the setting of cervical carotid dissection concluded that the safety and outcome of thrombolysis in patients with cervical artery dissection-related stroke appear similar to those for stroke from all causes, and intravenous alteplase should not be withheld from stroke patients with suspected cervical artery dissection.²⁰⁷ Data from the Cervical Artery Dissection and Ischemic Stroke Patients database showed that among 616 patients with stroke attributable to cervical artery dissection, 68 (11.0%) received alteplase, which was used in 55 (81%) intravenously. Thrombolized patients had more severe strokes (median NIHSS score, 16 versus 3; $P < 0.001$) and more often had occlusion of the dissected artery (66.2% versus 39.4%; $P < 0.001$). However, after adjustment for stroke severity and vessel occlusion, the likelihood for favorable outcome did not differ between the treatment groups. The authors concluded that “Thrombolysis was neither independently associated with unfavorable outcome nor with an excess of symptomatic bleedings.” In most RCTs, cervical carotid dissection was not considered a contradiction to intravenous alteplase.^{4,77}

Spontaneous intracranial dissection is rare; <100 cases have been reported.⁴²¹ It is usually seen in younger patients with fibromuscular dysplasia, cystic medial necrosis, and atherosclerosis. Affected patients can present with ischemic stroke with or without SAH.⁴²² Spontaneous intracranial dissection should be considered part of the differential diagnosis of internal carotid artery stenosis and occlusion, especially in younger patients. Current literature recommends anticoagulation as the sole means of therapy in cases of nonhemorrhagic intracranial dissection.^{421,422}

Aortic Arch Dissection and Cervicocephalic Arterial Dissection, Known or Suspected: Recommendations

1. **Intravenous alteplase in acute ischemic stroke known or suspected to be associated with aortic arch dissection is not recommended and is potentially harmful (Class III; Level of Evidence C).**
2. **Intravenous alteplase in acute ischemic stroke known or suspected to be associated with extracranial cervical arterial dissection is reasonably safe within 4.5 hours and is probably recommended (Class IIa; Level of Evidence C).**
3. **Intravenous alteplase usefulness and hemorrhagic risk in acute ischemic stroke known or suspected to be associated with intracranial arterial dissection remain unknown, uncertain, and not well established (Class IIb; Level of Evidence C).**

American Heart Association | American Stroke Association

Dural Puncture Within 7 Days

Neither the FDA label nor 2013 AHA/ASA guidelines²⁴ make any specific reference to risks of intravenous alteplase in the context of dural puncture.

The potential for lumbar epidural hematoma and neural element compression prompted the dural puncture contraindication to intravenous alteplase. Procedural information, including the indication for the cerebrospinal fluid study, number of attempts, and gauge of needle used, may inform the potential for procedure-site hemorrhage. There are limited case reports of spontaneous epidural hematomas in the literature after intravenous alteplase. However, most of the case reports describe spontaneous epidural hematoma after administration of both intravenous alteplase and heparin.^{423–425} The only case describing epidural hematoma after intravenous alteplase that does not specifically mention simultaneous administration of heparin was published in 1996 by Connolly et al.⁴²⁶ Although the authors do not specifically mention administration of heparin, heparinization was the standard of care at many centers at the time. Moreover, the hematoma occurred in a delayed fashion 10 days after intravenous alteplase. No case reports or literature exists on epidural hematoma after lumbar puncture or epidural anesthesia in the setting of intravenous alteplase administration alone. There are, however, case reports of spontaneous, post-region anesthesia and post-dural puncture epidural hematomas in the setting of heparinization.⁴²⁷ Concomitant administration of heparin and intravenous alteplase is absolutely contraindicated in the setting of recent dural puncture. However, in the absence of data or a case report to the contrary, dural puncture

should not be considered an absolute contraindication to intravenous alteplase alone. Given the capacious diameter of the lumbar canal with respect to the neural elements, it is unlikely that a hematoma of sufficient mass effect would accumulate to precipitate a neurological deficit. Ultimately, the clinician must weigh the indication for the initial lumbar puncture and potential thrombolysis benefit.

Dural Puncture Within 7 Days: Recommendation

- 1. Intravenous alteplase may be considered for patients who present with acute ischemic stroke, even in instances when they may have undergone a lumbar dural puncture in the preceding 7 days (Class IIb; Level of Evidence C).**

Psychogenic/Conversion/Malingering SM

Neither the FDA label nor the 2013 AHA/ASA guidelines²⁴ make any specific reference to SM as a contraindication to intravenous alteplase, aside from emphasizing the importance of establishing that the clinical presentation is consistent with acute ischemic stroke before treatment.

Intravenous alteplase is the only approved medical therapy in patients with acute ischemic stroke who present within 3 hours (or in selected cases 4.5 hours).²⁴ The benefit of intravenous alteplase rapidly declines over every minute of delay between symptom onset and treatment.⁴²⁸ Stroke teams, dedicated to swiftly assessing, diagnosing, and treating, are disadvantaged by limited time. Occasionally, a patient presenting with symptoms and signs of acute stroke will turn out to have a diagnosis other than cerebrovascular disease, a so-called mimic. If the true diagnosis of mimic is not determined swiftly, patients with SM may receive intravenous alteplase. Erroneous administration of intravenous alteplase to a patient without acute ischemic stroke is not without potential risks and harm, including intracranial and extracranial hemorrhage, minor and major, allergic phenomena such as angioedema, and associated wasted resources of drug and the obligatory postthrombolysis care in an intensive care unit associated with its administration. The proportion of acute stroke syndrome patients who are actually mimics varies between 1% and 25% in hospital-based registries.^{289,294,333,334} The prevailing thought has been that serious complications of intravenous alteplase are unlikely to occur in patients mimicking acute stroke. Multiple single-center studies of small numbers reported no serious complications in patients with SM who have received intravenous alteplase.^{277,290,340,429}

Zinkstok et al²⁹⁴ designed a study aimed to investigate the frequency and clinical characteristics of SMs in a large cohort of patients treated with intravenous alteplase and to assess safety of intravenous alteplase administration in patients who exhibit SMs. In a collaboration of 12 European stroke centers, Zinkstok et al assembled a multicenter observational cohort study including 5581 consecutive patients treated with intravenous alteplase. The investigators retrospectively determined the frequency and clinical characteristics of SMs and the final diagnosis.²⁹⁴ For safety, the investigators compared the sICH

(ECASS II definition) rate of SM patients with that of ischemic stroke patients.

In 100 of these patients (1.8%; 95% CI, 1.5–2.2), the final diagnosis was a pathogenesis other than stroke.²⁹⁴ Patients with SM were younger, were more frequently female, and had fewer vascular risk factors except smoking and previous stroke or transient ischemic attack.²⁹⁴ Patients with SM were treated at later time points than patients with acute ischemic stroke. The composition of SMs in the cohort was as follows: epileptic seizure, 41%; psychogenic disorder, 28%; migraine, 12%; demyelination, 5%; encephalitis, 3%; brain neoplasm, 2%; peripheral vestibulopathy, 1%; posterior reversible encephalopathy syndrome, 1%; brachial plexopathy, 1%; hypoglycemia, 1%; sinusitis, 1%; drug and alcohol intoxication, 1%; cervical myelopathy, 1%; and uncertain (but definitely not ischemic stroke), the remaining 2%.²⁹⁴ One patient, a 76-year-old man who was eventually diagnosed with epileptic seizure, had an sICH (ECASS II) causing hemianopsia with a favorable recovery at 3 months. A second man, 73 years old with an epileptic seizure related to a postoperative defect, experienced sICH (NINDS) with an excellent recovery. Compared with ischemic stroke patients, the rate of sICH (by any definition) in mimic patients was lower. No fatal sICH occurred in a mimic patient in this cohort. No orolingual edema was reported in mimic patients who received intravenous alteplase.²⁹⁴ Of the 2 SM patients who died over the course of the 3-month follow-up, 1 was an 86-year-old man with epilepsy who died suddenly at 2 weeks before the 3-month term had expired, and the other was a 75-year-old patient who died as a consequence of a brain neoplasm. SM patients treated with intravenous alteplase more often had a favorable outcome, as would be suspected (87.5% versus 55.5%), and excellent outcomes at 3 months (75.0% versus 39.5%; both $P < 0.0001$).²⁹⁴ Safety end points reported after intravenous alteplase in patients with ischemic stroke and SMs from this cohort are as follows: sICH (NINDS), 7.9% (95% CI, 7.2–8.7) and 2.0% (95% CI, 0.3–7.1), $P = 0.030$; sICH (ECASS II), 5.5% (95% CI, 4.9–6.1) and 1.0% (95% CI, 0.0–5.0), $P = 0.049$; fatal ICH, 2.7% (95% CI, 2.2–3.1) and 0.0% (95% CI, 0.0–3.7), $P = 0.115$; mortality, 14.4% (95% CI, 13.4–15.3) and 2.1% (95% CI, 0.3–7.3), $P < 0.0001$; and orolingual edema, 1.0% (95% CI, 0.1–1.5) and 0.0% (95% CI, 0.0–7.4), $P = 1.00$.²⁹⁴ This is the largest study of SMs in a consecutive intravenous alteplase cohort to date, and it reveals that the proportion of patients with SM treated with intravenous alteplase is small and that intravenous alteplase in SMs is safe because the rate of sICH was low and incidental death observed in SMs was not attributable to intravenous alteplase.²⁹⁴

Zinkstok et al²⁹⁴ reported 10 studies describing 219 patients with SM who received intravenous alteplase in a total of 3916 patients treated with intravenous alteplase and another 5 case reports. The settings of all studies were tertiary care hospitals. Three of these tertiary care hospitals also included satellite hospitals. SMs were retrospectively identified from hospital-based stroke registries in all studies but one. Studies unequivocally suggested that intravenous alteplase in SMs was safe.^{277,290,294,319,336–338,341,429–433} No instance of fatal sICH was reported. One case report described an sICH after intravenous alteplase in a SM patient with GBM.²⁷⁷ Common

characteristics of alteplase-treated patients who did not have acute ischemic stroke were lower NIHSS and less severe deficit at baseline, younger age, better outcomes, lower blood pressure, higher probability of psychiatric history, and shorter hospital stay.

Psychogenic/Conversion/Malingering SM: Recommendation

- 1. The risk of symptomatic intracranial hemorrhage in the SM population is quite low; thus, starting intravenous alteplase is probably recommended in preference over delaying treatment to pursue additional diagnostic studies (Class IIa; Level of Evidence B).**

Catheterization Laboratory Environment/Endovascular Complications/Stroke Syndrome

The FDA label emphasizes hemorrhagic risks of alteplase administration in patients who have recently undergone arterial puncture at a noncompressible site. Neither the FDA label nor the 2013 AHA/ASA guidelines²⁴ make specific reference to opportunities and risks associated with intravenous alteplase for acute ischemic stroke occurring as a complication around the time of or immediately after coronary or cerebral conventional catheter angiographic laboratory procedure.

Complications that are commonly associated with intravenous alteplase followed by angiography are hematoma at the femoral access site, ICH, and arterial dissection. Most studies have not found any significant procedure-related morbidity in conjunction with the use of intravenous alteplase followed by angiography.^{434–438} In part 1 of the Multi Mechanical Embolus Removal in Cerebral Ischemia (Multi MERCI) trial, procedure-related serious adverse events occurred in 11 patients (9.9%), but clinically significant procedural complications occurred in only 5 patients (4.5%).⁴³⁷ No patient receiving intravenous alteplase had a clinically significant procedural complication. In the Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment (SWIFT) trial of Solitaire flow restoration device compared with the Merci retriever in patients with acute ischemic stroke (a randomized, parallel-group, noninferiority trial), there was no significant difference in complications with and without intravenous alteplase among the cohort of patients who underwent treatment with the Solitaire device.⁴³⁶

In the United States, stroke is reported to occur in 0.05% to 0.1% of diagnostic cardiac catheterizations and in 0.18% to 0.44% of percutaneous coronary interventions in contemporary clinical practice.⁴³⁹ The incidence of stroke during a diagnostic cerebral angiogram is <1%.⁴⁴⁰ Treatment of acute ischemic stroke in patients who are undergoing (or have recently undergone) cardiac or cerebral angiographic procedures appears, on the basis of limited case report series, to lead to favorable outcomes with immediate neuroendovascular intervention, including local administration of alteplase if feasible and in instances when an intracranial arterial occlusion is demonstrable on angiography. An immediate endovascular approach may not be a feasible treatment strategy in many settings and in many circumstances; however, intravenous

alteplase may remain a consideration, depending on the usual eligibility criteria.⁴⁴¹ Such strokes should be treated according to general principles already outlined in the 2013 AHA/ASA guidelines²⁴ and this scientific statement. Because patients who undergo cardiac or cerebral angiographic procedures regularly receive concurrent anticoagulant and antiplatelet medications, previous sections in this statement have relevance in the determination of eligibility for intravenous alteplase treatment for a postprocedural stroke complication.

Catheterization Laboratory Environment/Endovascular Complications/Stroke Syndrome: Recommendation

- 1. Intravenous alteplase is reasonable for the treatment of acute ischemic stroke complications of cardiac or cerebral angiographic procedures, depending on the usual eligibility criteria (Class IIa; Level of Evidence A).**

Consent for the Incompetent Patient

As with any medical therapy that carries more than minimal risk, explicit informed patient consent for intravenous alteplase is indicated.

Deciding whether to use intravenous alteplase for a given patient with acute ischemic stroke within a narrow time window can be challenging for patients, family members, and emergency healthcare providers. Visual displays and instruments can assist individuals to swiftly comprehend the potential range of health benefits and risks associated with the administration of intravenous alteplase, both quantitatively and qualitatively.^{378,442,443}

For the incompetent patient, consent may be provided by a legally authorized representative who can provide proxy consent. A physician's note documenting explicit discussion in a consent conversation is acceptable. In some institutions, the patient or representative must sign a written consent form conveying the risks and benefits of therapy. In an emergency, when the patient is not competent and there is no available legally authorized representative to provide proxy consent, it is both ethically and legally permissible to proceed with fibrinolysis. Generally accepted legal and ethical doctrines recognize an exception to the obligation to obtain explicit informed consent in emergency situations in which immediate treatment is required to prevent more serious harm, the patient lacks decision-making capacity, and no substitute decision maker (surrogate) is available. Regulatory precedents set by the FDA and Department of Health and Human Services in the United States and by the World Medical Association internationally support the use of intravenous alteplase in patients lacking capacity when an alternative form of consent cannot be obtained within the treatment window.^{444–446}

Consent for the Incompetent Patient: Recommendations

- 1. In an emergency, when the patient is not competent and there is no immediately available legally authorized representative to provide proxy consent, it is**

recommended to proceed with intravenous alteplase in an otherwise eligible patient with acute ischemic stroke (Class I; Level of Evidence C).

- Visual displays that convey the benefits and the risks of intravenous alteplase can be useful to assist with shared decision making and aid in establishing informed consent (Class IIa; Level of Evidence B).**

Concurrent Antiplatelet Medication

Although antiplatelet medications have been administered concomitantly with and after intravenous alteplase administration for acute MI and pulmonary embolism, the FDA label cautions that the safety of concomitant use of antiplatelet medications with intravenous alteplase for the management of acute ischemic stroke is unknown.

Aspirin and other antiplatelet drugs are frequently used by patients with acute ischemic stroke. Contemporary alteplase registries and trials show that 30% to 50% of patients treated with alteplase are taking aspirin or other antiplatelet drugs.^{6,111,256} Antiplatelet drugs could potentially enhance the alteplase effect by improving recanalization but could also increase the risk of postalteplase symptomatic intracranial hemorrhage. This section reviews the safety and efficacy of alteplase use in patients already taking antiplatelet drugs for other indications and in patients given antiplatelet drugs soon after intravenous alteplase infusion.

Patients already taking antiplatelet drugs before ischemic stroke could have improved outcomes if the antiplatelet drugs facilitate recanalization or prevent early recurrence. However, analyses of stroke registries and clinical trial data do not show reduced disability or mortality in alteplase-treated prestroke antiplatelet drug users compared with nonusers.^{6,54,447–450} A secondary analysis of the Combined Lysis of Thrombus in Brain Ischemia Using Transcranial Ultrasound and Systemic TPA (CLOTBUST) trial of patients with MCA occlusions found that recanalization rates were not different in prestroke aspirin users compared with nonusers.¹⁸¹

Avoidance of antiplatelet drug use for 24 hours after alteplase was specified in the protocols of the 2 NINDS trials, the ECASS III trial, and the IST-3 trial. The FDA package label for alteplase cites this trial protocol stipulation and adds that the safety of antiplatelet drug use within 24 hours is unknown. The effectiveness of aspirin added to alteplase therapy was tested in the Antiplatelet Therapy in Combination With Alteplase Thrombolysis in Ischemic Stroke (ARTIS) trial. In that trial, subjects were randomized to 300 mg aspirin IV versus placebo. The trial was stopped early after enrollment of 642 patients because of excess sICH in the aspirin treatment arm (4.3% versus 1.6%; $P=0.04$). The proportion with a good outcome, defined as mRS score of 0 to 2, was not different in the aspirin arm versus the placebo arm (54.0% versus 57.2%; $P=0.42$). The ARTIS trial result is consistent with earlier trial evidence that showed an increased risk of harm in alteplase-treated subjects given aspirin soon after thrombolysis. The Multicentre Acute Stroke Trial–Italy (MAST-I) trial included subjects randomized to either streptokinase plus aspirin or streptokinase alone and found that the addition of aspirin increased the risk of fatal intracranial hemorrhage. A

Cochrane review of thrombolysis trials found that the odds of death were increased with earlier administration of antiplatelet drugs after thrombolysis, with most of the increased risk occurring when used within 24 hours. Whether the excess risk of sICH with early antiplatelet drug use is justified in certain situations of increased thrombotic risk, for example, in a patient with recent stent placement, is not known. More recently, an early-phase study demonstrated the safety of a regimen of lower-dose intravenous alteplase combined with the intravenous antiplatelet drug eptifibatide.⁴⁵¹ The efficacy of this regimen is being tested in a larger trial.

Single-center studies, smaller multicenter studies, and clinical trials have given conflicting results about the risk of sICH in prestroke antiplatelet drug users.^{109,346,448,452,453} These conflicting results may have arisen from inadequate sample sizes and publication bias. In the SITS-ISTR study of 31 627 alteplase-treated patients, the use of a single antiplatelet drug before stroke was associated with a 1.8-fold increase in the odds of sICH (95% CI, 1.5–2.1), and the use of dual therapy with aspirin and clopidogrel was associated with a 3.2-fold increase in the odds of sICH (95% CI, 1.9–5.2) in a multivariable analysis controlled for NIHSS, glucose, age, systolic blood pressure, weight, onset to treatment time, and history of hypertension.¹¹¹ In contrast, in a study of 10 242 alteplase-treated patients in the GWTG-Stroke registry, antiplatelet drug users had only a 1.29-fold increased odds of sICH (unpublished data), and antiplatelet drug use was not retained in the final prediction model for sICH that included NIHSS, age, systolic blood pressure, glucose level, Asian race, and sex. In this study, dual antiplatelet drug use was not captured in the database and therefore could not be analyzed.²⁵⁶ The reasons for the discrepant findings of these 2 large studies are unclear but could be related to differences in sample sizes, population characteristics, classification of sICH (the more conservative SITS-MOST definition was used in the European study compared with the broader NINDS definition in the US study), or antiplatelet drug classes and doses. In summary, current evidence suggests that antiplatelet drug monotherapy is possibly associated with a small increase in the risk of sICH and that dual therapy is probably associated with an even higher risk. More data are needed on different drug classes and doses and on the safety of antiplatelet drugs when used in combination with subtherapeutic warfarin or recent administration of novel OACs.

Despite the possible increased risk of alteplase-related sICH in patients taking antiplatelet drugs before their stroke, clinical trial evidence suggests that alteplase is still effective in this group. Post hoc subgroup analyses of both the NINDS alteplase stroke trials and the IST-3 trial show that the efficacy of alteplase did not differ in patients taking antiplatelet drugs before stroke. In the 2 NINDS alteplase stroke trials, there was no difference in the effect of intravenous alteplase according to prestroke antiplatelet drug use (ie, there was no interaction effect, $P=0.68$).⁵⁴ In the IST-3 trial, the odds for good outcome were 1.20 (95% CI, 0.87–1.65) in 1562 prestroke antiplatelet drug users compared with 1.02 (95% CI, 0.73–1.43) in 1473 nonusers (interaction $P=0.38$).⁶ Therefore, it seems likely that the small increased risk of harm from excess sICH in prestroke antiplatelet drug users is potentially outweighed by a larger

benefit from thrombolysis such that there is an overall net improvement in functional outcomes in prestroke antiplatelet drug users treated with intravenous alteplase. It may be reasonable to advise patients taking antiplatelet drugs and their families that there may be a small increased risk of bleeding if alteplase is used but that the small increased risk of bleeding does not negate the beneficial effect of alteplase. Analyses from the trials either grouped antiplatelet drug monotherapy and combination therapy together⁶ or analyzed only aspirin use.⁵⁴ Therefore, there are no separate data on the efficacy of alteplase in combination antiplatelet drug users. Additionally, antiplatelet drug combination therapy was rare but is increasingly prevalent on the basis of expanding indications for combination therapy in cardiovascular medicine; therefore, the number of combination therapy users would have been lower in past trials than in current practice. In a study of 11 865 patients in the observational SITS-ISTR registry that included 151 patients taking aspirin and clopidogrel before stroke, the risk of alteplase-related sICH was increased compared with patients not taking antiplatelet drugs (OR, 1.74 for sICH by NINDS definition; 95% CI, 1.11–2.73), but the probability of good outcome defined as an mRS score of 0 to 1 was similar (OR, 0.89; 95% CI, 0.62–1.29).⁴⁴⁷

No published data were identified that provided the efficacy or safety of alteplase with different doses of antiplatelet drugs, for example, after a loading dose of clopidogrel has been given, or in patients taking prasugrel or ticagrelor. No data were identified on the efficacy or safety of intravenous alteplase in patients recently treated with intravenous glycoprotein IIb/IIIa inhibitors. However, a previous randomized trial of abciximab for acute ischemic stroke was terminated early because of an increased risk of sICH compared with placebo, suggesting that there could be safety concerns.⁴⁵¹

Concurrent Antiplatelet Medication: Recommendations

1. The administration of aspirin (or other antiplatelet agents) as an adjunctive therapy within 24 hours of intravenous alteplase is not recommended (*Class III; Level of Evidence C*).
2. The concurrent administration of other intravenous antiplatelet agents that inhibit the glycoprotein IIb/IIIa receptor is not recommended outside a clinical trial (*Class III; Level of Evidence B*).
3. Intravenous alteplase is recommended for patients taking antiplatelet drug monotherapy before stroke on the basis of evidence that the benefit of alteplase outweighs a possible small increased risk of sICH (*Class I; Level of Evidence A*).
4. Intravenous alteplase is recommended for patients taking antiplatelet drug combination therapy (eg, aspirin and clopidogrel) before stroke on the basis of evidence that the benefit of alteplase outweighs a probable increased risk of sICH (*Class I; Level of Evidence B*).

Drug Use (Cocaine)

Neither the FDA label nor the 2013 AHA/ASA guidelines²⁴ make specific reference to ischemic stroke secondary

to drug use, but patients falling into this category were, in most instances, excluded from participating in thrombolysis trials.

Illicit drug use, particularly cocaine use, is a recognized risk factor for acute ischemic stroke in young patients.⁴⁵⁴ Occurring in 9% of the population, illicit drug use was the fifth most common cause of stroke in the Baltimore-Washington Young Stroke study of patients 18 to 44 years of age.⁴⁵⁵ A population-based study in 2005 found that 1 in 5 stroke patients 18 to 54 years of age used illicit drugs, with 6.6% of patients found to use cocaine.⁴⁵⁶ However, use of cocaine and other drugs is not restricted to the young. An urban tertiary hospital single-center study found that 11% of ischemic stroke patients undergoing urine toxicology screening tested positive for cocaine. The oldest patient with a positive test was 71 years of age, and 9% of all patients ≥50 years of age tested positive for cocaine.⁴⁵⁷

Proposed mechanisms of cocaine-associated ischemic stroke include vasoconstriction, increased platelet aggregation, accelerated atherosclerosis, and vascular cell death resulting in vessel weakening and dissection. The largest available published series on the use of alteplase in cocaine-associated ischemic stroke comprised 29 patients who were compared with 75 alteplase-treated patients with ischemic stroke without drug use.⁴⁵⁸ Although patients with cocaine-associated ischemic stroke had more severe strokes, no sICH was observed in the cocaine group, and the observed overall outcomes were similar between the 2 groups.

Ischemic strokes in amphetamine^{459,460} and marijuana⁴⁶¹ users have been reported. No published data are available on the use of alteplase in patients using amphetamines or marijuana.

Overall, limited data are available to justify withholding alteplase in otherwise eligible ischemic stroke patients who use illicit drugs.

Drug Use (Cocaine): Recommendation

1. Treating clinicians should be aware that illicit drug use may be a contributing factor to incident stroke. Intravenous alteplase is reasonable in instances of illicit drug use–associated acute ischemic stroke in patients with no other exclusions (*Class IIa; Level of Evidence C*).

Sickle Cell Disease

Neither the FDA label nor 2013 AHA/ASA guidelines²⁴ make specific reference to intravenous alteplase use in ischemic stroke secondary to sickle cell disease (SCD).

SCD is one of the most common hereditary disorders that affect the hemoglobin structure.^{462,463} It predominantly affects African or Afro-Caribbean ethnic groups.⁷¹ Normally, the hemoglobin molecule has 2 components: α and β . A mutation in a gene on the chromosome 11 that codes for the β subunit of the hemoglobin is responsible for SCD. The structural changes in the hemoglobin molecules (called hemoglobin S) cause red blood cells to be more rigid, irregular, and fragile, getting stuck in the blood vessels and unable to transport and deliver oxygen effectively.^{463,464}

Sickle cell crisis consists of episodes of pain caused by vascular occlusion. Most common triggers include hypoxia, fever, infections, dehydration, and exposure to cold temperatures.^{463,464} Arterial and venous stroke are the most fearful complications of SCD, most commonly affecting children.⁷¹ In the Cooperative Study of Sickle Cell Disease (CSSCD) that included 4082 patients with SCD from 23 US centers over a 10-year period, the annual incidence of stroke (any type) was 0.46%/y. In adults with SCD, the underlying stroke mechanism is diverse as a result of the combination of traditional vascular risk factors and, less likely, vascular occlusion caused by sickle cell crisis.

Children homozygous for the sickle cell gene mutation (SCD-SS) had a higher rate of 0.61%/y. Most common risk factors for stroke in patients with SCD include low hemoglobin levels, high white cell count, hypertension, silent brain infarction, history of chest crisis, and high mean velocity (>200 cm/s) on transcranial Doppler.⁴⁶⁵ The Stroke Prevention Trial in Sickle Cell Anemia (STOP) randomized 130 children 2 to 16 years of age to receive transfusions (n=63) or standard care (n=67). STOP revealed that blood transfusions reduced the risk of stroke from 10%/y to 1%/y.⁴⁶⁶

Since then, optimal hydration, correction of hypotension and hypoxemia, and exchange transfusion for patients with elevated mean velocities on transcranial Doppler to decrease hemoglobin S below 30% have become standard practice.^{71,76,467}

More recently, a single-blind, randomized, clinical trial including 196 children (mean age, 10 years) with sickle cell anemia revealed that regular blood transfusions significantly decreased the risk of a silent or recurrent stroke compared with standard care (observation group; 2.0 versus 4.8 events per 100 years at risk; RR, 0.41; 95% CI, 0.12–0.99; $P=0.04$). The authors suggested that regular blood transfusion therapy would reduce the incidence of the recurrence of cerebral infarct in children with sickle cell anemia.⁴⁶⁸

There is very little literature on the use of alteplase in patients with SCD.^{71,467} Sidani et al⁴⁶⁹ described a 21-year-old man with hemoglobin S who presented with an extensive venous sinus thrombosis that failed blood cell exchange and intravenous heparin. Alteplase was administered with recanalization of the veins. There are no reports in the literature of the use of alteplase for arterial stroke in patients with SCD. Considering the low prevalence of stroke and sickle cell and the difficulty in recognizing stroke in children, it is unlikely that evidence will become available from randomized trials. The topic of intravenous alteplase in children with acute ischemic stroke is addressed in greater detail in a previous section of this statement.

SCD: Recommendations

1. **Acute management of ischemic stroke resulting from SCD should include optimal hydration, correction of hypoxemia, correction of systemic hypotension, and blood exchange to reduce the percentage of hemoglobin S levels (Class I; Level of Evidence B).**
2. **Intravenous alteplase for children and adults presenting with an acute ischemic stroke with known SCD is not well established (Class IIb; Level of Evidence C).**

Conclusions/Summary

In our review of the current literature, it is clear that the levels of evidence supporting individual exclusion criteria for intravenous alteplase vary widely. Some exclusions and myths already have extensive scientific study such as the clear benefit of alteplase treatment in elderly stroke patients, in those with severe stroke, in those with diabetes mellitus and hyperglycemia, and in those with minor EICs evident on CT. Some exclusions such as recent intracranial surgery are likely based on common sense and very likely will never have a randomized, clinical trial to evaluate safety. Most contraindications or warnings range somewhere in between. However, the differential impact of each exclusion factor varies not only with the evidence base behind it but also with the frequency of the exclusion within the stroke population, the probability of the coexistence of multiple exclusion factors in a single patient, and the variation in practice among treating clinicians.

From our review, our group would like to identify the following high-priority research areas for future study:

1. Alteplase treatment of patients with mild ischemic stroke. On the basis of surveys of stroke centers and experts and a review of the literature, there is good evidence for clinical equipoise, a suggestion of potential benefit, and wide practice variation, in combination with likely a lower-than-average risk associated with treatment. The PRISMS trial is currently enrolling patients to evaluate this concept.⁴⁷⁰ The inclusion of milder patients, if proven beneficial, has great potential to broadly increase the number of ischemic stroke patients eligible for alteplase. We would consider patients with “rapidly improving symptoms” who have improved to only having minor deficits within this category of mild symptoms. Our group has a strong consensus that patients with improving symptoms but still with significant deficits that are otherwise eligible for alteplase should be treated.
2. Multimodal cerebral imaging to identify treatment candidates among previously alteplase-ineligible patients. The promise of developing a “tissue clock” based on tissue viability rather than an arbitrary time window is extremely appealing. This is especially relevant to patients who wake up with their deficits ($\approx 20\%$ of ischemic stroke patients) and it is very unclear when the stroke actually occurred. However, for multimodal imaging to significantly affect alteplase eligibility, the time window must be substantially lengthened, likely >8 to 12 hours from onset. Small increments in lengthening the time window are not likely to significantly increase the numbers of eligible patients on the basis of the patterns of patient arrival to medical attention. These multimodal imaging techniques clearly warrant further study, especially in terms of the natural history of infarct appearance in these imaging techniques as the infarct progresses and standardization of imaging techniques.
3. International consensus/harmonization of guidelines for alteplase inclusion/exclusion. As mentioned in the methodology section, we intentionally did not address the varying exclusion criteria and restrictions across the

world and instead focused on the FDA regulations and AHA/ASA guidelines. However, we believe that harmonization of the guidelines for use would be valuable and potentially could reduce confusion about the differences between guideline statements. We suggest that an international task force to harmonize the alteplase treatment guidelines would be an appropriate first step.

4. Alteplase treatment of patients with ischemic stroke who may be anticoagulated. As the population ages, use of anticoagulation will continue to increase, making a thorough understanding of the risks and benefits of alteplase treatment in the setting of anticoagulation even more important. The introduction of novel anticoagulants has further complicated this issue, and the risks associated with these newer agents are largely unknown.
5. Alteplase treatment of patients with periprocedural or perioperative ischemic stroke. We note that in general patients undergoing procedures are typically at a higher risk for ischemic stroke but are also at higher risk for bleeding complications after a surgical procedure. To further complicate matters, each individual procedure likely has its own individual bleeding risks, making the study of a homogeneous population nearly impossible. However, more frequent surgical and endovascular surgical or interventional procedures among patients at risk for stroke would be a reasonable place to start evaluating the risks of treatment such as coronary bypass surgery or peripheral vascular disease repair. In addition, studies of stroke prevention strategies during the perioperative and periprocedural period, including the risks of stopping antithrombotic medications, would be ideal.
6. Alteplase treatment of patients with acute ischemic stroke who have had recent ischemic stroke. The existing evidence appears not to justify totally excluding patients with a history of any size and severity of ischemic stroke in the preceding 3 months from receiving intravenous alteplase for an acute ischemic stroke. It currently is unknown how soon after stroke it is relatively safe to administer intravenous alteplase for an acute ischemic stroke (1 day, 1 week, 1 month, or 3 months) and how best to quantitatively and qualitatively estimate the potential of increased risk of sICH on the basis of the duration of time since the prior stroke, infarct volume, infarct severity, location of prior stroke, and neurovascular imaging characteristics. Studies to address these questions would further the field's collective understanding of the scientific rationale behind this particular contraindication.
7. Alteplase treatment of patients with preexisting disabilities and dementia who sustain an acute ischemic stroke. Obtaining a better understanding of the complex

interactions that affect patient outcome after thrombolysis should be a priority for future research. Clearly, age alone should not be an exclusion, nor should a preexisting extremely mild dementia, for example. However, as more and more comorbidities are added to a patient's history, the likelihood of a good outcome probably becomes less and less. Which ones are most important? There are several risk prediction scores currently in the literature, but many of these are predictive of only hemorrhagic transformation risk. Any risk prediction modeling research would need to include both the risk of hemorrhagic transformation and the chances of an improved outcome after intravenous alteplase and would need to be prospectively validated in a controlled study rather than implemented purely on the basis of epidemiological data.

The writing group suggests that the following topics are of lower yield for increasing/improving access or eligibility for alteplase treatment:

1. Evaluation of treatment of elderly stroke patients. Although there is good consensus about the benefit of alteplase in the elderly stroke patient among stroke experts in the United States, this consensus does not extend to other countries and is still listed as a caution on the FDA package insert. However, our group believes that the literature supporting treatment in the elderly is substantial, and further study would not likely add much to this evidence. Instead, our group suggests further education of the medical community about this literature to dispel the myth that elderly patients do not benefit from alteplase.
2. Uncommon exclusions from alteplase. Although it would be ideal to have definitive science behind every single eligibility criteria for alteplase treatment of acute ischemic stroke, we recognize that the most uncommon exclusions will likely never be feasible to study, and we suggest focusing limited resources on other, higher-priority research questions. We would add several criteria to this list of rarer exclusions, including but not limited to small, asymptomatic, unruptured intracranial aneurysms and small, asymptomatic, incidentally discovered benign intracranial neoplasms, that is, meningioma.

Acknowledgments

We wish to acknowledge Mayo Clinic Library and Medical Informatics Services personnel Kay E. Wellik, Ann M. Farrell, and Patricia J. Erwin for their assistance developing bioinformatics database search strategies.

Appendix: Comparison of AHA/ASA Acute Stroke Management Guidelines and Previous and New FDA Prescribing Information for Alteplase (Activase) Treatment in Acute Ischemic Stroke

Criterion	AHA/ASA Acute Stroke Management Guideline 2013 ²⁴	Old Alteplase (Activase) PI (Updated 2009)	New Alteplase (Activase) PI (February 2015)
Prior stroke	Exclusion: prior stroke within 3 mo	Contraindication: recent (within 3 mo) previous stroke	Removed entirely
Seizure at onset	Relative exclusion: seizure at onset with postictal neurological impairments	Contraindication: seizure at the onset of stroke	Removed entirely
Bleeding diathesis/OACs	Exclusion: Platelet count <100 000/mm ³ Heparin received within 48 h, resulting in abnormally elevated aPTT Current use of anticoagulant with INR >1.7 or PT >15 s Current use of direct thrombin inhibitors or direct factor Xa inhibitors with elevated sensitive laboratory tests	Contraindication: known bleeding diathesis including but not limited to: Current use of OACs (eg, warfarin sodium), an INR >1.7, or a PT >15 s Administration of heparin within 48 h preceding the onset of stroke with an elevated aPTT at presentation Platelet count <100 000/mm ³ Warning for all indications: patients currently taking OACs	Bleeding diathesis remains a contraindication, but all laboratory values and specific examples removed
ICH	Exclusion: history of previous ICH	Contraindication: history of ICH	Contraindication removed Warning added for recent ICH
BP	Exclusion: Elevated BP (systolic >85 mm Hg or diastolic >10 mm Hg)	Contraindication: uncontrolled hypertension at the time of treatment (eg, >185 mm Hg systolic or >110 mm Hg diastolic)	Contraindication: current severe uncontrolled hypertension remains, specific BP values removed Warning for BP >175/110 mm Hg remains for all alteplase (Activase) indications
Blood glucose	Exclusion: blood glucose <50 mg/dL	Warning: because of the increased risk for misdiagnosis of acute ischemic stroke, special diligence is required in making this diagnosis in patients whose blood glucose values are ≈50 or >400 mg/dL	Removed entirely
Severe stroke	Not listed	Warning: patients with severe neurological deficit (NIHSS score >22) at presentation; there is an increased risk of ICH in these patients	Removed entirely
Mild stroke	Relative exclusion: only minor or rapidly improving stroke symptoms (clearing spontaneously)	Warning: safety and efficacy in patients with minor neurological deficit or with rapidly improving symptoms have not been evaluated; therefore, treatment of patients with minor neurological deficit or with rapidly improving symptoms is not recommended	Removed entirely
Neuroimaging findings	Exclusion: CT demonstrates multilobar infarction (hypodensity >1/3 cerebral hemisphere)	Warning: Major early infarct sign (substantial edema, mass effect, or midline shift on CT)	Removed entirely
SAH	Exclusion: symptoms suggest SAH	Contraindication: Suspicion of SAH on pretreatment evaluation	Contraindication: subarachnoid hemorrhage
Use in specific populations			
Pregnancy	Relative exclusion	Warning: pregnancy Category C	No change
Nursing mothers	Not listed	Not mentioned	Unknown risk
Children	Inclusion: ≥18 y of age	Indicated for adults	Pediatric use not established
Elderly	Not listed	Warning for all indications: advanced age (eg, >75 y) may increase risks	Warning added: age >77 y was 1 of several interrelated baseline characteristics associated with an increased risk of ICH; efficacy results suggest a reduced but still favorable clinical outcome
Gastrointestinal or genitourinary bleeding	Warning: gastrointestinal or genitourinary bleeding within the past 21 d	Warning: gastrointestinal or genitourinary bleeding within the past 21 d	Warning: gastrointestinal or genitourinary bleeding

AHA/ASA indicates American Heart Association/American Stroke Association; aPTT, activated partial thromboplastin time; BP, blood pressure; CT, computed tomography; FDA, US Food and Drug Administration; ICH, intracerebral hemorrhage; INR, international normalized ratio; NIHSS, National Institute of Health Stroke Scale; OAC, oral anticoagulant; PI, prescribing information; PT, prothrombin time; and SAH, subarachnoid hemorrhage.

Disclosures

Writing Group Disclosures

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This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be “significant” if (a) the person receives \$10 000 or more during any 12-month period, or 5% or more of the person’s gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns \$10 000 or more of the fair market value of the entity. A relationship is considered to be “modest” if it is less than “significant” under the preceding definition.

*Modest.

†Significant.

Reviewer Disclosures

Reviewer	Employment	Research Grant	Other Research Support	Speakers' Bureau/Honoraria	Expert Witness	Ownership Interest	Consultant/ Advisory Board	Other
Karen Furie	Rhode Island Hospital	None	None	None	None	None	None	None
John Horowitz	University of Adelaide (Australia)	None	None	None	None	None	None	None
Marcella Wozniak	University of Maryland	None	None	None	None	None	None	None

This table represents the relationships of reviewers that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all reviewers are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives \$10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns \$10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

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