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Absolute and Relative Contraindications to IV rt-PA for Acute Ischemic Stroke

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Abstract

Most of the contraindications to the administration of intravenous (IV) recombinant tissue plasminogen activator (rtPA) originated as exclusion criteria in major stroke trials. These were derived from expert consensus for the National Institute of Neurological Disorders and Stroke (NINDS) trial. Despite the fact that the safety and efficacy of IV rtPA has been repeatedly confirmed in large international observational studies over the past 20 years, most patients with acute ischemic stroke disappointingly still do not receive thrombolytic treatment. Some of the original exclusion criteria have proven to be unnecessarily restrictive in real-world clinical practice. It has been suggested that application of relaxed exclusion criteria might increase the IV thrombolysis rate up to 20% with comparable outcomes to thrombolysis with more conventional criteria. We review the absolute and relative contraindications to IV rtPA for acute ischemic stroke, discussing the underlying rationale and evidence supporting these exclusion criteria.

Keywords

acute stroke, thrombolytic therapy, tissue plasminogen activator, contraindications

Absolute Contraindications

Acute Intracranial Hemorrhage

The finding of intracranial hemorrhage (ICH) on brain imaging is an absolute contraindication to administering intravenous (IV) recombinant tissue plasminogen activator (rtPA) for acute ischemic stroke in the most recent American Heart Association (AHA) guidelines and the Activase (alteplase, rtPA) (Genentech, Inc) drug label.[1] This includes intraparenchymal hemorrhage, subarachnoid hemorrhage, intraventricular hemorrhage, epidural hematoma, subdural hematoma, or hemorrhagic conversion of infarction. There are no published reports or studies assessing the safety of IV rtPA in this setting because the risks clearly outweigh any potential benefits.

History of ICH

Both the 2013 AHA guidelines and the drug label for Activase (alteplase, rtPA) consider a history of ICH to be an absolute contraindication.[1] There are little data regarding the risks of lysis in this population and it likely varies considerably based on individual patient characteristics. A handful of cases are published within larger reviews of patients receiving "off-label" IV thrombolysis. In one review of a total of 499 patients, 3 had a prior history of ICH.[2] None of these patients had a symptomatic ICH (sICH) after thrombolysis. Two achieved a favorable functional outcome at 3 months.[2] In another study reviewing 135 patients who were treated with rtPA despite a formal contraindication, 3 patients had history of prior ICH and one of these had sICH.[3] The risk of IV rtPA in patients with history of ICH probable varies according to several individual factors including (1) the time elapsed since ICH, (2) cause of prior ICH and whether there was definitive treatment (eg, clipping or coiling of an aneurysm or arteriovenous malformation [AVM]), (3) surgical evacuation of hematoma, and (4) volume of residual encephalomalacia. We think it may be reasonable to administer IV rtPA in some circumstances, but the benefit-to-risk ratio should be assessed on an individual basis.

The use of susceptibility-weighted sequences in magnetic resonance imaging (MRI) has increased the detection of asymptomatic cerebral microbleeds. In nonthrombolysis stroke studies, the number of microbleeds correlates with the frequency of ICH,[4] but the presence of known microbleeds is not a contraindication to the administration of IV rtPA. One large

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multicenter study pooled analysis of MRI data from patients receiving IV thrombolysis.[5] A total of 242 microbleeds were identified by T2*-weighted images in 86 (15%) of the 570 patients. The proportion of patients with sICH was higher in patients with microbleeds (5.8%) compared to those without microbleeds (2.7%), but this difference was not statistically significant.[5] Given the current evidence, IV rtPA should not be withheld from patients because of microbleeds seen on MRI.

Severe Uncontrolled Hypertension

Uncontrolled hypertension to values exceeding a systolic of 185 mm Hg or diastolic of 110 mm Hg is an exclusion criterion to IV rtPA according to the 2013 AHA guidelines and the drug label.[1] This is likely derived from an exclusion criterion for the National Institute of Neurological Disorders and Stroke (NINDS) trials.[6] The relationships between blood pressure (BP), antihypertensive treatment, and clinical outcomes in acute stroke are complex. Hypertension has been associated with increased risk of poor outcomes and ICH in several studies.[7-9] In the Safe Implementation of Treatments in Stroke (SITS) registry, higher systolic BP (SBP) after lysis was independently associated with worse outcomes and an increased risk of ICH.[7] The association between SBP and sICH was linear, while the association between SBP and clinical outcome was U-shaped. In a post hoc analysis of the NINDS trial, antihypertensive therapy given *before* thrombolysis was not associated with differences in outcomes. However, patients with hypertension who received antihypertensives *after* randomization were less likely to have a favorable outcome at 3 months.[10]

Results of other studies show baseline BP is not an independent predictor of ICH or poor outcomes.[11-13] In 1 study of 351 rtPA-treated patients, higher pretreatment SBP was associated with worse rates of recanalization, but SBP was not independently associated with outcome.[12] In the rtPA-treated patients from the early Cleveland area experience, there was no significant difference in the proportion with severe hypertension between those with sICH and those without.[14] Severe hypertension does not need to preclude treatment with IV rtPA for patients with acute stroke, provided it can be controlled with antihypertensive medications. The use of antihypertensives to achieve BP control in patients prior to rtPA appears to be safe.

Serious Head Trauma or Stroke in Previous 3 Months

The 2013 AHA guidelines and the drug label consider significant head trauma or stroke within the previous 3 months as exclusion criteria to administering IV rtPA for acute stroke.[1] Posttraumatic cerebral infarction is reported in 2% to 10% of patients with severe head trauma, but giving thrombolytics to this population is concerning. Patients with trauma are often coagulopathic. Systemic injuries and fractures may increase the risk of systemic hemorrhagic complications. Cerebral contusions, skull fractures, diffuse axonal injury, and traumatic ICH could increase the risk of ICH. In a small review of patients treated in a protocol violation, 1 patient was treated with IV thrombolysis 3 weeks after suffering severe head trauma and suffered a fatal sICH.[15] Two larger European retrospective studies of patients treated with IV rtPA off label included a very small number of patients with recent head trauma, but there were no details specific to this population reported.[16,17] Although data are extremely limited, we think this exclusion criterion is reasonable as the risks in this setting are likely prohibitive.

Patients with acute stroke who have had a recent ischemic stroke within the previous 3 months are presumed to be at higher risk of ICH if given IV rtPA. These patients were excluded in the landmark NINDs trial.[6] The efficacy and safety in such situations are largely unknown and probably varies highly, given individual characteristics such as size and mechanism of previous infarction, age, and severity of recurrent stroke. Specific details about cases receiving IV rtPA for stroke twice within 3 months have been rarely reported. One report details a patient who was successfully treated with a second dose (reduced to 50 mg) of IV rtPA 90 hours after the first dose after he had an arterial reocclusion. This patient had a favorable outcome.[18] With a plasma half-life α of approximately 5 minutes, rtPA is rapidly cleared from the circulation under normal metabolic circumstances.[18] Repeat IV thrombolysis may be reasonable to consider in select cases, particularly with small volume of previous infarction, but the risks are unknown.

Thrombocytopenia and Coagulopathy

Thrombocytopenia. Although it is unnecessary to await platelet counts prior to administering IV rtPA unless there is a suspected thrombocytopenia, a platelet count <100 000/mm^3 is a contraindication for giving IV rtPA for stroke according to both AHA guidelines and the drug insert.[1] Hemorrhagic complications in patients with thrombocytopenia who receive IV rtPA have not been evaluated in a prospective study or randomized trial. From a combined 14 306 patients from multiple studies, only approximately 20 patients with platelets <100 000 mm^3 who received IV rtPA for stroke have been reported in detail.[2,3,19,20] Of these, only 1 patient had documented sICH, but the extremely small number of published cases precludes solid conclusions about the safety of IV thrombolysis in this circumstance.

Coagulopathy. There is similarly a paucity of data about the efficacy or safety of IV rtPA for acute stroke in the setting of abnormal coagulation tests. The risk of all types of hemorrhage may be increased with IV rtPA if a patient is systemically anticoagulated. The presence of an active bleeding diathesis or coagulopathy is a contraindication to the administration of IV rtPA for the treatment of acute ischemic stroke.[1] Suspected coagulopathies are commonly due to anticoagulant therapy. Other potential causes include liver

cirrhosis, end-stage renal disease, hematologic malignancy, vitamin K deficiency, sepsis, and antiphospholipid antibody syndrome. Cardiologists found early success with a multifaceted treatment approach to acute coronary artery occlusions by combining anticoagulation with systemic fibrinolysis, although higher activated partial thromboplastin time (aPTT) values (and higher heparin doses) have been associated with higher rates of ICH.[21] Data pertaining to patients with stroke with a prolonged aPTT who were treated with IV rtPA are scarce. In total, about 162 patients have been reported in the English literature and sICH was reported in 6 (3.7%) patients.[2,11,15,19,20] Counterintuitively, in that analysis there was a statistically significant difference in odds of favorable outcome with IV thrombolysis that favored the patients with prolonged aPTT (odds ratio [OR] 1.57, 95% confidence interval [CI] 1.02-2.41).[20] One of the larger single studies to contribute patients was a prospective study of thrombolysis in clinical practice in 57 US medical centers.[11] The specific aPTT at the time of IV rtPA administration in these studies was generally not reported.[19,11]

In the most recent AHA guidelines, ''current use of anticoagulant with international normalization ratio (INR) > 1.7 or partial thromboplastin (PT) > 15 seconds'' is an absolute contraindication to IV rtPA treatment.[1] Approximately 115 patients with warfarin-treated stroke having INR >1.7 at the time of IV thrombolysis have been reported in the English literature, derived mostly from large registries.[2,11,15,17,19,20,22,23] Of these, sICH was reported in only 1 patient. Most studies did not provide information about the rates of any ICH or functional outcomes as these patients were studied among larger groups. An elevated INR can be caused by other disorders such as hepatic disease or hematological disorders. In 1 large analysis of 2755 thrombolyzed patients pooled from trials, there were 138 patients with INR >1.7 from any cause and an additional 14 with INR >1.7 due to oral anticoagulant therapy.[20] In the 138 patients with high INR due to reasons other than anticoagulation, the odds for a more favorable outcome for thrombolyzed patients compared with controls, after adjustment for age and baseline NIHSS, slightly favored the patients with INR >1.7, but this difference was not statistically significant (OR 1.21, 95% CI 0.82-1.78). It is not clear why there was a trend for improved rates of favorable outcome in patients with prolonged INR and aPTT. In speculation, it is possible that these were very well selected patients with otherwise relatively low risk of hemorrhagic transformation and that the additional anticoagulant effect actually improved recanalization.

The safety of IV rtPA in patients with stroke who take warfarin who have subtherapeutic INR at the time of stroke has been disputed. The current AHA/American Stroke Association guidelines accept IV rtPA treatment for patients treated within 3 hours of onset with an INR $\leq$1.7,[1] while the European license indicates that it is contraindicated if a patient takes oral anticoagulants regardless of INR.[24] 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.[2,25-31] In 2 meta-analyses, the larger of which included 284 patients, the ORs for sICH was increased for warfarin-treated patients (OR 2.6, 95% CI 1.1-5.9 and adjusted OR 4.1 [1-16.1]) but these analyses were not both adjusted for potential confounders.[30,32] Data from 2 large registries (Get-With-The-Guidelines and SITSr) 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 in the setting of a subtherapeutic INR does not independently increase the risk of sICH.[22,23]

Low-Molecular-Weight Heparin

Low-molecular-weight heparins (LMWHs) are longer acting and have greater bioavailability than unfractionated heparin. Intravenous thrombolysis for stroke is contraindicated if the patient is taking therapeutic doses of LMWH because of the presumed high risk of hemorrhagic complications. Reports of IV thrombolysis given to patients taking LMWH are scarce in the literature. One study included 21 thrombolyzed patients receiving LMWH, 18 of who had been administered a dose within the preceding 24 hours.[25] Most, however, were taking prophylactic doses and only 5 were prescribed therapeutic doses. Intracranial hemmorage occurred in 8 (38%; 3 were symptomatic). Seven (33%) achieved a favorable outcome and 6 (29%) died. Compared to patients not anticoagulated, those 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.[25] Most of these patients were hospitalized at the time of stroke, however, and may have had comorbidities that confounded the associations. 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.[2] It is most prudent to avoid giving IV rtPA if a patient has had a therapeutic dose of LMWH within the previous 24 hours.

Direct Thrombin Inhibitors

Dabigatran and argatroban directly inhibit thrombin, preventing the formation of fibrin from fibrinogen. The appeal of direct thrombin inhibitors compared to traditional vitamin K antagonists is multifactorial: more predictable pharmacokinetics, lack of requirement for routine laboratory monitoring, fewer drug–drug interactions, and possibly increased cost-effectiveness.[33] The safety and efficacy of IV rtPA in patients who have been taking direct thrombin inhibitors is not well studied. Furthermore, if hemorrhages do occur, management strategies and reversal of anticoagulation are still controversial.

The published experience is limited to mostly case reports.[34-39] Only 1 ICH has been reported, which was fatal. Direct thrombin inhibitors have also been studied as an adjuvant to IV rtPA for the treatment of acute ischemic stroke. In a pilot study of 65 patients with acute stroke who received Argatroban along with IV rtPA, sICH occurred in 3 (4.6%) patients.[40] Because of such limited data on dabigatran and IV rtPA, the safety and efficacy of thrombolysis in patients taking direct thrombin inhibitors is not known. Although the INR and pTT are not adequately reliable indicators of the anticoagulation effect of dabigatran, the thrombin time (TT) is sensitive to the presence of dabigatran activity.[41] Based on our current understanding of pharmacokinetics, IV rtPA may be considered reasonable in some cases if patients have normal TT, aPTT, and PT, but this should be a subject of future research.

Factor Xa Inhibitors

Clinicians may expect to see an increasing number of patients anticoagulated with oral factor Xa inhibitors apixaban or rivaroxaban. These agents have been shown to be either superior (apixaban) or noninferior (rivaroxaban) to warfarin for preventing secondary stroke associated with atrial fibrillation and reducing bleeding complications.[42,43] Direct factor Xa inhibitors may prolong the PT and aPTT but not with sufficient reliability to estimate the anticoagulant effects accurately. In some cases cautious treatment may be pursued according to the medication's elimination half-life, but until a reliable and prompt method to measure their anticoagulant effect is available, it should be assumed that patients taking these medications are at higher than ordinary risk. Given that so few patients have been reported and that much of the data come from registries or studies in which bias is likely, we think these patients should not routinely receive IV rtPA unless part of research studies.

Severe Hypoglycemia or Hyperglycemia

Measurement of blood glucose is a necessary requisite before the administration of IV rtPA. The main reason for this condition is exclusion of severe hypoglycemia, which can infrequently mimic stroke symptoms. Even more rarely, severe hyperglycemia can also produce focal neurological deficits. Previous versions of the AHA guideline for acute stroke treatment listed glucose levels below 50 mg/dL (2.7 mmol/L) and above 400 mg/dL (22.2 mmol/L) as contraindications for thrombolysis, but the most recent edition only keeps hypoglycemia as an exclusion.[1] Meanwhile, the Food and Drug Adminitration (FDA) package insert for Activase (alteplase, rtPA) recommends "special diligence" in making the diagnosis of stroke in patients whose glucose levels are <50 or >400 mg/dL.

In practice, severe hypoglycemia is exceptionally confused with a stroke by experienced examiners. Although focal deficits (in particular hemiparesis) can occur, they are typically associated with altered consciousness or seizures. Patients are also characteristically diaphoretic. Prompt resolution after dextrose administration is diagnostic. Areas of restricted diffusion can be caused by hypoglycemic episodes, but they are generally bilateral and seen in comatose patients.[44] Hyperglycemia is common in patients with acute stroke and can be severe in diabetic patients. Yet, it is exceptionally a cause of focal neurological deficits in the absence of changes in the level of alertness.

Another reason to measure blood glucose is because hypoglycemia and hyperglycemia can worsen brain ischemia, and hyperglycemia is also associated with decreased chances of recanalization and increased risk of ICH.[45-48] Persistent hyperglycemia, rather than only baseline hyperglycemia, may be more strongly associated with these deleterious effects.[44] Although there is no proof that emergency correction of hyperglycemia can improve outcomes in acute ischemic stroke or facilitate recanalization, it appears reasonable to treat hyperglycemia (eg, aiming for a glucose level <180-200 mg/dL) as long as inducing any degree of hypoglycemia is strictly avoided.

The safety of thrombolysis in patients with severe hypoglycemia or hypoglycemia has been insufficiently studied. In a large analysis of the Virtual International Stroke Trials Registry (VISTA), only 9 patients with glucose <50 mg/dL (5 treated with rtPA) and 23 with glucose >400 mg/dL (6 treated with rtPA) were identified among a total of 9613 patients registered.[20] In these small subgroups of patients, outcomes were not affected by thrombolysis and there were no cases of sICH among those treated.

In summary, there is no convincing evidence to consider glucose disturbances as contraindications for IV rtPA administration. It is reasonable to treat with rtPA those patients with suspected stroke who present with severe hyperglycemia. We also think it is reasonable to treat patients with stroke symptoms and severe hypoglycemia who do not improve promptly after dextrose infusion.

Early Radiographic Ischemic Changes

Signs of early ischemia on the initial head computed tomography (CT) are not absolute contraindications to administering IV rtPA to patients with stroke, but this has been an area of controversy. In the 2013 AHA guidelines, IV thrombolysis is recommended if these changes are present, regardless of their extent.[1] Signs of early ischemia (loss of distinction of the definition of basal ganglia, sulcal effacement, focal swelling and mass effect, and loss of definition of the junction of gray and white matter) need to be distinguished from regions of frank hypodensity indicating established brain infarction. The aim of thrombolysis is to reperfuse brain parenchyma that is ischemic but viable (penumbra). Patients with a substantial "mismatch" between the region of relatively small core infarction and a larger area of surrounding penumbra are

patients who may benefit from rtPA, regardless of whether there is subtle radiographic evidence of ischemic changes. Although newer imaging modalities—CT and MR perfusion scans—are now available—these are more labor intensive and time consuming than noncontrast CT. Treatment that is guided by perfusion imaging has not been shown to improve outcomes of patients who receive rtPA. Thus, we do not think perfusion imaging should be routinely performed in patients prior to IV thrombolysis. In our practice, we use perfusion imaging in select patients; for example, for patients with symptoms of unclear time-of-onset such as "wake up strokes".

In contrast to the subtle radiographic signs of early ischemia, frank hypodensity on CT reflects more severe and irreversible brain injury and increases the risk of hemorrhagic transformation. If regions of hypodensity encompass more than one-third of the affected cerebral hemisphere, IV thrombolysis is contraindicated and should not be administered.[1] Judging the extent and degree of ischemia compared to infarction is not always straightforward. Even among experienced neuroradiologists and neurologists, the interrater agreement to determine whether ischemia affects less than or greater than one-third of the middle cerebral artery (MCA) territory is only moderate (κ .4).[49] Results of a post hoc analysis of the European Cooperative Acute Stroke Study (ECASS) suggested that the extent of hypoattenuation on head CT was a predictor of response to thrombolysis.[50] Patients with brain regions of hypoattenuation affecting less than or equal toonethird of the MCA territory had increased odds of favorable outcome (OR 3.43, 95% CI 1.61-7.33), whereas patients with regions of hypoattenuation encompassing greater thanonethird the MCA territory had a nonstatistically significant decrease in odds of favorable outcome (OR 0.41, 95% CI 0.06-2.70). Furthermore, and likely the explanation for the association with clinical outcomes, the risk of sICH was increased.[50]

Relative Contraindications

Advanced Age

The Activase (alteplase, rtPA) drug insert lists "advanced age (eg, older than 75 years)" as a warning in that the risks of IV rtPA may be increased. Advanced age is not considered a contraindication or exclusion in the AHA guidelines.[1] Of the patients enrolled in early clinical trials of IV thrombolysis for stroke, only about 0.5% were older than the age of 80 years.[51] The NINDS trial did not specifically exclude elderly patients, but the mean age was 69 years.[6] The upper limit for inclusion in the ECASS trials was 80 years.[52-54] Age is an independent risk factor for poor outcome in patients with ischemic stroke, regardless of whether IV rtPA is given. Short- and long-term mortality rates are twice as high in patients >85 years old compared to younger patients.[55,56]

The third international stroke trial (IST-3), an international randomized controlled trial included 1617 patients older than the age of 80 years.[57] Patients were randomized to rtPA or placebo within 6 hours of symptom onset. The primary end point was the proportion of patients alive and independent at 6 months, which was not significantly different between the 2 groups (37% of the rtPA group and 35% of the control group [$P = .181$]). In a subgroup analysis, a significant difference existed in the adjusted effect of treatment between patients >80 years and those younger, suggesting a greater benefit in the very elderly patients. In addition, a systematic review analyzing 7012 patients from 12 trials showed that patients older than80 years of age benefited similar to those younger, especially when treatment was initiated early.

Another study included 3472 thrombolyzed patients >80 years old from the SITS-International Stroke Thrombolysis Registry and compared them to control patients from the neuroprotective VISTA registry.[58] The distribution of mRS scores at 3 months was better for thrombolyzed patient both in the very elderly patients and in the younger patients.

A fairly consistent message has emerged from several observational studies: octogenarians and nonagenarians have higher mortality rates and less chance of achieving favorable outcomes than patients <80, but similar rates of sICH.[16,59-63] The lower rates of good outcomes may partly reflect the numerous comorbidities of elderly patients as well as their decreased ability to regain functions through rehabilitation. In several studies, the advanced age subgroups had statistically significantly higher rates of congestive heart failure, ischemic heart disease, and hypertension.[60,62,64,65]

In summary, existing evidence does not support the exclusion of patients older than 80 years from receiving rtPA for acute stroke. Favorable outcomes are less frequent and mortality rates are higher, but this is also true for untreated patients and it may reflect increasing comorbidities and less potential for rehabilitation. Rates of sICH are comparable. The safety profile of rtPA in the very elderly patients in most studies suggests that it is possible to appropriately select elderly patients for thrombolysis and the best evidence available indicates that the benefit received from IV rtPA is not diminished.

Mild or Improving Stroke Symptoms

Although mild or rapidly improving neurological deficits have been often listed as a relative exclusion criterion for IV thrombolysis and the FDA label does not recommend the use of Activase (alteplase, rtPA) for minor stroke symptoms, available data indicate that 20% to 30% of patients with mild or improving symptoms when thrombolysis is being considered can be affected by substantial disability at 3 months.[66-68] Mild strokes are often defined in the literature by an NIHSS score $\leq$4. However, this operational definition does not always represent minor deficits for the patient. For instance, severe monoparesis (even loss of manual dexterity for an individual depending on this ability to perform her job), gait imbalance, aphasia, or severe visual field deficit can all be disabling

deficits in isolation and in those instances the NIHSS will be $\leq$4. Furthermore, some patients with mild symptoms can have proximal intracranial vessel occlusion and they are at greater risk of neurological deterioration and persistent disability.[68,69] Patients with early improvement in deficits may also have greater chances of subsequent neurological decline.[70]

Current AHA guidelines state that IV thrombolysis may be considered in patients with mild stroke deficits and those with rapidly improving symptoms (class IIb, level of evidence C) and recommend further research to clarify the value of thrombolysis in these patients.[1] Limited evidence suggests that thrombolysis is safe and effective in patients with mild stroke and this includes the findings from the seminal NINDS trial, which actually enrolled a minority of patients with NIHSS $\leq$4.[71,72] The multicenter, prospective, randomized, and double-blind trial PRISMS is currently being conducted to evaluate whether IV Activase (alteplase, rtPA) administered within 3 hours of symptom onset improves outcomes in patients with mild stroke (defined as NIHSS $\leq$ 5).

Until more evidence becomes available, we think it is most reasonable to decide whether to administer thrombolysis based on the significance of the current deficit (regardless of whether it is improving) to the specific individual. If the patient would have limitations in his life should the deficit remain present, we opt to treat with thrombolysis. For patients with rapidly improving symptoms in whom thrombolysis is not deemed necessary but who had severe deficits initially, it is prudent to consider obtaining vascular imaging to exclude proximal arterial occlusion while the patient is still in the emergency department.

Severe Stroke and Coma

Initial severity of deficits is the main determinant of stroke outcome regardless of whether thrombolysis is administered. Severe strokes (variably defined as NIHSS >20 or >25) are typically caused by large infarctions, which may have a higher risk of hemorrhagic transformation. This is reflected in the FDA package insert for Activase (alteplase, rtPA) warning that the risks of ICH are higher in patients with severe stroke. However, there is solid evidence that IV thrombolysis is beneficial to patients with severe strokes and in fact these patients may derive the greatest benefit from the treatment.

Analysis of the NINDS data demonstrated that IV rtPA administration was associated with improved outcomes in patients with NIHSS >20.[73] In the small subgroup of patients with NIHSS >25 in IST-3, the beneficial effect of IV thrombolysis appeared magnified even when patients were enrolled within 6 hours of symptom onset.[57] Similarly, in an analysis of 9613 patients in the VISTA those with NIHSS >22 had higher odds of a better functional outcome.[20] This is not surprising. It stands to reason that patients with very severe deficits are much less likely to regain good function unless timely reperfusion occurs.

Although it is probably true that severe strokes truly carry greater risk of sICH, available evidence is not conclusive. Not all studies confirm an increased risk of hemorrhage in severe strokes.[74] Yet, reperfusion injury is the most common mechanism of symptomatic hemorrhage after thrombolysis, and it is more likely for patients with large areas of ischemia to develop this type of injury if thrombolysis achieves recanalization. That said, the chance of a favorable outcome is increased by the use of IV rtPA after accounting for that hemorrhagic risk.

Coma was a contraindication for enrollment in NINDS.[6] The rationale for the exclusion of comatose patients was to prevent the enrollment of possible stroke mimickers. Although coma is a very uncommon presentation of stroke, it can occur in patients with basilar artery occlusion for whom IV thrombolysis can be beneficial.[75] Therefore, coma per se should not be considered a contraindication for IV rtPA and should be administered when basilar artery occlusion is suspected.

Current AHA guidelines[1] do not mention severe strokes (or coma) as a relative contraindication for IV thrombolysis within 3 hours, but cautions against treating patients with NIHSS >25 beyond 3 hours, given that these patients were excluded from the ECASS-3 trial (ECASS-3 2009) and the safety of rtPA in the extended time window for these severe strokes is not proven. We fully agree that there should not be a cutoff above which thrombolysis is not indicated, at least within 3 hours from symptom onset.

Recent Major Surgery

The Activase (alteplase, rtPA) insert lists recent major surgery (eg, coronary artery bypass graft, obstetrical delivery, and organ biopsy) as a warning but not an absolute contraindication. The AHA guidelines also consider this a relative contraindication,[1] but it is not listed as a contraindication in the European Stroke Initiative Recommendations.[24] Arbitrary definitions of ''recent'' and ''major'' may be problematic and the time frames used in large studies have differed. For example, the NINDS trial excluded patients with major surgery within the previous 14 days,[6] while the ECASS trials excluded patients with major surgery within the preceding 3 months.[52,54]

The concern about administering IV rtPA to patients who have recently undergone surgery is a risk of hemorrhage within the surgical bed. While clearly a valid concern, the specific type and location of surgery and ability to control potential bleeding complications should be considered before discarding the option of administering IV rtPA. Of course the severity of stroke deficits also needs to be considered when weighing the estimated risks and benefits of thrombolysis in these cases.

There is little evidence directly supporting this contraindication. There are a few studies of patients given off-label IV rtPA for acute stroke that included small subsets of patients

with recent surgery. In one, 8 patients had undergone surgery within 3 months.[2] In this very small group, the rates of sICH (1 of 8) and poor outcome (3 of 8) were not extraordinarily high. Notably, none of these patients had systemic hemorrhage, which is the purported reason for excluding these patients from IV lysis.

In a stroke registry that included 1104 patients with rtPA-treated stroke, 13 had undergone surgery or trauma within the preceding 3 months. Of the patients with recent surgery, there were 2 systemic hemorrhages—1 after a pacemaker implantation and 1 after perianal surgery. Both of these patients received blood transfusions, but there were no major hemorrhages.[16] Additional cases indicate that bleeding in the site of the recent surgery may require invasive interventions—to achieve hemostasis or to evacuate the hematoma—and transfusion but still be compatible with favorable neurological recovery. There are sparse data regarding thrombolysis for patients with acute stroke, and undoubtedly there is some publication bias toward the reporting of cases without major complications. Each patient needs to be assessed on an individual basis. If the risk of systemic hemorrhage from IV thrombolysis is considered too high in a postoperative patient with acute ischemic stroke and suspected large vessel occlusion, endovascular therapy may be a reasonable and even potentially safer option.

Arterial Puncture of Noncompressible Vessel

Arterial puncture of a noncompressible vessel within 7 days preceding acute stroke symptoms is a warning on the Activase (alteplase, rtPA) insert and is a relative contraindication to administering IV rtPA according to AHA guidelines.[1] This scenario is extremely rare and would most likely occur in critically ill patients who had recent catheterization of the subclavian or internal jugular veins. Other situations in which noncompressible veins are accessed are during placement of pacing or defibrillation leads, dialysis catheters, pulmonary artery catheters, or transcatheter heart valve placements. A patient undergoing one of these procedures may be less functional and more ill than the general population in which IV rtPA has been studied, and the ratio of risks to potential benefits in this subgroup may be substantially different as well. 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 likely justify this exclusion criterion, although there is no existing data in the published literature to support or oppose this recommendation.

Recent Gastrointestinal or Genitourinary Hemorrhage

The 2013 AHA guidelines consider gastrointestinal (GI) or urinary tract bleeding within the previous 21 days as a relative exclusion criterion to the administration of IV rtPA for acute ischemic stroke. Active internal bleeding is an absolute contraindication. ''Recent'' GI or genitourinary (GU) hemorrhage is considered a warning on the drug label. Data pertaining to the efficacy and safety of IV rtPA for stroke in the setting of recent GI hemorrhage are extremely limited and probably subject to selection and publication biases. In 1 study, only 1 such patient (with hematuria) was treated with IV thrombolysis. This patient did not suffer sICH and had mRS of 1 at 90 days.[2]

As is the case for most relative contraindications, the potential risks and benefits of IV thrombolysis in this subset of patients most likely varies considerably according to several factors. Twenty-one days has been arbitrarily chosen and in some cases may be unnecessarily cautious. Factors to consider include the time elapsed since hemorrhage, the severity of stroke deficits, the cause and severity of the hemorrhage, and what treatments were provided for the prior bleeding episode. Patients with severe stroke deficits who have had occult GI/GU hemorrhages or diffuse or multifocal lesions susceptible to bleeding may be safer candidates for the consideration of intra-arterial stroke therapy, as the risk of systemic IV thrombolysis may be prohibitive in these patients.

Seizure at Onset

Seizure at onset of stroke symptoms with postictal residual neurological impairments is considered a relative contraindication to IV rtPA in the AHA guidelines.[1] The rationale to exclude such patients is that a focal neurologic deficit in this setting is more likely due to a stroke mimic—postictal Todd paralysis—rather than acute cerebral ischemia. These entities are not mutually exclusive, however, as seizures can rarely occur at the onset of acute ischemic stroke.[76] Notably, the risk of sICH after thrombolysis of stroke mimics is exceedingly low.[77,78] Furthermore, historical features of seizure activity at onset might be misleading.

Most of the evidence regarding thrombolysis in patients with seizures at onset comes from retrospective reviews of prospectively collected patients for registries. In total, there are almost 300 patients with seizure at onset that received IV rtPA for stroke-like symptoms described in the English literature.[77-83] Of these, sICH has been reported in only 2 patients, one with a remote history of surgical removal of a brain tumor. In a recent survey, 91% of stroke neurologists would recommend IV rtPA in patients with seizures at symptom onset.[84]

Recent Myocardial Infarction

A history of recent acute MI in the 3 months prior to stroke is a relative contraindication to IV thrombolysis according to the most recent AHA guidelines,[1] but it is not a contraindication in the European guidelines[24] or according to the drug label. It also was not an exclusion criterion in the NINDs or ECASS trials. The main concerns about giving rtPA to these patients are (1) the potential for myocardial hemorrhage predisposing to myocardial wall rupture, (2) postmyocardial infarction

Table 1. Summary of patients with brain tumors who received TPA.

	Age/Gender	Lysis Indication	NIHSS	Tumor Location	Tumor Size, cm	Tumor Type	ICH
Neil	77/M	Stroke	4	CPA	3.3 × 1.3	Acoustic neuroma	None
Neil	74/F	Stroke	13	Parafalcine	n/a	Meningioma	None
Garcia	57/M	Stroke	7	Temporal lobe	"Very small"	GBM	None
Grimm	80/M	Stroke	n/a	Temporal lobe	n/a	GBM	sICH
Hsieh	60/F	Stroke	11	Frontal skull base	2.0	Meningioma	None
Etgen	72/F	Stroke	12	Frontal	2.5	Meningioma	None
Rubenshtein	66/M	STEMI	–	Pituitary	1.8 × 1.5	Pituitary adenoma	None
Rubenshtein	77/F	STEMI	–	n/a	0.8 × 0.8	Meningioma	None
Jaffe	62/F	STEMI	–	CPA	1.0	Meningioma	None
Han	72/M	PE	–	Temporal lobe	2.5	GBM	None

Abbreviations: NIHSS, National Institute of Health Stroke Scale; ICH, intracranial hemorrhage; CPA, cerebellopontine angle; GBM, glioblastoma multiforme; sICH, symptomatic ICH; STEMI, ST-segment elevation myocardial infarction; PE, pulmonary embolism; F, female; m, male; n/a not available.

pericarditis that may become hemorrhagic, and (3) possible ventricular thrombi that could be embolized due to lysis. Myocardial wall rupture is a rare complication of MI and is becoming even less frequent as immediate intervention has become standard for ST-segment elevation myocardial infarction (STEMI). Wall rupture occurs only following transmural infarction and the highest risk is within 2 to 5 days. When patients receive IV lysis for an indication of MI, there is not much difference between the incidence of cardiac rupture among those who receive thrombolysis (1%-8%) compared to those who do not receive thrombolysis (1%-5%).[85]

Data on thrombolysis for stroke in the setting of recent MI are very scarce and most of what is reported are case reports, undoubtedly subject to publication bias. Case reports describe 5 elderly women who developed cardiac rupture and hemopericardium after receiving rtPA for stroke. Only one had a well-documented recent MI—a 93-year-old woman who presented with concurrent STEMI.[86] Another had coronary artery bypass grafting surgery 16 days before, and another had dyspnea several days prior to presentation with nonspecific changes on electrocardiogram.[87] Of the 5, 4 were fatal.[86-88] Sudden hypotension, occurring approximately 30 minutes to 2 hours after completion of rtPA, should raise suspicion for this complication.

Following an MI, myocardial fibrosis and scarring are complete by the sixth or seventh week. Based on this, it has been suggested that the time after MI to be considered a contraindication for IV thrombolysis should be shortened to 7 weeks.[85] The type of MI, in addition to the severity of stroke symptoms, should also factor in the decision-making process. Patients with non-STEMI, particularly those that do not involve the anterior cardiac wall, may be at lower risk of this complication, but there are no solid data to estimate risks or guide treatment in this subset of patients.

Central Nervous System Structural Lesions

The presence of intracranial neoplasm, AVM, or aneurysm is a contraindication per the AHA guidelines and the drug label. The risks of administering IV rtPA to patients with stroke having intracranial neoplasms are not well known. Published literature is limited to case reports, most of which were "successful."[16,89-91] The cases with sufficient details reported are summarized in Table 1. Only 1 patient who had an ICH has been published, a patient with a temporal lobe glioblastoma multiforme that was not known and manifested as mild mass effect on the original CT.[92] In addition to the detailed case reports, several others have been included in larger reports of patients who received off-label rtPA for stroke. For example, IV thrombolysis has been administered without sICH to 3 additional patients with meningiomas, 1 with cholesteatoma, and 1 with paranasal tumor.[16] There are also several reports of patients with intracranial neoplasms (meningiomas and pituitary adenoma) who received IV thrombolysis for STEMI or pulmonary embolism.[93-95] Notably, despite a higher dose of lytics and with concomitant systemic anticoagulation, these patients did not have ICH. The possibility of publication bias again should be recognized, but these cases illustrate that IV thrombolysis can be safe in some patients with intracranial neoplasms, perhaps particularly so if the neoplasm is a relatively small and extra-axial in location.

The safety of IV thrombolysis in patients with unruptured intracranial aneurysms has been reported in case reports or retrospective case series (Table 2). The rates of sICH have not been statistically different between those with aneurysms (0%-13%) compared to those without (1%-10%), but sample sizes are small.[96-98,100] There have been no cases of aneurysm rupture induced by IV rtPA reported in the English literature. Although the probability of selection bias and publication bias need to be considered, these series suggest that IV rtPA can be safely administered to patients with unruptured incidental intracranial aneurysms. It should be noted there is a lack of data on the risk of ICH in patients with large or giant aneurysms, which may be associated with higher risk.

Dementia

Dementia was not listed as an exclusion criterion in most major thrombolysis trials and is not mentioned as a contraindication for rtPA in current acute stroke guidelines. Still, the

Table 2. Summary of Intracranial Hemorrhage Rates in Reported Patients With Intracranial Aneurysms Who Received Intravenous Thrombolysis for Stroke.

	Patients With Aneurysm, n	sICH Aneurysm, n (%)	sICH no Aneurysm, n (%)	Any ICH Aneurysm, n (%)	Any ICH No Aneurysm, n (%)
[96]	22	0 (0)	10 (4.7)	3 (13.6)	41 (19.1)
[97]	8	1 (12.5)	6 (3.7)	n/a	n/a
[98]	10	1 (10)	1 (1.1)	2 (20)	9 (9.5)
[99]	8	1 (12.5)	n/a	3 (37.5)	63 (33.9)

Abbreviations: ICH, intracranial hemorrhage; sICH, symptomatic ICH; n/a not available.

question whether IV rtPA is safe and effective in patients with dementia having acute ischemic stroke often arises in routine clinical practice. Baseline dementia is associated with lower utilization of rtPA,[99] and this is because of the perception that it raises the risk of hemorrhage and is unlikely to be beneficial. [101] Actual data, albeit limited, do not support those contentions.

Unsurprisingly, dementia is associated with worse outcomes after stroke[102,103] even among patients who receive thrombolysis.[103] However, dementia per se does not appear to increase the risk of death (at discharge, 30 days, or even 1 year) or institutionalization and is only associated with a trend toward greater functional disability when the analysis is appropriately adjusted for cofactors.[103] Similarly, dementia did not significantly increase the risk of ICH compared with matched controls in 2 studies analyzing large patient cohorts.[99,104]

Consequently, it appears to be safe to administer thrombolysis to patients with acute stroke and preexistent dementia. Whether thrombolysis is effective to improve functional outcomes in these patients remains to be elucidated. Therefore, the decision whether to administer rtPA needs to be individually judged depending on the previous level of function and the severity of the stroke deficits.

Declaration of Conflicting Interests

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