Debunking 7 Myths That Hamper the Realization of Randomized Controlled Trials on Intra-Arterial Thrombolysis for Acute Ischemic Stroke

Alfonso Ciccone, MD; Luca Valvassori, MD; Roberto Gasparotti, MD; Francesco Scomazzoni, MD; Elena Ballabio, MD; Roberto Sterzi, MD

Background and Purpose—Although intravenous (IV) thrombolysis is the standard treatment for patients with ischemic stroke occurring within 3 hours from symptom onset, a few interventional neuroradiologists have been treating this category of patients by an intra-arterial (IA) route for >25 years. However, evidence is still required to support the clinical feeling that IA treatment, which needs longer time and greater complexity, leads to a better outcome. Therefore, the objective of the present review was to analyze beliefs and myths underlying the selection of patients for IA thrombolysis.

Methods and Results—We identified and debunked the following myths on IA thrombolysis: (1) IA thrombolysis works better than IV because it achieves higher recanalization rates; (2) IA thrombolysis works better than IV after the 3-hour window; (3) IA thrombolysis works better than IV in vertebrobasilar stroke; (4) carotid duplex, transcranial doppler, CT angiography, or MRA should be used to screen for major vessel occlusion treatable with IA thrombolysis; (5) to be treated with IA thrombolysis, patients should be selected with diffusion/perfusion MRI; (6) IA thrombolysis should be used as a “rescue” therapy for IV thrombolysis; and (7) the efficacy of IA thrombolysis depends on the thrombolytic agent or the device used.

Conclusion—Evidence on acute stroke management with IA thrombolysis is scant. Therefore, neither clinicians nor patients have enough information to make truly informed decisions about the most appropriate treatment. Only randomized controlled trials can clear uncertainties about the possible superiority of IA over IV thrombolysis. Regrettably, case series on IA treatment have limited the organization of such trials and have only favored the spread of myths. (Stroke. 2007;38:2191-2195.)

Key Words: cerebrovascular accident ■ cerebrovascular disease ■ interventional neuroradiology ■ ischemia ■ neuroradiology ■ randomized controlled trials ■ stroke ■ thrombolysis ■ systematic reviews

Sophisticated technological resources in the neurosciences have grown incredibly in recent decades and many advanced stroke centers can now obtain information about the occluded vessel, the ischemic penumbra, and irreversible brain damage in the first hours from stroke onset. However, technological development has not always been followed by similar growth in evidence of its role in patient management and selection to therapies like intra-arterial (IA) thrombolysis, which is where high technology, manual dexterity, and clinical decisions merge.

The authors of the present review witnessed this gap between evidence and technology, having a leading role in an ongoing multicenter randomized controlled trial (RCT), named Synthesis,1 comparing IA and intravenous (IV) thrombolysis for acute ischemic stroke. Like in other RCTs on acute ischemic stroke, the trial proponents encountered many practical and organizational difficulties that limited participation. Some theoretical issues, raised while contacting centers in Europe, prompted the authors to identify 7 myths worth debunking on the basis of today’s evidence.

The 7 Myths

IA Thrombolysis Works Better Than IV Thrombolysis Because It Achieves Higher Recanalization Rates

Overall, the recanalization rates reported in the literature are higher with IA than IV thrombolysis. In angiographic controlled trials of IV recombinant tissue plasminogen activator (rt-PA), partial or complete recanalization of middle cerebral arteries was reported in approximately one-third2–4 compared...
with two-thirds of cases with IA recombinant pro-urokinase and IV heparin in the PROACT II trial.\textsuperscript{5} In vertebrobasilar occlusion, recanalization rates are reported to be 53% for IV therapy and 65% for IA.\textsuperscript{6}

However, inferences from this information should be drawn with caution, because there is no direct comparison between the 2 approaches in single RCTs and because recanalization after a stroke and clinical outcome do not necessarily correlate, probably because other factors such as depth and duration of the ischemia, baseline stroke severity, collateral circulation, lesion location, and lesion volume are important in determining clinical outcome. Recanalization may be followed by different clinical scenarios, including improvement, any improvement or neurological worsening, and death caused by reperfusion brain edema\textsuperscript{7–9} and intracerebral hemorrhage.\textsuperscript{10} Approaches based on recanalization as a primary outcome measure have therefore drawn criticism.\textsuperscript{11} Arterial reopening at angiograms is probably important and, it is hoped, linked to a better outcome, but obviously the final clinical status must be evaluated in the patient and not only in the patient’s vessels.

### IA Thrombolysis Works Better Than IV after the 3-Hour Window

The fact that data on IV thrombolysis beyond the 3 hours are still inconclusive,\textsuperscript{12} whereas IA therapy was claimed to be effective within 6 hours from symptoms onset has led to the myth that IA thrombolysis is more effective than IV thrombolysis after the 3-hour window. However, the Cochrane meta-analysis\textsuperscript{10} of the 2 RCTs on IA thrombolysis (PROACT\textsuperscript{13} and PROACT II\textsuperscript{14}) shows that the risk reduction of being dead or independent with IA treatment has a wide confidence interval (Table), which included the possibility that the benefit was very substantial or negligible (treatment with clinical improvement even beyond the 6-hour window\textsuperscript{6} of IA thrombolysis for carotid stroke (even if early treatment onset proved to be the most important factor for successful IA thrombolysis in acute vertebrobasilar occlusion too\textsuperscript{6}) has led to the idea that vertebrobasilar artery stroke is more suitable for IA thrombolysis than carotid stroke.\textsuperscript{6,14} Moreover, IA thrombolysis for vertebrobasilar stroke seems to be life-saving, as opposed to IV r-tPA, which reduces long-term disability but does not change mortality\textsuperscript{10} (but data on IV thrombolysis come mainly from carotid stroke\textsuperscript{15}). The point is that in this case, too, we do not know whether IA is more convenient than IV thrombolysis.\textsuperscript{15} The 2 approaches have never been compared in a RCT, in either vertebrobasilar or carotid stroke.

Recently Lindsberg and Mattle\textsuperscript{6} published a systematic analysis on published case series reporting the outcome of basilar artery occlusion after IA (344 patients) and IV (76 patients) thrombolysis. Making due allowance for the potential biases involved in such indirect comparisons, there were no differences between the effects of the 2 approaches and the authors conclude that a RCT is needed to compare them.

After the Cochrane review,\textsuperscript{10} another RCT was published on IA thrombolysis\textsuperscript{16} for vertebrobasilar stroke. Sixteen patients with stroke and angiographic evidence of posterior circulation occlusion were randomized to be treated within 24 hours after stroke onset with IA urokinase (UK) or control (no thrombolysis). This RCT, which was stopped before reaching the 200 patients planned on account of slow recruitment and withdrawal of UK from the market, was definitely underpowered, and the small difference in outcome between the 2 groups may be explained by chance. Moreover, as the authors themselves point out,\textsuperscript{16} one potential criticism of this study was the requirement that patients underwent angiography before randomization. A better option would have been to randomize patients before angiography and test the effectiveness of the complete IA approach, of which angiography and its associated risks are an integral part.

### Carotid Duplex, Transcranial Doppler, CT Angiography, or MRA Should Be Used to Screen for Major Vessel Occlusion Treatable With IA Thrombolysis

This myth is based on the assumption that IA is more effective than IV thrombolysis in major vessel occlusion and that it is essential to identify a major vessel occlusion with a noninvasive diagnostic examination before angiography for the selection of patients. Although no RCTs have compared the 2 approaches, an indirect comparison shows higher recanalization rates for major vessel occlusion with IA than IV thrombolysis, as already mentioned in relation to myth 1. However, looking at clinical outcome, subgroup analyses in the NINDS trial showed a benefit of IV thrombolysis for each subtype of ischemic stroke (small vessel, cardioembolic, large vessel),\textsuperscript{17} and these observations were consistent with
subsequent reports. Allocating treatment of stroke patients to IV rt-PA on the basis of the presumed stroke mechanism therefore may be unnecessary. Such testing may in fact cause delays that could compromise the efficacy of treatment.

Other authors reported that neither IV rt-PA nor IA thrombolysis using rt-PA or UK within 6 hours of onset improved outcome in cases of carotid T occlusion (internal carotid artery occlusion that extends from the carotid siphon into the proximal segments of the middle and anterior cerebral arteries—the worst case of supratentorial ischemia), but Georgiadi et al reviewed this concept in their series of 42 consecutive patients with acute T occlusion. They reported recanalization of middle cerebral arteries with better clinical outcome in 12 of 18 patients treated with IV rt-PA within 3 hours of stroke onset and concluded that the exact knowledge of the site of occlusion is not necessary before applying thrombolytic therapy within the 3-hour window, because the presence of carotid T occlusion should not alter management. Cases of carotid T occlusion successfully treated with IA thrombolysis have been reported, but others showed that recanalization and good clinical outcome can be achieved by IV thrombolysis too, with a rate comparable to that of the IA approach.

Another justification for a non-invasive examination to detect major vessel occlusion is to avoid the risk of unnecessary angiography before IA thrombolysis in patients without large-vessel occlusion. However, different authors found a significant association between the neurological examination in terms of NIHSS scores and the presence and location of a vessel occlusion. Therefore, not only does the identification of the site of the occlusion with time-consuming, noninvasive diagnostic examinations not modify the patient management but also the clinical examination is an accurate and probably adequate tool to identify whether there is a major vessel occlusion.

To Be Treated With IA Thrombolysis Patients Should Be Selected With Diffusion/Perfusion MRI
The efficacy of IV rt-PA within 3 hours after onset of symptoms has been proved only for patients selected with CT, but the role of neuroimaging in the selection of patients for thrombolysis has changed in the past decade. The need to identify patients with salvageable tissue beyond the 3-hour window favored the introduction of new technologies like diffusion/perfusion MRI. Although several imaging modalities can identify the ischemic penumbra, the most practical is MRI, which shows up any perfusion-weighted imaging and diffusion-weighted imaging (PWI-DWI) mismatch. According to this model, the diffusion abnormality represents the irreversibly injured tissue, whereas the region with perfusion abnormality but no diffusion lesion (the mismatch region) identifies hypoperfused tissue that is thought to be potentially salvageable tissue at risk of infarction. PWI-DWI mismatch, visible in 80% to 86% of stroke patients examined in the acute phase, is interpreted as a predictor of infarct growth into the area of the initial perfusion abnormality and could represent the region salvageable with thrombolytic therapy. It has been suggested that in patients with tissue at risk as defined by MRI, it is safe and effective to expand the time window for IV-tPA up to 6 hours. The DIAS (Desmoteplase In Acute Stroke) trial, which recruited 102 patients in a 3- to 9-hour window on PWI-DWI mismatch selection criteria with the aim of testing the efficacy of IV desmoteplase, showed that treated patients had favorable and dose-dependent radiological and clinical treatment responses and a low hemorrhage risk. However, despite the potential usefulness of this approach, the simple PWI-DWI mismatch model does not optimally define the ischemic penumbra. According to Rivers et al it is still not clear which “semiquantitative” perfusion parameter most closely identifies final infarct volume, cerebral blood flow or mean transit time, because patients without PWI-DWI mismatch are just as likely to have lesion growth as those with mismatch and therefore should not be excluded from acute stroke treatment. PWI does in fact have a tendency to overestimate tissue at risk because of inclusion of regions of benign oligemia, where there is mild hypoperfusion or normal perfusion, in the visible zone of perfusion abnormality. However, DWI lesions may contain viable tissue.

At present, we cannot conclude that patients with acute stroke selected for thrombolysis with MRI have better outcomes than patients selected on simple CT criteria. It is still not clear which is the best perfusion imaging method for reproducibly quantifying the relationship between infarct and salvageable tissue. Until ongoing trials testing the predictive value of DWI-PWI MRI for favorable response to thrombolytic agents are concluded, it seems unreasonable to exclude patients from treatment if MRI do not show ischemic penumbra, and the adoption of diffusion/perfusion MR for selecting patients for thrombolytic therapy should be set out in research protocols.

IA Thrombolysis Should Be Used as a “Rescue” Therapy for IV Thrombolysis
Combined therapy is based on the idea of combining the advantages of IV thrombolysis (speed of initiation, ease of use, and widespread availability) with those of an IA approach (titrated dosing, mechanical aids to recanalization, and possible superior and earlier recanalization) allowing for early IV treatment while the resources to deliver IA therapy are organized.

The Cochrane review identified only one study on the combined approach, the EMS Bridging Trial, a double-blind, randomized, placebo-controlled, pilot study comparing combined IV plus local IA rt-PA with local IA rt-PA alone. Clinical outcomes were not improved despite a higher recanalization rate with combined IV and IA therapy, but inferences are obligatorily limited because of the small number of patients.

Recently, several case series have been published on the combined approach. The main one, funded by the NINDS, reported intracranial hemorrhage rates and clinical outcomes at 3 months in 80 subjects similar to those in the NINDS IV rt-PA–treated subjects. The authors concluded that an RCT of standard IV rt-PA compared with a combined IV and IA approach is needed.

The problem with the combined-therapy approach is that it is based on the assumption, yet to be proved, that IA thrombolysis may add some benefits compared with IV treatment, without increasing the risk of hemorrhagic transformation. Second, it exposes all the patients to the angio-
The Efficacy of IA Thrombolysis Depends on the Thrombolytic Agent or the Device Used

Retepase, streptokinase, UK, pro-UK, rt-PA, and lyoplasminogen have been used for IA thrombolysis. When IA UK and IA rt-PA were compared,38 recanalization time and recanalization rates were not significantly different. These results were confirmed years later, also on clinical outcomes.39 Another study comparing IA retepase and IA UK found no significant differences in recanalization, outcome, mortality, and intracranial hemorrhage.40

The picture is more complex if IA devices and recanalization strategies are considered. Mechanical maneuvers are meant to accompany (or even substitute) drug injection with the theoretical goal of making recanalization faster and more complete but has the potential drawback of increasing risks attributable to manipulation of vessels. A line can be drawn between disaggregation/dislocation/tunneling on one side and retraction/aspiration on the other; the former aims at helping the intrinsic or pharmacological fibrinolytic action through mechanical expansion of the surface of the thrombus exposed to blood and is based on the assumption that this goal outweighs the risks related to migration of distal fragments, and the latter is aimed at preserving the integrity of the thrombus, also preventing peripheral migration, to attempt thrombus extraction in one or in the fewest possible maneuvers.

If the devices available to attempt these maneuvers are considered, the choices expand further. Only for mechanical retraction, 2 devices have been specifically tested in clinical but not RCTs41 and are already available on the market (Merci, Concentric Medical, and Catch, Balt). Mechanical disaggregation has long been performed with guidewires and microcatheters.42 Sophisticated instruments for thrombus disaggregation (in some cases associated with aspiration) based on various physical forces such as ultrasound,43 laser-generated photoacoustic stimulus, and rheolytic vortex produced by high-pressure currents have been developed and tested in small safety pilot clinical trials, with promising results.43,44 The literature is rich in anecdotal reports of successful off-label use, for cerebrovascular stroke, of devices intended for other purposes or for the same purpose in other districts (snakes, angioplasty balloons or stents, and catheters for thrombus suction).45–49 At this stage, the procedural choices of the interventional neuroradiologist seem to depend more on the type of occlusion, circumstances, and experience than on a specific device, and planning RCT on a specific device seems to satisfy the companies that produce it more than the users and, most important, the patient. No strategy, in terms of drugs and devices used in the same procedure, has so far proved more successful than others.

Conclusions

The available trials leave uncertainties, and there are no data on the comparison of IA thrombolysis with IV rt-PA. The recently published guidelines for the early management of patients with ischemic stroke, from the Stroke Council of the American Heart Association/American Stroke Association,50 stated: “At present, no evidence is available to show that intra-arterial thrombolysis is superior to intravenous treatment. Therapy should not be withheld from patients who are eligible for treatment with intravenous thrombolysis so that medications can be administered intra-arterially, except in the setting of a comparative research clinical trial.”

Hundreds of stroke patients treated with IA thrombolysis have been reported in scientific journals and many others are discussed at conferences. These are all case reports or case series that help increase knowledge, improving technical procedures and the definition of the indications for IA thrombolysis, but they are inadequate to prove the effectiveness of treatment. Regrettfully, case series on IA treatment have limited the organization of RCT and have favored the spread of myths.

Centers with experience in IA thrombolysis are invited to take part in an RCT to answer a clinically and scientifically relevant question, ie, to verify the safety and effectiveness of IA thrombolysis in stroke, to standardize the IA treatment, at present largely based on emotions and circumstances, and to overcome the belief that IA thrombolysis remains a game for few rather than a therapy to test against the burden of stroke.

Disclosures

The authors of the present review are involved in an ongoing multicenter randomized controlled trial, named Synthesis, comparing intra-arterial and intravenous thrombolysis for acute ischemic stroke. A.C. is the principal investigator; L.V., R.G., F.S., and R.S. are members of the steering committee; and E.B. is the clinical monitor.

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