

# Technology Insight: recanalization with drugs and devices during acute ischemic stroke

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## SUMMARY

Revascularization therapy is pivotal to saving ischemic brain from infarction. Two major randomized trials of intravenous thrombolytic therapy have established clear clinical benefit, especially for strokes caused by small-vessel occlusion. Ischemic stroke caused by large-vessel intracranial occlusion carries higher morbidity, however, and intravenous thrombolytics are less capable of opening these large vessels. This observation makes a case for delivering thrombolytics directly into the clot, or simply removing the clot mechanically. Intra-arterial thrombolytic drugs have been shown to be effective for treating middle cerebral artery occlusions in a major randomized trial. In the past 2 years, a family of mechanical thrombectomy catheters designed to remove rather than dissolve the offending clot has received FDA clearance. Such devices offer alternative therapy to patients who cannot receive thrombolytics, and can also be used in combination with thrombolytics to safely restore cerebral perfusion. Mechanical techniques have not been directly compared with intra-arterial thrombolytic strategies, but these devices might be superior to thrombolytics within vessels with particularly high clot burden, such as the carotid terminus and the basilar artery. Comprehensive stroke centers are currently available in major metropolitan areas to treat stroke via intra-arterial means, and are likely to become 'hubs' to 'spoke' hospitals that are credentialed as primary stroke centers. This design will allow any patient timely access to state-of-the-art stroke treatment tailored to their needs.

**KEYWORDS** intra-arterial thrombolytics, intravenous thrombolytics, ischemic stroke, mechanical embolectomy, MERCI trial

## REVIEW CRITERIA

The author searched the PubMed database from 1966 through 2006 for randomized trials of intravenous and intra-arterial thrombolytic treatment, as well as trials using mechanical embolectomy.

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## INTRODUCTION

Stroke is a substantial cause of morbidity and mortality, being the third leading cause of death in the US. It is estimated that around 750,000 cases of stroke occur each year, and survivors constitute the majority of disabled people nationally. A new optimism has emerged over the past decade, however, as we have witnessed the advent of the first FDA-approved treatment for stroke (in 1996) and more recently, in 2004, the first FDA-cleared device for stroke therapy. The issue of how and when to apply each method of therapy is an evolving clinical science. In view of the recent advent of mechanical techniques to open cerebral vessels during acute stroke, this review will focus specifically on intra-arterial treatments, and will propose a strategy of stroke triage that can be employed by institutions with either limited or advanced resources.

## BACKGROUND

Endovascular stroke therapy is directed at the timely revascularization of large intracranial vessels. The term 'large vessel' usually applies to vessels that are larger than 1.5–2 mm. These vessels serve as the main conduits for cerebral blood flow, and are distinct from small vessels, which are typically in the 100–500  $\mu\text{m}$  range. Large intracranial vessels include the intracranial carotid artery (ICA), the middle cerebral artery (MCA), the anterior cerebral artery, the basilar artery, and the vertebral arteries. Large-vessel strokes are associated with a particularly high level of morbidity, and they pose an independent risk of poor neurological outcome.<sup>1</sup> The risk of death from MCA occlusions ranges from 25% to 74%;<sup>2,3</sup> the corresponding figures are 22–53% for ICA occlusions,<sup>4,5</sup> and 30–75% for basilar occlusions<sup>6,7</sup>—mortality approaches 100% if the basilar artery remains occluded.<sup>8,9</sup> Small-vessel strokes carry considerably less mortality, respond well to intravenous recombinant tissue plasminogen activator (rtPA) therapy, and are inaccessible by mechanical endovascular therapies.

Cerebral tissue is highly sensitive to ischemia, and complete absence of cerebral blood flow will cause irreversible infarction within 4–10 minutes. In ischemic stroke, blood flow within the irrigated territory typically does not cease as it does in global ischemia; a gradation in blood flow exists from the most poorly perfused tissue to the least affected areas. Depending on the magnitude and duration of low blood flow, the tissue will experience one of three fates: first, if the flow is low enough, the tissue will infarct; second, if the flow is low enough to impair tissue metabolism but not cause infarction, the tissue can be revived if flow is restored; or third, if flow is sufficiently high, but still reduced compared with the normal situation, the tissue will suffer no ill consequence. Neural tissue in the first category is termed ‘core’, to indicate its central location in the developing infarct. Tissue within the second category, known as ‘penumbral’ tissue, ceases function at the onset of ischemia, and if perfusion is not restored this tissue will eventually infarct, typically over a course of hours to days. In clinical stroke, patients typically develop a core infarct within minutes to hours, yet the penumbra is present for hours following the onset of ischemia and therefore might be salvaged if the intracranial vessel is opened. Saving the penumbral tissue is the focus of all ischemic stroke therapy.

#### MITIGATING STROKE: THROMBOLYTIC REVASCLARIZATION THERAPY

Revascularization therapy lies at the heart of the process of saving penumbral tissue from infarction. Reperfusion therapies involve the application of an antithrombotic or thrombolytic drug, or mechanical techniques to physically remove the clot from the occluded vessel.

Two human clinical trials have provided evidence that thrombolytic therapy improves neurological outcomes. The first was the National Institute of Neurological Disorders and Stroke (NINDS) rtPA trial, in which patients were randomized to receive intravenous rtPA (0.9 mg/kg, 10% bolus followed by 90% infused over 1 hour) or placebo within 3 hours of symptom onset.<sup>10</sup> On the basis of various functional neurological outcome assessments at 3 months, patients who received rtPA were 30–50% more likely to have a good neurological outcome than were controls, but mortality was unaffected by treatment. Although there was no confirmation of vascular recanalization performed in this landmark trial, the mechanism of action of the drug and significant

clinical benefit supports the hypothesis that rtPA was beneficial in restoring blood flow and mitigating the amount of brain injury.<sup>4,8,11,12</sup> Several other placebo-controlled studies involving intravenous thrombolytics have been performed with longer time windows (typically up to 5–6 hours), and when the results of all trials are combined, rtPA appears to be effective up to 4.5 hours following symptom onset.<sup>13</sup> Currently, intravenous rtPA is only used if it can be given within 3 hours of symptom onset.

Subsequent studies using transcranial Doppler ultrasound have confirmed that rtPA opens intracranial vessels, and recanalization is enhanced by the presence of ultrasound energy delivered to the clot.<sup>14</sup> Even with the application of ultrasound, however, the MCA only opens around 16% of the time, probably because the drug does not achieve a high enough concentration for large clots when delivered intravenously. Rates of vascular recanalization in other vessels such as the basilar artery or the ICA terminus are likely to be much lower, because of higher clot burdens. In the NINDS study, patients who received rtPA were 10 times more likely to suffer a clinically significant intracranial hemorrhage compared with placebo controls (6% vs 0.6%).<sup>10</sup> Intracranial hemorrhage following ischemic stroke probably occurs when ischemic tissue is reperfused. As some vessels spontaneously recanalize, some patients will experience an intracranial hemorrhage as part of the natural history of the disease, and it is likely that the risk of hemorrhage depends on the timing of reperfusion. If a thrombolytic drug is circulating at the time of reperfusion, the hemorrhage rate is expected to increase even more. This potentially devastating side effect of rtPA has slowed the adoption of rtPA as a treatment for acute ischemic stroke.

The second major study of reperfusion therapy in acute ischemic stroke was the Prolyse® (Imarx Therapeutics, Inc, Tucson, AZ) in Acute Cerebral Thromboembolism (PROACT-II) trial.<sup>2</sup> Patients with acute MCA occlusions were randomized to intra-arterial delivery of an investigational plasminogen activator (prourokinase [pro-UK]) or saline placebo within 6 hours of stroke symptom onset; all patients received intravenous heparin. The primary outcome was neurological function at 3 months using the modified Rankin Scale (mRS). Overall, 40% of patients who received pro-UK had a good neurological outcome (defined as mRS ≤2) compared with 25% who received placebo ( $P=0.04$ ). Recanalization was

observed in 66% of pro-UK treated patients and 18% of placebo patients ( $P < 0.001$ ). The symptomatic intracranial hemorrhage rate was 10%; this was 4% higher than the rate reported in the NINDS rtPA trial. This higher rate of hemorrhage is probably related to two mechanisms: first, local delivery of drug directly into the occluded vessel leads to a higher intravascular plasminogen activator concentration, thereby increasing the risk of bleeding during reperfusion; and second, the rate of reperfusion is likely to be higher for MCA occlusions if the drug is instilled directly into the clot than if it is given intravenously, and hemorrhage risk depends to some extent on recanalization. This study established a close link between recanalization and clinical outcome, and established a method to restore brain perfusion for MCA occlusions. The FDA requires an additional study before it will consider approving the drug, however, so there are as yet no FDA-approved plasminogen activator drugs for intra-arterial delivery. Nevertheless, endovascular surgeons use rtPA or urokinase for this procedure, and until mechanical thrombectomy became approved, intra-arterial thrombolysis was the prevailing method for opening large vessels during stroke beyond the 3-hour window.

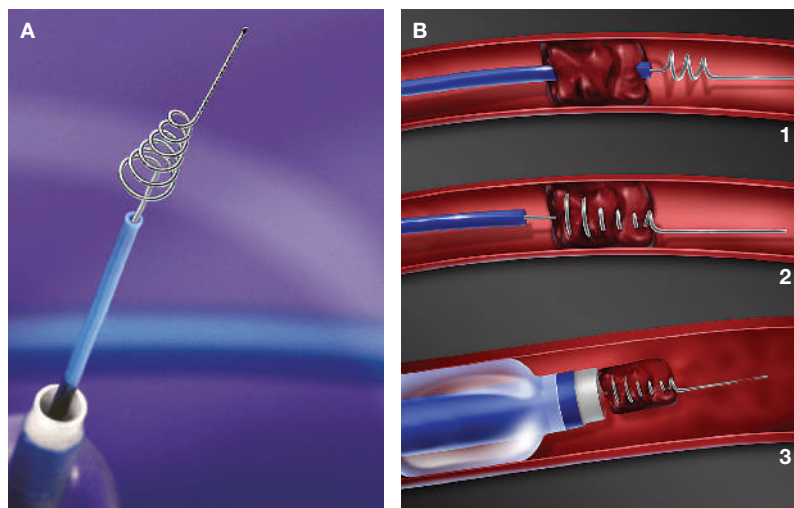
To provide better delivery of acute stroke therapy to stroke patients within the US, the concept of the primary stroke center was established.<sup>15</sup> Such centers have organized stroke teams that can respond to acute stroke patients and administer intravenous rtPA according to protocol. The designation of primary stroke center follows credentialing by an accrediting agency for a fee, and the center is required to keep quality assurance data on stroke patients, including how many rtPA-eligible patients receive rtPA, along with other assessments of quality. Establishing a primary stroke center allows emergency medical service referrals to bypass hospitals in the immediate proximity to travel to the nearest credentialed stroke center, so that precious time is not lost. Recently, the concept of comprehensive stroke centers was advanced to indicate those centers that not only qualify as primary stroke centers but also have endovascular capability.<sup>16</sup> Although there is as yet no official credential for such centers, between 150 and 200 such hospitals already exist. As there are more primary stroke centers than comprehensive stroke centers, stroke care in the US might evolve towards a system of initiating rtPA treatment in eligible patients at the

primary center, then rapidly transferring the patient to the nearest comprehensive center for intervention if relevant.<sup>17</sup>

This combination of treating with intravenous rtPA followed by intra-arterial delivery of more rtPA if a large-vessel occlusion is found on angiography has been the focus of past and current research. The Emergency Management of Stroke bridging trial<sup>18</sup> and the Interventional Management of Stroke Study part I (IMS-I)<sup>19</sup> and IMS-II<sup>20</sup> studied the feasibility and safety of administering an accelerated dose of intravenous rtPA (0.6 mg/kg; 10–15% bolus, and the remaining 85–90% infused over 30 minutes) followed by conventional angiography, with up to 0.3 mg/kg rtPA administered intra-arterially if a large-vessel occlusion is found. The IMS-I trial reported a recanalization rate of 56% in a range of intracranial vessel occlusion locations. Although no control arm was used in this trial, this rate is likely to be superior to that seen by natural history (estimated at 18% recanalization at 2 hours following initial angiography<sup>2</sup>). The final results of the IMS-II trial have not yet been published, but preliminary data have been presented.<sup>20</sup> If further study shows this strategy to be beneficial (see below), primary stroke centers will need to modify the dose of rtPA on the basis of the presence or absence of a large-vessel occlusion. This distinction is difficult to make clinically, but is made easier by performing CT angiography at the time of the initial stroke.

#### MITIGATING STROKE: MECHANICAL REVASCULARIZATION THERAPY

Although thrombolytic therapies have been shown to be efficacious in acute ischemic stroke, there are several reasons to consider a direct mechanical strategy, whereby the offending blood clot is physically removed rather than dissolved. Thrombolytic drugs carry the risk of systemic and intracranial hemorrhage, which can be life-threatening (approximately 50% mortality<sup>10</sup>). Many patients have contraindications to plasminogen activators, such as recent surgery, trauma or bleeding disorders. Finally, intravenously administered rtPA is only marginally effective at restoring perfusion for large-vessel occlusions<sup>4,14</sup>—the types of stroke that carry the highest mortality and morbidity. Removal of the intravascular clot carries the intuitive appeal that vascular patency is restored and the offending clot is removed from the body so that it cannot become dislodged and block a more distal



**Figure 1** The mechanical clot retriever. **(A)** Model X6, which was used in the Mechanical Embolus Removal in Cerebral Ischemia (MERCi) trial. The device is a flexible, tapered NiTiNol wire that is advanced through the center of a microcatheter. **(B)** The microcatheter is advanced across the intravascular clot after first traversing the clot with a 0.014 in. (0.36 mm) guide wire. The device is then extended out beyond the clot (1), then within the clot (2) to fully ensnare the clot. The balloon on the proximal guide catheter is inflated to arrest flow in the vascular segment to prevent upstream embolization (3), then the device and the microcatheter are withdrawn into the guide catheter while applying suction. Following aspiration, the balloon is deflated and flow restored.

vessel. Depending on the technical expertise of the physician and the method used, recanalization could potentially occur much more quickly compared with the relatively slower enzymatic dissolution of the clot.

The first mechanical thrombectomy was performed by craniotomy and arteriotomy in 1954,<sup>21</sup> and a relatively large series of 20 patients was reported on in 1985.<sup>22</sup> These observations established physical evidence of a thromboembolic mechanism in acute ischemic stroke. After the advent of routine coronary angiography and coronary angioplasty, interest grew in endovascular clot removal. Initial attempts were made using a Fogarty catheter to retrieve clot, but arterial dissection and creation of cavernous carotid fistulae raised safety concerns.<sup>23</sup> Catheter techniques from a transfemoral approach using a goose-neck snare<sup>24</sup> or the Neuronet device<sup>25</sup> showed that clot retrieval was possible.

NiTiNol is an alloy of nickel and titanium that has several useful properties for catheter-based medical devices. The alloy is stronger than other flexible metals, and has the property of memory whereby once it is annealed in a particular shape it retains that shape even after marked deformation,

such as when straightened within a microcatheter. This allows the device (Figure 1) to be extruded from a linear catheter, and, once extended outside the catheter, to regain its tapering helical shape. Stiffness is a function of the exact composition of the alloy, so engineers can create a device that is strong enough to engage the clot, yet flexible enough to remove it without traumatizing the intracranial vessel.

The device shown in Figure 1 was invented by Pierre Gobin, MD, an endovascular surgeon at University of California, Los Angeles, and later refined and manufactured by Concentric Medical, Inc. of Mountain View, CA. The device was first used as a tool to remove foreign material within a cerebral vessel, like a misplaced coil during aneurysm treatment. Once cleared by the FDA for that indication, endovascular surgeons gained some experience with the device for clot removal during large-vessel ischemic stroke. This led to a company-sponsored, FDA-approved study of the device for opening cerebral vessels during acute stroke.

For an investigational drug, the preferred trial design to achieve FDA approval is a randomized, placebo-controlled trial, but the approval process for medical devices is different.<sup>26</sup> Specifically, the FDA rules for device approval focus on safety and allow non-clinical surrogates for efficacy. The FDA, therefore, is a gatekeeper to prevent unsafe devices from being marketed, but the ultimate question of whether the device actually works to improve clinical outcome is left to clinician scientists to resolve. Study of the clinical efficacy of a novel thrombectomy device at the time that the trial was being designed would require randomization to either no treatment or intra-arterial delivery of a plasminogen activator. As no plasminogen activator was then—or is now—approved for intra-arterial use, this study design would require an investigational device to be compared with an investigational drug; at the time of the trial design there was little precedent for such a study. Randomization to no treatment was also problematic because many endovascular surgeons believed the results of the PROACT-II trial, and felt uncomfortable withholding off-label plasminogen activator to these patients.

This constellation of issues influenced the design of the Mechanical Embolus Removal in Cerebral Ischemia (MERCi) trial. The MERCi study design was a prospective, single-armed trial whereby the device was deployed in all patients, and the outcome was recanalization of the cerebral vessel

**Table 1** Primary results of the major trials of intra-arterial treatment for acute large-vessel stroke.

Study	n	Recanalization		Outcome (mRS $\leq 2$ )		Mortality		Symptomatic ICH		Baseline NIHSS	
		Rx	Control	Rx	Control	Rx	Control	Rx	Control	Rx	Control
PROACT-II <sup>2</sup>	180	66%	18%	40%	25%	25%	27%	12	2	17	17
IMS-I <sup>19</sup>	80	56%	ND	43%	ND	16%	ND	6.3%	ND	18	ND
IMS-II <sup>20</sup>	73	NA	ND	45%	ND	16%	ND	11%	ND	19	ND
MERCI <sup>27</sup>	151	60%	ND	28%	ND	44%	ND	7.8%	ND	20	ND
Multi MERCI <sup>29</sup>	123	69%	ND	34%	ND	31%	ND	9.0%	ND	19	ND

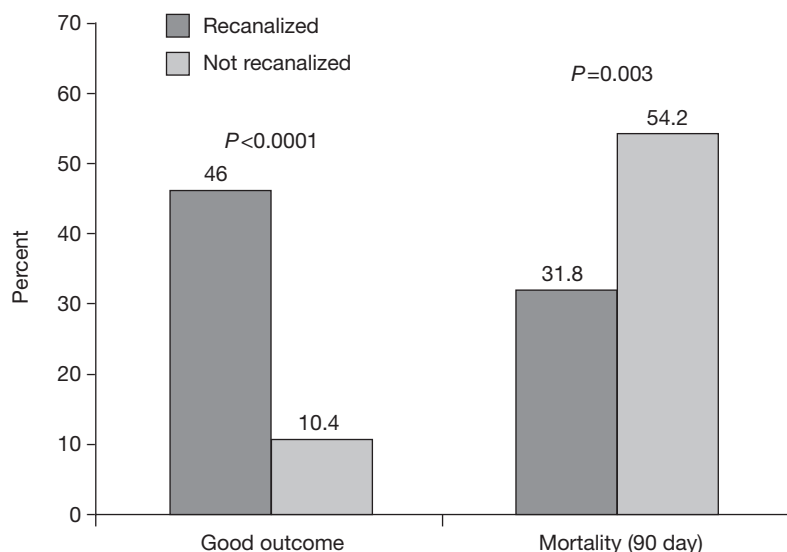
PROACT-II was the only trial with a control arm. IMS-II recanalization rate is yet to be published. Abbreviations: PROACT-II, Prolyse<sup>®</sup> in Acute Cerebral Thromboembolism; IMS, Interventional Management of Stroke; MERCI, Mechanical Embolus Removal in Cerebral Ischemia; mRS, modified Rankin Scale; ICH, intracranial hemorrhage; NIHSS, NIH Stroke Scale; n, number of studied patients; NA, not applicable; ND, not done; Rx, treated group.

compared with the control arm of the PROACT-II study.<sup>2</sup> This historical control represented the only documentation of the spontaneous recanalization rate of a cerebral vessel (MCA vessels only) using the gold standard of conventional angiography. In the PROACT-II trial, after angiographic documentation of complete MCA occlusion within hours of symptom onset, 18% of vessels recanalized 2 hours after the first angiogram while patients received intravenous heparin and no other intervention.

The MERCI trial enrolled 141 patients over 31 months at 25 US centers.<sup>27</sup> Patients were eligible if they had an acute stroke and angiographic confirmation of a large-vessel occlusion of the vertebral arteries, basilar artery, ICA, ICA terminus, or the MCA stem or first division of the MCA, scored 8 or more points on the NIH Stroke Scale (NIHSS), and could be treated within 8 hours of symptom onset. Patients who had already been treated with intravenous rtPA were excluded. The primary outcomes were recanalization and safety (potential complications included vascular perforation, arterial dissection, or embolization of a previously uninvolved vascular segment), and the secondary end point, measured by the mRS, was clinical outcome at 3 months. The device restored perfusion 48% of the time, which was significantly higher than the PROACT-II control value of 18% ( $P < 0.0001$ ). Investigators were allowed to use additional thrombolytic agents if clot remained in more distal branches that were not accessible to the device, or if the vessel failed to open at all. Overall, with or without adjuvant thrombolytic drug, recanalization of the target vessel was achieved 60% of the time (Table 1). Significant procedural complications (vascular perforation [ $n = 3$ ], subarachnoid hemorrhage

without observed perforation [ $n = 3$ ], embolization of the anterior cerebral artery [ $n = 1$ ], and groin hemorrhage requiring transfusion [ $n = 3$ ]) occurred in 7.1% of cases. Symptomatic intracranial hemorrhage occurred 7.8% of the time—in six cases (4.2%), this was attributable to procedural complications. Overall, the mortality rate was 44%. The mortality rate reported in MERCI was among the highest of any reported prospective series (Table 1), and was probably high because of the severity of the stroke, the inclusion of basilar-artery and ICA-terminus strokes, the relatively older age in the series, and probable inclusion of patients in MERCI who were more medically ill compared with patients in other trials. Taking only those patients who would have been eligible for PROACT-II (MCA only, age  $\leq 80$ , maximum NIHSS of 30), however, and adjusting for age and NIHSS score, the mortality seen in MERCI was comparable to that seen in PROACT-II.<sup>27</sup> This comparison implies that the mortality seen in MERCI was not caused by the procedure itself. A similar comparison with NINDS rtPA-treated patients supports this interpretation.<sup>28</sup> The symptomatic intracranial hemorrhage rate in MERCI was lower than the 10% rate reported in PROACT-II, but the rate was higher than that of the NINDS intravenous rtPA study. This higher rate indicates that some of the hemorrhages were caused by reperfusion injury, as most of the symptomatic hemorrhages had no observable vascular damage with the device. The MERCI device has been adopted at several US centers, and provides an alternative strategy for stroke care at these institutions.

As discussed above, the concept of intravenous rtPA treatment followed by referral of patients to a comprehensive stroke center is a practical strategy to provide endovascular therapy to the



**Figure 2** Outcome of mechanical clot retrieval. Difference in good outcome (score on modified Rankin Scale  $\leq 2$ ) and mortality at 90 days depending on whether the target vessel was opened (recanalized) or not. *P* values calculated using Fisher's exact test. Data from the Mechanical Embolus Removal in Cerebral Ischemia (MERC) trial.<sup>27</sup>

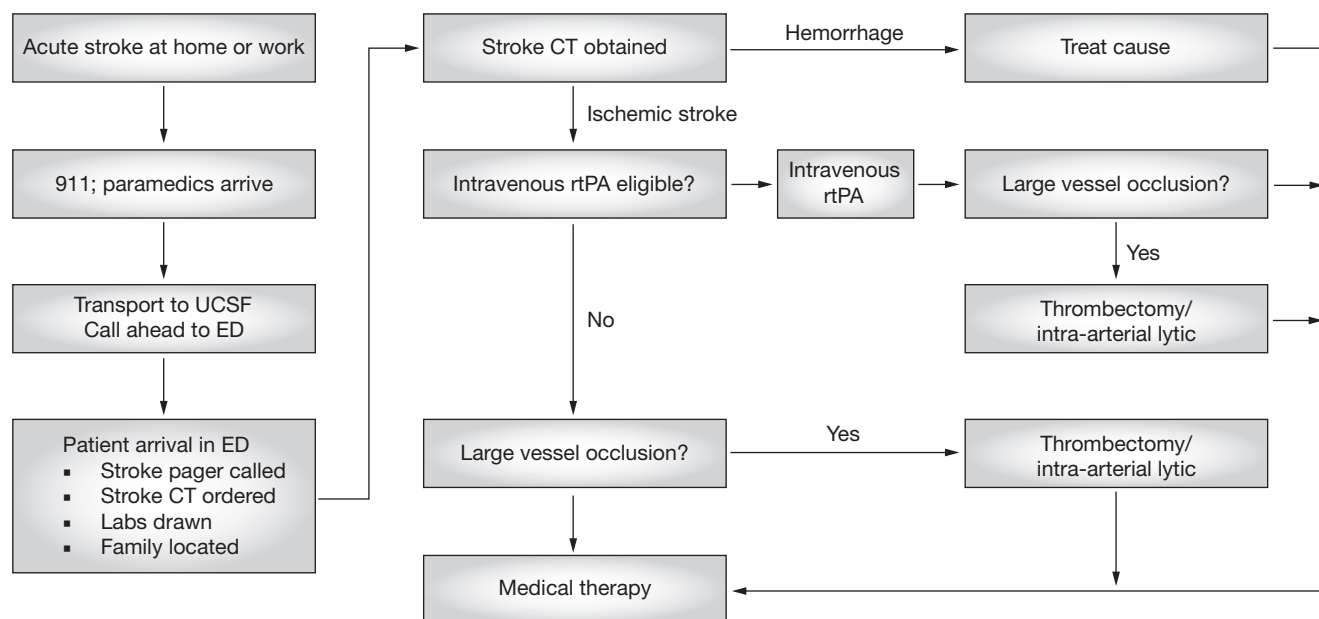
wider public. Although the safety of intra-arterial rtPA following intravenous rtPA has been studied,<sup>18–20</sup> it was unclear whether it was safe to perform thrombectomy following intravenous rtPA treatment. For this reason, and also to test a newer generation device, known as L5, the Multi MERCI trial was initiated. This trial was nearly identical to MERCI, but differed in that it included patients in whom intravenous rtPA had failed; by definition, these patients had received intravenous rtPA within established guidelines, and then had conventional angiographic confirmation of a large-vessel occlusion. Investigators were instructed to attempt thrombectomy first, and could use up to 24 mg of intra-arterial rtPA to treat distal clots not accessible by the device, or in an attempt to open the target vessel if thrombectomy had failed to open it. Results of the first 111 patients treated in this trial were recently published, and they showed that the recanalization rate was higher, the mortality was lower, and the percentage of good outcomes was higher at 3 months than in the original MERCI trial, with a comparable procedural complication rate and symptomatic intracranial hemorrhage rate (Table 1).<sup>29</sup> Fewer intracranial hemorrhages were seen in the group treated with rtPA, indicating that it is safe to pretreat patients with rtPA and then attempt thrombectomy if the vessel

fails to recanalize. The higher recanalization rate might be attributable to the use of a newer generation device, or increased operator experience with the technique.

#### UNANSWERED QUESTIONS AND THE FUTURE OF ENDOVASCULAR THERAPY

The MERCI and Multi MERCI trials were single-armed studies using historical controls, and therefore do not establish the clinical efficacy of the device. It is likely, however, that mechanical recanalization of vessels does improve outcome. For example, good clinical outcomes were predicted in univariate analysis by recanalization in the MERCI trial, and mortality was predicted by failure to recanalize (Figure 2). With a multivariate model of good outcome using all clinical and angiographic variables collected in the MERCI trial, good outcome was independently predicted by recanalization (odds ratio 12.8, 95% CI 3–56), and lack of recanalization, increasing age and higher baseline NIHSS score independently predicted mortality.<sup>28</sup> Clinical outcome, therefore, is not only dependent on age and baseline stroke severity, but is also influenced by the presence of a large-vessel occlusion,<sup>1</sup> and whether or not this vessel can be opened. The prognostic significance of vascular opening was confirmed by PROACT-II, and in many other case series, especially for those reporting use of intra-arterial thrombolytics within the basilar artery.<sup>9</sup> As the extent of cerebral infarction varies significantly from patient to patient, however, the claim that mechanical thrombectomy actually treats stroke by improving outcome is currently unsubstantiated, which has generated considerable discussion,<sup>30–32</sup> some even before the publication of the primary data.<sup>33,34</sup> A controlled trial (MR RESCUE, ClinicalTrials.gov registration number NCT00094588) of thrombectomy compared with medical therapy alone is ongoing to test whether thrombectomy definitively improves clinical outcome in a randomized, prospective clinical trial.

Further device innovation is likely to improve on the recanalization rate found in the MERCI trial; already, newer generation devices are being tested in the Multi MERCI trial with a favorable trend (Table 1).<sup>29</sup> Use of any mechanical device will probably be limited to large proximal intracranial vessels, so some combination of thrombolytic therapy with the device might be necessary to completely eradicate clot. It is still unclear how thrombolytic agents and mechanical



**Figure 3** Algorithm used at the University of California, San Francisco for patients with acute ischemic stroke. The 'stroke CT' is a multidetector CT protocol whereby noncontrast CT, CT perfusion and CT angiography (CTA) are obtained immediately upon medical stabilization.<sup>35,36</sup> Patients who are eligible for intravenous recombinant tissue plasminogen activator (rtPA) receive intravenous rtPA and then proceed to conventional angiography, provided that the CTA reveals a large-vessel occlusion and attempted thrombectomy can be initiated within 8 hours of symptom onset. Intra-arterial rtPA is used to open persistently closed vessels if it can be administered within 6 hours of symptom onset. If the patient is ineligible for intravenous rtPA, and the CTA shows a large-vessel occlusion, angiography is performed for attempted thrombectomy up to 8 hours following stroke onset; intra-arterial rtPA might also be used up to 6 hours after onset if the patient does not have a bleeding contraindication. All patients are admitted to a neuroscience intensive care or close-monitoring unit afterwards, where close attention is paid to their blood pressure, airway and safety. Abbreviations: UCSF, University of California, San Francisco; ED, Emergency Department; rtPA, recombinant tissue plasminogen activator.

thrombectomy should be combined to safely and effectively restore vascular patency, or how best to combine intravenous and intra-arterial lytic therapy. IMS-III (ClinicalTrials.gov registration number NCT00359424) will investigate the safety and efficacy of intravenous rtPA alone compared with intravenous rtPA combined with endovascular treatment with the MERCI Retriever, the EKOS ultrasonic catheter, or further rtPA given intra-arterially. This study will further explore the safety of giving intravenous rtPA first followed by rapid transit to the angiography suite, and will provide important information on the clinical outcomes of patients treated with intravenous rtPA alone compared with those undergoing more-aggressive intervention.

Mechanical reperfusion of the brain carries risk, and introduction of mechanical devices into the arteries of the brain must be done with skill. Even in the best hands, however, there is still a risk that reperfusion of the brain might have serious consequences in the form of reperfusion hemorrhage. In PROACT-II,

the risk of developing a symptomatic intracranial hemorrhage in patients who received intra-arterial thrombolysis was 10%.<sup>2</sup> If rtPA is given intravenously, this risk is around 6%.<sup>10</sup> In the MERCI trial, the rate of symptomatic intracranial hemorrhage was 7.8%, which lies between the risks of intra-arterial and intravenous thrombolytics. Some of these hemorrhages were related to vascular perforation with the device, but the others were related to reperfusion of a blood vessel injured by the stroke itself. Reperfusion hemorrhage, therefore, is not simply related to the use of thrombolytic agents, but is also a function of ischemic injury to the vascular wall and how the artery responds to restoration of blood flow.

It is important for comprehensive stroke centers to address how they currently treat acute ischemic stroke. The acute stroke protocol currently used at the author's institution is shown in Figure 3. Such an algorithm can incorporate the administration of rtPA at primary stroke centers, followed by urgent

referral to the comprehensive stroke center if there is confirmation of a large-vessel occlusion. Proper financial models must be considered when planning such systems. Effective from 1 October 2006, hospitals will receive increased reimbursement from Medicare for stroke patients treated with mechanical embolectomy. Under this reimbursement code, hospitals will be better able to recoup the cost of endovascular intervention. This reimbursement scheme is an important step in the creation of a viable system of primary stroke centers and regional comprehensive stroke centers so that more patients will have access to the most-advanced therapies for acute ischemic stroke.

**KEY POINTS**

- Intravenous recombinant tissue plasminogen activator (rtPA) has been shown to improve outcome in patients with ischemic stroke if given within the first 3 hours, and perhaps up to 4.5 hours
- Strokes from large-vessel intracranial occlusion carry high morbidity and respond poorly to intravenously administered thrombolytics
- Intra-arterial thrombolytics significantly restore perfusion within intracranial large arteries, particularly the middle cerebral artery, but no drug is FDA approved for this use
- Mechanical thrombectomy significantly restores patency in large-vessel stroke, and revascularization portends better clinical outcome
- Mechanical thrombectomy can be safely combined with intravenous and intra-arterial thrombolytic treatments
- The exact selection of treatment modalities is probably patient-specific, and is the subject of ongoing investigations
- The marriage of primary and comprehensive stroke centers in the US is likely to be a viable solution to bring state-of-the-art stroke treatment to anyone with acute stroke

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**Competing interests**

The author has declared associations with the following company: Concentric Medical. See the article online for full details of the relationship.