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ACR Appropriateness Criteria® on Cerebrovascular Disease

Robert L. DeLaPaz
Columbia University Medical Center, rld17@columbia.edu

Franz J. Wippold II
Mallinckrodt Institute of Radiology

Rebecca S. Cornelius
University of Cincinnati

Sepideh Amin-Hanjani
University of Illinois College of Medicine

Edgardo J. Angtuaco
University of Arkansas for Medical Sciences

See next page for additional authors

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Robert L. DeLaPaz, MD[a], Franz J. Wippold II, MD[b], Rebecca S. Cornelius, MD[c], Sepideh Amin-Hanjani, MD[d,e,f], Edgardo J. Angtuaco, MD[g], Daniel F. Broderick, MD[h], Douglas C. Brown, MD[i], Jeffrey L. Creasy, MD[j], Patricia C. Davis, MD[k], Charles F. Garvin, MD[l], Brian L. Hoh, MD[e,f,m], Charles T. McConnell Jr, MD[n], Laszlo L. Mechtler, MD[o,p], David J. Seidenwurm, MD[q], James G. Smirniotopoulos, MD[r], Paul J. Tobben, MD[s], Alan D. Waxman, MD[t,u], and Greg J. Zipfel, MD[e,f,v]

Stroke is the sudden onset of focal neurologic symptoms due to ischemia or hemorrhage in the brain. Current FDA-approved clinical treatment of acute ischemic stroke involves the use of the intravenous thrombolytic agent recombinant tissue plasminogen activator given <3 hours after symptom onset, following the exclusion of intracerebral hemorrhage by a noncontrast CT scan. Advanced MRI, CT, and other techniques may confirm the stroke diagnosis and subtype, demonstrate lesion location, identify vascular occlusion, and guide other management decisions but, within the first 3 hours after ictus, should not delay or be used to withhold recombinant tissue plasminogen activator therapy after the exclusion of acute hemorrhage on noncontrast CT scans. MR diffusion-weighted imaging is highly sensitive and specific for acute cerebral ischemia and, when combined with perfusion-weighted imaging, may be used to identify potentially salvageable ischemic tissue, especially in the period >3 hours after symptom onset. Advanced CT perfusion methods improve sensitivity to acute ischemia and are increasingly used with CT angiography to evaluate acute stroke as a supplement to noncontrast CT. The ACR Appropriateness Criteria® are evidence-based guidelines for specific clinical conditions that are reviewed every 2 years by a multidisciplinary expert panel. The guideline development and review include an extensive analysis of current medical literature from peer-reviewed journals and the application of a well-established consensus methodology (modified Delphi) to rate the appropriateness of imaging and treatment procedures by the panel. In those instances in which evidence is lacking or not definitive, expert opinion may be used to recommend imaging or treatment.

Key Words: Appropriateness Criteria®, stroke, transient ischemic attack, TIA, thrombolysis, hemorrhage, aneurysm

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[a]Columbia University Medical Center, New York, New York.
[b]Mallinckrodt Institute of Radiology, St Louis, Missouri.
[c]University of Cincinnati, Cincinnati, Ohio.
[d]University of Illinois College of Medicine, Chicago, Illinois.
[e]American Association of Neurological Surgeons, Rolling Meadows, Illinois.
[f]Congress of Neurological Surgeons, Schaumberg, Illinois.
[g]University of Arkansas for Medical Sciences, Little Rock, Arkansas.
[h]Mayo Clinic Jacksonville, Jacksonville, Florida.
[i]Hampton Roads Radiology Associates, Norfolk, Virginia.
[j]Vanderbilt University, Nashville, Tennessee.
[k]Northwest Radiology Consultants, Atlanta, Georgia.
[l]St Luke's Center for Diagnostic Imaging, Chesterfield, Missouri.
[m]University of Florida, Gainesville, Florida.
[n]Good Samaritan Hospital, Cincinnati, Ohio.
[o]Dent Neurologic Institute, Amherst, New York.
[p]American Academy of Neurology, St Paul, Minnesota.
[q]Radiological Associates of Sacramento, Sacramento, California.
[r]Uniformed Services University of the Health Sciences, Bethesda, Maryland.
[s]Presbyterian Hospital, Charlotte, North Carolina.
[t]Cedars-Sinai Medical Center, Los Angeles, California.
[u]Society of Nuclear Medicine, Reston, Virginia.
[v]Washington University School of Medicine, St Louis, Missouri.

Corresponding author and reprints: Robert L. DeLaPaz, MD, American College of Radiology, 1891 Preston White Drive, Reston, VA 20191; e-mail: rld17@columbia.edu.

The ACR seeks and encourages collaboration with other organizations on the development of the ACR Appropriateness Criteria® through society representation on expert panels. Participation by representatives from collaborating societies on the expert panel does not necessarily imply society endorsement of the final document.

This article is a revised version of the ACR Appropriateness Criteria® on Cerebrovascular Disease. Practitioners are encouraged to refer to the complete version at http://www.acr.org/ac.

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SUMMARY OF LITERATURE REVIEW

Introduction/Background

Diseases of the cerebral vasculature are often manifested as stroke, a generic term encompassing a range of ischemic and hemorrhagic lesions. There are approximately 795,000 new (610,000) or recurrent (185,000) strokes per year in the United States, an average of 1 every 40 seconds [1]. Stroke is the third leading underlying or contributing cause of death in the United States, behind heart disease and cancer, accounting for 1 in every 18 (137,265) deaths in 2006, an average of 1 death every 3 to 4 minutes [1]. Of all strokes, 87% are ischemic, 10% are intracerebral hemorrhages, and 3% are subarachnoid hemorrhages [1]. Significant functional disability is common in nonfatal cases, and stroke is a leading cause of serious, long-term disability in the United States [1]. The estimated direct and indirect cost of stroke in the United States in 2009 was $68.9 billion [1].

Imaging and Stroke Risk

Because of the gravity of stroke's sequelae, considerable effort has been expended to identify risk factors for the disease and strategies for stroke prevention in high-risk patients [2]. Although the diagnostic accuracies of duplex ultrasound, CT angiography (CTA), MR angiography (MRA) and time-resolved contrast-enhanced MRA are all high for internal carotid artery stenosis (70% to 99%) [3,4], only ultrasound seems to offer cost-effective initial screening. Combined use of ultrasound and contrast-enhanced MRA is an increasingly common practice [5-9].

Multislice CTA is promising, but relatively few rigorous studies have been done, and the technique remains limited by the large intravenous (IV) contrast injection volumes required, the potential contrast toxicity or reaction, the radiation dose, and the plaque calcification that may obscure the stenosis [4,10,11]. The predictive value of carotid stenosis for symptomatic cerebral ischemia may be further improved by direct characterization of the atherosclerotic plaque [12,13].

Elevated ischemic stroke risk in patients with chronic carotid stenosis or occlusion can also be identified by using single photon-emission CT and research xenon CT methods, which show reduced cerebral vascular reserve after acetazolamide challenge, or by elevated oxygen extraction fraction using ^{15}O PET [14-16]. Although there is limited experience with MR and CT perfusion methods for this purpose, elevated cerebral blood volume seems to correlate with reduced cerebral vascular reserve and increased stroke risk [17,18], and these modalities are more widely available than PET.

Clinical Characteristics of Stroke

Clinically, stroke is most often characterized by the ictal onset of focal neurologic symptoms due to ischemia or hemorrhage into the brain. Ischemic infarction can be classified into various subgroups on the basis of the mechanism of the ischemia (hemodynamic or thromboembolic) and the pathology of the vascular lesion: atherosclerotic, lacunar, cardioembolic, or indeterminate.

Thrombolytic Treatment

Current clinical practice in the United States is based on the 1996 FDA approval of the thrombolytic agent recombinant tissue plasminogen activator (rtPA) given intravenously, preferably <1 hour and no later than 3 hours after symptom onset, after the exclusion of intracerebral hemorrhage by a noncontrast CT (NCCT) scan [19]. The Joint Commission has included these criteria in its requirements for stroke center designation [20]. Recommendations also include the performance of NCCT within 25 minutes of admission and expert interpretation within 20 minutes (45-minute "door-to-interpretation" time) [21]. Recent increases in public awareness, emergency medical response, and the establishment of dedicated stroke centers have resulted in 19% to 60% of admissions arriving at treatment centers <3 hours after symptom onset. However, after appropriate medical exclusions, successful treatment with rtPA, without symptomatic major hemorrhage, is limited to 3% to 8.5% of ischemic stroke admissions [21-24].

Transient Ischemic Attack

Traditionally, if focal neurologic symptoms continued for >24 hours, stroke was diagnosed; otherwise, a focal neurologic deficit lasting <24 hours was defined as a transient ischemic attack (TIA). However, this time-based definition of TIA may be inadequate and misleading, potentially leading to inappropriate delays in diagnosis and treatment. A "tissue-based" definition has been proposed that considers all acute focal neurologic deficits as possible infarcts and classifies them as "acute neurovascular syndromes" or "acute ischemic cerebrovascular syndromes" on the basis of the degree of certainty of tissue ischemic injury, which is determined primarily by tissue and vascular imaging studies [25-27]. Because most transient ischemic neurologic symptoms (70%) last for ≤ 2 hours and 30% to 50% show tissue injury on MR diffusion-weighted imaging (DWI) [26,28,29], the American Stroke Association recently proposed a new definition of TIA as "a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction" [25,28]. This change reflects the growing emphasis on the earliest possible diagnosis and treatment of acute ischemia and the use of NCCT for exclusion of hemorrhage and MRI for definitive infarct diagnosis [21,28].

MRI

Rapid and accurate diagnosis of ischemia, completed infarction, and hemorrhage has become paramount in im-

portance for treating acute cerebrovascular disease because of the demonstrable benefit (and hemorrhage risk) of acute IV and intra-arterial thrombolytic therapy for cerebral ischemia in prospective clinical trials [22-24,30-37]. MRI in the form of DWI has been shown to be exquisitely sensitive to acute infarction within minutes of the precipitating ictus, with sensitivity of 88% to 100% compared to NCCT's mean sensitivity of 66% (range, 20%-87%) [38-41]. The specificity of DWI for ischemic injury is also high (95%-100%), although small reductions in apparent diffusion coefficient (eg, 20% below normal) can represent reversible ischemia that may not progress to completed infarct [42]. Additional information obtainable through the combined use of dynamic cerebral blood volume techniques (perfusion-weighted imaging [PWI] as well as vascular imaging [MRA]) makes MRI an appealing tool for diagnosis and treatment monitoring of acute cerebrovascular disease [41-45].

However, enthusiasm for MRI in the setting of acute stroke has been tempered by the variable and confounding appearance of hemorrhage. Recent experience using T2* (gradient-echo) imaging to detect low-signal parenchymal hemorrhage and fluid-attenuated inversion recovery scans to detect high-signal subarachnoid blood (subarachnoid hemorrhage) have helped renew interest in MRI as a first-line modality in patients with acute, focal neurologic deficits [46-48]. However, there is currently insufficiently widespread clinical experience to recommend MRI over CT for routine exclusion of parenchymal hemorrhage or to withhold rtPA therapy in the presence of microhemorrhages on MRI within the first 3 hours after ictus [21,47].

Because of the small percentage of patients with acute stroke treated within the 3-hour limit, there is growing interest in expanding the treatment window without increasing hemorrhage risk. A pooled risk-benefit analysis of existing rtPA trials using NCCT scan exclusion of hemorrhage has suggested that treatment may be safe in some patients out to 4.5 hours after ictus [22,32], but FDA and American Stroke Association recommendations have not yet been modified to include this expanded treatment window in published guidelines. In addition, several current clinical trials are focused on the use of thrombolytic and neuroprotective agents combined with MRI techniques to expand the treatment window by identifying the "ischemic penumbra," the underperfused yet viable halo of brain parenchyma around or interspersed with the region of completed infarction that is at risk for progressing to infarction. Gadolinium bolus dynamic susceptibility contrast MR PWI measures tissue blood flow parameters (cerebral blood flow, cerebral blood volume, mean transit time, and time to peak) on the basis of the central volume principle and is being used to identify the volume of tissue with reduced blood flow, which is then compared with the volume of presumed infarcted tissue as indicated by restricted diffusion (reduced apparent diffusion coefficient on DWI). When the low-blood flow tissue volume is larger than the restricted diffusion volume by ≥20%, a perfusion-diffusion (PWI-DWI) "mismatch" is said to exist as an indicator of potentially salvageable tissue. Imaging of oxygen metabolism may further define potentially salvageable tissue within this mismatch zone by demonstrating regions of elevated oxygen extraction fraction in stage II "misery perfusion," including DWI-positive (restricted diffusion) regions [14,49,50]. Images of oxygen metabolism can be acquired using ^{15}O PET or experimental MRI methods, and images of hypoxemic tissue can be obtained with ^{18}F fluoromisonidazole PET, but these imaging techniques are not currently available in general clinical practice [50-52]. Currently, there is insufficient scientific evidence or widespread clinical experience to recommend these diagnostic approaches for routine thrombolytic treatment beyond the 3-hour window after symptom onset [53].

CT

On the basis of ready availability and high sensitivity to the presence or absence of acute blood, NCCT historically has been the preferred modality for initial imaging of suspected stroke but has lacked a similar sensitivity to acute ischemia and infarction. The relatively low sensitivity of NCCT to early ischemic injury (only one-third to two-thirds of lesions detected in various studies) and the variable quantitation and interpretation of ischemic changes have limited their use in early stroke management.

A recent resurgence in the use of CT for initial stroke evaluation has occurred with the increasing clinical availability of CT perfusion and CTA. CT perfusion is acquired by rapid scanning during a bolus IV contrast infusion, and blood flow parameters (cerebral blood flow, cerebral blood volume, mean transit time, and time to peak) are calculated on the basis of the central volume principle. This has transformed CT into a technique with high sensitivity to cerebrovascular abnormalities and early perfusion deficits, detectable before observable low-density changes on NCCT [39,54]. Quantitative CT perfusion measurements of cerebral blood flow parameters have been proposed as a means of discriminating between infarct and penumbra and have been compared favorably with MRI [55-61]. These measurements, plus the ability to quickly identify acute hemorrhage and vascular occlusive lesions as well as the ubiquitous availability of CT scanners, have been suggested as the key advantages of CT over MRI for acute stroke evaluation. However, greater risks of renal toxicity, contrast reaction, or fluid overload from iodinated contrast materials vs gadolinium, the variability in CT perfusion quantitative methods [61], and the lack of a direct measure of cellular

viability such as diffusion restriction mitigate these advantages over MRI [62].

Acute Stroke and Advanced Imaging

It should be emphasized that the current FDA-approved treatment for acute ischemic stroke symptoms is IV rtPA within 3 hours of symptom onset and that the recommended imaging study is NCCT to exclude acute hemorrhage. The multimodality MRI and CT studies described above may be useful to confirm the stroke diagnosis and subtype, demonstrate lesion location, identify vascular occlusion, and guide other management decisions within and beyond the 3-hour period. But the American Stroke Association guidelines and others specifically recommend that emergency IV rtPA treatment within the first 3 hours after ictus not be delayed in order to obtain multimodality imaging studies and that treatment not be withheld on the basis of either positive or negative MRI or CT findings, other than acute hemorrhage on NCCT [47,53,60,63-65].

A more complete literature review is available at http://www.acr.org/SecondaryMainMenuCategories/quality_safety/app_criteria/pdf/ExpertPanelonNeurologicImaging/CerebrovascularDiseaseDoc2.aspx (see Variant 1).

Assumptions

All patient scenarios should be addressed as though the patient had been referred for imaging after a history and physical examination that include neurologic, vascular, and ophthalmoscopic examinations.

ANTICIPATED EXCEPTIONS

Nephrogenic systemic fibrosis is a disorder with a scleroderma-like presentation and a spectrum of manifestations that can range from limited clinical sequelae to fatality. It seems to be related to both underlying severe renal dysfunction and the administration of gadolinium-based contrast agents. It has occurred primarily in patients on dialysis, rarely in patients with very limited glomerular filtration rates (ie, <30 mL/min/1.73 m^2), and almost never in other patients. There is growing literature regarding nephrogenic systemic fibrosis. Although some controversy and lack of clarity remain, there is a consensus that it is advisable to avoid all gadolinium-based contrast agents in dialysis-dependent patients unless the possible benefits clearly outweigh the

Variant 1. New focal neurologic defect, fixed or worsening; <3 hours

Radiologic Procedure	Rating	Comments	RRL
CT head without contrast	9	Noncontrast head CT, to exclude acute intracranial hemorrhage, is needed prior to rtPA thrombolytic therapy. Delaying or withholding rtPA thrombolysis in the 3-hour window after symptom onset on the basis of multimodality MRI (DWI, PWI, GRE, or MRA) or CT (CTP or CTA) may not be medically appropriate.*	☢☢☢
MRI head with or without contrast	8	Consider DSC PWI if stenosis found. MRI with DWI preferred if thrombolytic treatment not delayed or withheld.†	O
MRA head and neck with or without contrast	8	Combined vascular and cerebral evaluation should be considered.†	O
CT head with contrast	8	Combined vascular and cerebral evaluation should be considered.*	☢☢☢
CTA head and neck with contrast	8	Combined vascular and cerebral evaluation should be considered.*	☢☢☢
CT perfusion head	6	In this scenario, CTP and CTA are equally useful and can be obtained together (with two injections on most scanners or one injection on volume CT) (but should not delay rtPA therapy decision).*	☢☢☢
Arteriography neck	5	If intra-arterial therapy is considered.	☢☢☢
Arteriography cervicocerebral	5	If intra-arterial therapy is considered.	☢☢☢
Ultrasound carotid with Doppler	2		O
Ultrasound transcranial with Doppler	2		O
MRI functional head	1		O
MRI spectroscopy head	1		O
^{15}O PET head	1		☢☢☢
^{99m}Tc HMPAO SPECT head	1		☢☢☢☢

Note: Rating scale: 1, 2, and 3 = usually not appropriate; 4, 5, and 6 = may be appropriate; 7, 8, and 9 = usually appropriate. Variant tables addressing 10 additional cerebrovascular disease scenarios are available at http://www.acr.org/SecondaryMainMenuCategories/quality_safety/app_criteria/pdf/ExpertPanelonNeurologicImaging/CerebrovascularDiseaseDoc2.aspx. CTA = CT angiography; CTP = CT perfusion; DSC = dynamic susceptibility contrast; DWI = diffusion-weighted imaging; GRE = gradient echo; HMPAO = hexamethylpropyleneamine oxime; MRA = MR angiography; PWI = perfusion-weighted imaging; RRL = relative radiation level; rtPA = recombinant tissue plasminogen activator; SPECT = single photon-emission CT.
*See text under "Relative Radiation Level Information" for important radiation dose warnings with multiple or repeated CT procedures.
†See statement regarding contrast in text under "Anticipated Exceptions."

Table 1. Relative radiation level designations

Relative Radiation Level	Adult Effective Dose Estimate Range (mSv)	Pediatric Effective Dose Estimate Range (mSv)
O	0	0
☢	<0.1	<0.03
☢☢	0.1-1	0.03-0.3
☢☢☢	1-10	0.3-3
☢☢☢☢	10-30	3-10
☢☢☢☢☢	30-100	10-30

Note: Relative radiation level assignments for some of the examinations cannot be made, because the actual patient doses in these procedures vary as a function of a number of factors (eg, region of the body exposed to ionizing radiation, the imaging guidance that is used). The relative radiation levels for these examinations are designated as not specified.

risk and to limit the type and amount in patients with estimated glomerular filtration rates < 30 mL/min/1.73 m^2. For more information, please see the ACR's *Manual on Contrast Media* [66].

RELATIVE RADIATION LEVEL INFORMATION

CT stroke protocols combining brain NCCT, CTA, and CT perfusion may produce a relative radiation level (RRL) of ☢☢☢, and repeated use of this protocol in an individual patient may result in high radiation exposure (eg, RRL of ☢☢☢☢) to the scalp and eyes.

Potential adverse health effects associated with radiation exposure are an important factor to consider when selecting the appropriate imaging procedure. Because there is a wide range of radiation exposures associated with different diagnostic procedures, an RRL indication has been included for each imaging examination. The RRLs are based on effective dose, which is a radiation dose quantity that is used to estimate population total radiation risk associated with an imaging procedure. Patients in the pediatric age group are at inherently higher risk from exposure, both because of organ sensitivity and longer life expectancy (relevant to the long latency that appears to accompany radiation exposure). For these reasons, the RRL dose estimate ranges for pediatric examinations are lower compared with those specified for adults (Table 1). Additional information regarding radiation dose assessment for imaging examinations can be found in *ACR Appropriateness Criteria®: Radiation Dose Assessment Introduction* [67].

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