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Gregory J. del Zoppo, Jeffrey L. Saver, Edward C. Jauch, Harold P. Adams, Jr and on
behalf of the American Heart Association Stroke Council
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Expansion of the Time Window for Treatment of Acute Ischemic Stroke With Intravenous Tissue Plasminogen Activator

A Science Advisory From the American Heart Association/American Stroke Association

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Edward C. Jauch, MD, MS, FAHA; Harold P. Adams, Jr, MD, FAHA;
on behalf of the American Heart Association Stroke Council

Current guidelines for the management of patients with acute ischemic stroke published by the American Heart Association Stroke Council include specific recommendations for the administration of intravenous recombinant tissue plasminogen activator (rtPA).¹ Despite its effectiveness in improving neurological outcomes, the majority of patients with ischemic stroke are not treated with rtPA, largely because they arrive after the currently approved 3-hour time limit for administration of the medication. One of the potential approaches to increase treatment opportunities has been the designation of a longer time window for treatment.²⁻⁴

A recent prospective study, the European Cooperative Acute Stroke Study (ECASS)-3, has provided new data on rtPA (alteplase) treatment in the 3-to-4.5-hour window.⁵ The circumstances surrounding this study are important.

In 2002, the European Medicines Evaluation Agency granted license for the use of rtPA for the treatment of ischemic stroke patients within 3 hours of symptom onset on condition of (1) the completion of a prospective registry of patient treatment experience with rtPA given within the 3-hour window from symptom onset (Safe Implementation of Thrombolysis in Stroke—Monitoring Study, or SITS-MOST)⁶ and (2) the completion of a prospective, randomized, placebo-controlled trial of rtPA administered between 3 and 4.5 hours after stroke onset, ECASS-3.⁵ SITS-MOST, which used a specified protocol, reported that the frequency of symptomatic intracerebral hemorrhage (per the SITS-MOST definition) at 24 hours after rtPA was 1.7% (95%

confidence interval [CI] 1.4% to 2.0%; Figure 3 in Wahlgren et al⁶). The frequency of symptomatic intracerebral hemorrhage per the Cochrane/National Institute of Neurological Disorders and Stroke (NINDS) definition at 24 hours after rtPA was 7.3% (95% CI 6.7% to 7.9%). By comparison, this frequency was slightly less than 8.6% in data taken from a pool of randomized, controlled trials (Figure 2 in Wahlgren et al⁶). For efficacy, the frequency of scores of 0, 1, and 2 on the combined modified Rankin scale at 90 days was 54.8% (95% CI 53.5% to 56.0%) among rtPA patients, which was comparable to the pooled sample.⁶ These findings appear to confirm the potential safety of rtPA within the 3-hour window in European centers.

In addition, the Safe Implementation of Thrombolysis in Stroke—International Stroke Treatment Registry 3-to-4.5-hour study (SITS-ISTR 3-to-4.5 hour), a post hoc sampling of limited data acquired between December 2002 and November 2007 from the ongoing international registry (SITS-ISTR), compared 11 865 patients treated with rtPA within 3 hours of symptom onset with 664 patients who received treatment within 3 to 4.5 hours.⁷ Most (72%) of the patients treated after 3 hours were treated between 3 and 3.5 hours. Although there were several weaknesses in that study, no differences between the 3-to-4.5-hour cohort and the <3-hour cohort were apparent with respect to symptomatic intracerebral hemorrhage, mortality, or modified Rankin Scale score of 0 to 2 at 90 days.⁷ SITS-ISTR is an ongoing registry that includes experience from SITS-MOST, non-European centers, and active studies.

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 advisory was approved by the American Heart Association Science Advisory and Coordinating Committee on April 22, 2009. A copy of the advisory is available at <http://www.americanheart.org/presenter.jhtml?identifier=3003999> by selecting either the “topic list” link or the “chronological list” link (No. LS-2097). To purchase additional reprints, call 843-216-2533 or e-mail kelle.ramsay@wolterskluwer.com.

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Table. 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> Additional studies with focused objectives needed IT IS REASONABLE to perform procedure/administer treatment	CLASS IIb <i>Benefit ≥ Risk</i> Additional studies with broad objectives needed; additional registry data would be helpful Procedure/Treatment MAY BE CONSIDERED	CLASS III <i>Risk ≥ Benefit</i> Procedure/Treatment should NOT be performed/administered SINCE IT IS NOT HELPFUL AND MAY BE 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	is not recommended is not indicated should not is not useful/effective/beneficial may be harmful

*Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as gender, age, history of diabetes, history of prior myocardial infarction, history of heart failure, and prior aspirin use. 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. Even though randomized trials are not available, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

†In 2003, the ACC/AHA Task Force on Practice Guidelines developed a list of suggested phrases to use when writing recommendations. All guideline recommendations have been written in full sentences that express a complete thought, such that a recommendation, even if separated and presented apart from the rest of the document (including headings above sets of recommendations), would still convey the full intent of the recommendation. It is hoped that this will increase readers' comprehension of the guidelines and will allow queries at the individual recommendation level.

In 2008, ECASS-3, a multicenter, prospective, randomized, placebo-controlled trial that enrolled patients to best medical treatment together with either rtPA (n=418) or placebo (n=403) between 3 and 4.5 hours after symptom onset, was completed.⁵ The dosing regimen was 0.9 mg/kg (maximum of 90 mg), with 10% given as an initial bolus and the remainder infused over 1 hour, exactly what is stated in the current guidelines.¹ Initially, the trial restricted enrollment to patients treated within 4 hours of stroke onset, then increased the permitted time window to 4.5 hours (median treatment interval ≈4 hours). The trial excluded persons older than 80 years, those with a baseline National Institutes of Health Stroke Scale score >25, those taking oral anticoagulants, and those who had the combination of a previous stroke and diabetes mellitus. Otherwise, the exclusion and inclusion criteria for the trial were similar to those contained in the American Heart Association Stroke Council guidelines for treating persons within 3 hours of stroke onset.¹ Ancillary medical care was similar

to that included in the current guidelines except that patients were permitted to receive parenteral anticoagulants for prophylaxis of deep vein thrombosis within 24 hours after treatment with rtPA.

Symptomatic intracranial hemorrhage (according to the ECASS-3 definition) was diagnosed in 10 subjects treated with rtPA (2.4%) and 1 subject who had been given placebo (0.2%; odds ratio [OR] 9.85, 95% CI 1.26 to 77.32, $P=0.008$).⁵ Symptomatic intracranial hemorrhage, as defined by the criteria used in the NINDS study, was diagnosed in 33 subjects treated with rtPA (7.9%) and 14 subjects given placebo (3.5%; OR 2.38, 95% CI 1.25 to 4.52, $P=0.006$). The increased incidence of symptomatic intracranial hemorrhage with the use of thrombolytic agents is consistent with the experience with rtPA in other clinical trials that tested the agent.^{3,5,8-13} In ECASS-3, the incidence of intracerebral hemorrhage was not increased greatly despite the parenteral administration of anticoagulants for prevention of deep vein thrombosis within the first 24 hours after rtPA treatment.

The frequency of the primary efficacy outcome in ECASS-3 (defined as modified Rankin Scale score of 0 to 1 at 90 days after treatment) was significantly greater with rtPA (52.4%) than with placebo (45.2%; OR 1.34, 95% CI 1.02 to 1.76; risk ratio 1.16, 95% CI 1.01 to 1.34; $P=0.04$). The point estimate for the degree of benefit seen in ECASS-3 (OR for global favorable outcome 1.28, 95% CI 1.00 to 1.65) was less than the point estimate of benefit found in the pool of patients enrolled from 0 to 3 hours after stroke symptoms in the NINDS study (OR 1.9, 95% CI 1.2 to 2.9)^{5,8} and was similar to that in a single pooled analysis of the results of subjects enrolled in the 3-to-4.5-hour window in previous trials of rtPA (OR 1.4).⁸⁻¹³ However, the overlap in CIs limits conclusions about these observations. Global favorable outcome was assessed as a modified Rankin Scale score of 0 to 1, a Barthel Index score ≥ 95 , a National Institutes of Health Stroke Scale score of 0 or 1, and a Glasgow Outcome Scale score of 1. In ECASS-3, mortality in the 2 treatment groups did not differ significantly, although it was nominally higher among the subjects treated with placebo.⁵

The ECASS-3 trial represents an important advance in the treatment of acute ischemic stroke. The results, which are consistent with the results in this time window from previous studies and pooled analyses of previous trials,^{3,4,11} provide level B evidence that intravenous rtPA can be given safely to carefully selected patients treated 3 to 4.5 hours after stroke and that intravenous rtPA given in this time period can improve outcomes after stroke in a selected group of patients. Confirmation of the ECASS-3 outcome is encouraged.

Recommendations

Patients who are eligible for treatment with rtPA within 3 hours of onset of stroke should be treated as recommended in the 2007

guidelines.¹ Although a longer time window for treatment with rtPA has been tested formally, delays in evaluation and initiation of therapy should be avoided, because the opportunity for improvement is greater with earlier treatment.

rtPA should be administered to eligible patients who can be treated in the time period of 3 to 4.5 hours after stroke (**Class I Recommendation, Level of Evidence B**). The eligibility criteria for treatment in this time period are similar to those for persons treated at earlier time periods, with any one of the following additional exclusion criteria: Patients older than 80 years, those taking oral anticoagulants with an international normalized ratio ≤ 1.7 , those with a baseline National Institutes of Health Stroke Scale score > 25 , or those with both a history of stroke and diabetes. Therefore, for the 3-to-4.5-hour window, all patients receiving an oral anticoagulant are excluded regardless of their international normalized ratio. The relative utility of rtPA in this time window compared with other methods of thrombus dissolution or removal has not been established. The efficacy of intravenous treatment with rtPA within 3 to 4.5 hours after stroke in patients with these exclusion criteria is not well established (**Class IIb Recommendation, Level of Evidence C**) and requires further study.

Ancillary care for patients receiving rtPA at 3 to 4.5 hours after ischemic stroke should be similar to that included in the 2007 American Heart Association Stroke Council Guidelines.¹

These recommendations, which are based on peer-reviewed publications, should be reevaluated after the results of regulatory agency review of detailed, nonpublicly available data are known. The recommendations use the American Heart Association's classification of recommendations and levels of evidence shown in the Table.

Disclosures

Writing Group Disclosures

Writing Group Member	Employment	Research Grant	Other Research Support	Speakers' Bureau/Honoraria	Ownership Interest	Consultant/Advisory Board	Other
Gregory J. del Zoppo	University of Washington	None	None	None	None	None	None
Harold P. Adams, Jr	University of Iowa	Grant to University of Iowa to provide continuing medical education on management of acute stroke (Genentech)*	None	Optum Health* (lecture on emergency treatment of stroke); National Stroke Association* (developed educational program for stroke care)	None	None	None
Edward C. Jauch	Medical University of South Carolina	NIH grant (IMS3 Trial-Study Executive Committee)†	Novo Nordisk*	None	None	Genentech*	None
Jeffrey L. Saver	University of California at Los Angeles	Boehringer Ingelheim*	Concentric*	Concentric Medical*; Boehringer Ingelheim*; Ferrer*	None	CoAxia*; Talecris*; ev3*; Ferrer*; Concentric Medical*; Cygnis*	NIH* (IMS3 Trial and CLEAR Trial)

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 (1) the person receives \$10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (2) 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
Colin Derdeyn	Washington University	None	Genentech*	None	Genentech*	nFocus*	WL Gore & Associates†	None
Philip Gorelick	University of Illinois	None	None	Boehringer-Ingelheim†	None	None	Genentech*	None
Pooja Khatri	University of Cincinnati	NIH K23†	None	None	None	None	None	None
Tanya Turan	Medical University of South Carolina	NIH/NINDS for SAMMPRI\$ Director of Risk Factor Management†	AAN Foundation Clinical Research Training Fellowship†	None	Expert witness in medical malpractice stroke cases*	None	None	None

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*Modest.

†Significant.

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