Improving patient selection for endovascular treatment of acute cerebral ischemia: a review of the literature and an external validation of the Houston IAT and THRIVE predictive scoring systems

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Outcome after intraarterial therapy (IAT) for acute ischemic stroke remains variable, suggesting that improved patient selection is needed to better identify patients likely to benefit from treatment. The authors evaluate the predictive accuracies of the Houston IAT (HIAT) and the Totaled Health Risks in Vascular Events (THRIVE) scores in an independent cohort and review the existing literature detailing additional predictive factors to be used in patient selection for IAT. They reviewed their center’s endovascular records from January 2004 to July 2010 and identified patients who had acute ischemic stroke and underwent IAT. They calculated individual HIAT and THRIVE scores using patient age, admission National Institutes of Health Stroke Scale (NIHSS) score, admission glucose level, and medical history. The scores’ predictive accuracies for good outcome (discharge modified Rankin Scale score ≤ 3) were analyzed using receiver operating characteristics analysis. The THRIVE score predicts poor outcome after IAT with reasonable accuracy and may perform better than the HIAT score. Nevertheless, both measures may have significant clinical utility; further validation in larger cohorts that accounts for differences in patient demographic characteristics, variation in time-to-treatment, and center preferences with respect to IAT modalities is needed. Additional patient predictive factors have been reported but not yet incorporated into predictive scales; the authors suggest the need for additional data analysis to determine the independent predictive value of patient admission NIHSS score, age, admission hyperglycemia, patient comorbidities, thrombus burden, collateral flow, time to treatment, and baseline neuroimaging findings. (DOI: 10.3171/2011.3.FOCUS1144)

Key Words • intraarterial therapy • acute cerebral ischemia • futile recanalization • patient selection • predictive scale validation • vascular disorders

Stroke is the third leading cause of mortality and is a similarly significant cause of disability in the US; of the 795,000 annual cases of stroke per year, 87% are considered to be ischemic or resulting from a clot in the cerebral vasculature that obstructs the flow of oxygen and nutrients to the brain. Rates of morbidity and mortality due to cerebral ischemia are expected to increase as a large portion of our population grows closer to the age of greatest cerebrovascular risk. The standard of care for acute stroke patients presenting to emergency service within 3 hours of symptom onset is IVtPA, or aspirin if presenting outside of the 3-hour time window. There is an increased risk of hemorrhagic transformation when IVtPA is administered after 3 hours from onset, and aspirin is not thought to provide sufficient therapeutic benefit to acute stroke patients; thus, practitioners have turned to IAT as a treatment option for acute ischemic stroke. The problem with IAT, however, is that only 40%–50% of patients with successful recanalization of blood vessels demonstrate positive, long-term functional outcomes.
In the scope of acute ischemic stroke, endovascular intervention is not synonymous with therapeutic benefit, and it is important that medical practitioners acknowledge this fact and begin to treat patients accordingly. Stroke victims presenting to the hospital after hours or days of ischemia—far outside the therapeutic window for salvage of viable tissue—have irreversible damage that IAT will not clinically change. Further, futile intervention is not a simply benign procedure in these situations—patients with little chance of clinical benefit may be more likely to experience complications with intraarterial procedures involving tPA and mechanical devices, indicating that the risks outweigh the benefits in many cases. Beyond clinical considerations, one must consider that IAT is invasive, expensive, and requires a specially trained team. In light of clinical and practical considerations, selection of patients likely to benefit from IAT, as opposed to performing this risky procedure on all acute ischemic stroke patients not eligible for IVtPA therapy, is imperative. Specialists posit that a number of baseline factors could be useful in predicting functional outcomes in patients being considered for IAT, better enabling neurospecialists to select the best candidates for treatment.

Recently, the Agency for Healthcare Research and Quality of the US Department of Health and Human Services produced a draft technical brief on mechanical thrombectomy for acute ischemic stroke, providing scientific advice to the Centers for Medicare and Medicaid Services, a document that ultimately attests to the quantity of scientific evidence that IAT is a clinically efficacious procedure for acute ischemic stroke and the rationale for medical insurance coverage of the procedure. One of the document’s most salient points is that a lack of clinical equipoise in the current culture of IAT use for acute ischemic stroke and that more standards are needed for selection of candidates likely to benefit from intervention.

We sought to compare the application of two predictive scoring systems that have been shown to be able to select ideal candidates for IAT—the Houston IAT (HIAT) and THRIVE—to the Columbia University Endovascular Neurosurgery Patient Database. These scores were developed based on patient characteristics found to be predictors of outcome after IAT regardless of recanalization status. We also review the existing literature and provide an analysis of predictors of futile recanalization after IAT.

**Methods**

All patients who underwent neuroendovascular intervention at Columbia Presbyterian Hospital from 2004 through 2010 were enrolled in the Endovascular Neurosurgery Patient Database. Patients with the diagnosis of acute ischemic stroke who underwent either intraarterial thrombolysis or mechanical thrombectomy were included in the study. Demographic and admission clinical and radiographic characteristics were retrospectively acquired (Table 1). Outcome was assessed at discharge using the mRS. The HIAT and THRIVE scores were calculated for each patient based on the following variables: age, admission NIHSS score, admission blood glucose concentra-

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* Values represent numbers of patients unless otherwise indicated.

<table>
<thead>
<tr>
<th>HIAT*</th>
<th>THRIVE†</th>
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* Based on Hallevi et al., 2009.
† Based on Flint et al., 2010.

**Results**

One hundred fifty-one patients treated at Columbia Presbyterian Hospital during the study period met the initial inclusion criteria; 74 had sufficiently complete outcome data for analysis. Patients’ HIAT scores were calculated on a scale of 0–3, as detailed in Table 2. Patients with a HIAT score of 0 or 1 were considered “low-risk,” whereas those...
with a HIAT score of 2 or 3 were considered “high-risk”; 68.5% of low-risk patients and 90% of high-risk patients had poor outcome (p = 0.07). THRIVE scores were calculated on a scale of 0–9 points, as detailed in Table 2. Patients with THRIVE scores of 0–2 were considered “low-risk,” those with scores of 3–5 as “medium-risk,” and those with scores of 6–9 as “high risk”; 46.15% of low-risk, 76.32% of medium-risk, and 86.96% of high-risk patients experienced poor outcome (p = 0.03). The HIAT and THRIVE scores demonstrated an area under the ROC curve of 0.616 (95% CI 0.481–0.752, p = 0.133) and 0.733 (95% CI 0.594–0.871, p = 0.003), respectively (Fig. 1). The THRIVE score was found to be a significant predictor of patient outcome following IAT for acute cerebral ischemia. The HIAT score trended toward predicting outcome, but was not found to achieve statistical significance. Univariate analyses of additional factors found that the following are significantly independent predictors of outcome following IAT: age (p = 0.013), history of hypertension (p = 0.006), history of tobacco use (p = 0.031), and admission NIHSS score (p = 0.047). Patient sex, history of atrial fibrillation, history of DM, history of hyperlipidemia, history of congestive heart failure, admission prothrombin time, admission international normalized ratio, admission partial thromboplastin time, admission values for serum sodium level, serum creatinine, and serum troponin were not found to be significant predictors in univariate analyses in our patient cohort (Table 3).

**Review**

**Forms of IAT and Existing Study Findings**

Intraarterial therapy has become widely used to treat ischemic strokes and comprises a number of pharmaceutical or mechanical techniques used to enter the intracranial arteries and eradicate a blood clot to restore blood flow to the brain. Patients in whom recanalization is achieved do appear to have better outcomes and lower mortality than those patients without recanalization. A recent study analyzing the effects of recanalization found that there is a 4- to 5-fold increase in the odds of a positive functional outcome and a 4- to 5-fold decrease in the odds of death in patients whose vessels do regain patency.49 While various forms of IAT have FDA approval for their technical efficacies, there remains to be any conclusive study or guidelines as to the exact populations and situations in which IAT has been shown to be clinically efficacious.

Intraarterial administration of pharmaceutical agents can typically be undertaken up to 6 hours after symptom onset—delivering a larger dose of thrombolytic agent than is used intravenously—directly through a catheter to the ischemic core.49 A major risk of this intervention is the occurrence of symptomatic intracranial hemorrhage following thrombolytic administration, necessitating that its use be carefully considered in conjunction with other patient factors.50,52,55,59 Many studies have demonstrated higher recanalization rates and reduced systemic exposure to the drug after IAT than experienced in patients given the drug intravenously.55 One clinical series reports higher early recanalization rates (50%–80% of cases) compared with intravenous treatment (30%–50% of cases).52,53

Large intracranial thrombi often resist intravenous or intraarterial administration of thrombolytic agents, and in these cases many physicians turn to intraarterial mechanical thrombectomy to achieve recanalization. These mechanical devices have gained FDA approval for tech-

![Fig. 1. Receiver operating characteristic curves illustrating predictive discrimination of admission HIAT and THRIVE scores for an mRS score of 3 or less at discharge. Data are expressed as area under the curve (95% CI). AUC = area under the curve.](image-url)
neurological efficacy based on the results of many studies, including the PROACT II, MERCI, and Multi-MERCI trials. The PROACT II study authors reported that vessel patency was achieved in 48% of patients treated with the Merci retriever (Concentric Medical, Inc.) and 81% of patients treated with the Penumbra system (Penumbra, Inc.), compared with 18% patients who experienced spontaneous recanalization.55

Physicians have demonstrated that combined use of mechanical and pharmaceutical intervention can also result in recanalization. A study that looked at the utility of the Penumbra system alone or in conjunction with intraarterial administration of pharmaceutical thrombolytic agents reported a 93% revascularization rate; 52% of patients had complete revascularization and were more likely to experience positive clinical outcomes.8 Another recent study found a combined use of aggressive mechanical clot disruption with a low-dose of intraarterial urokinase to be safe and effective in achieving recanalization in IVtPA failures; complete recanalization was achieved with aggressive microcatheter-microwire clot disruption in 83% of patients, and 67% of patients had an excellent outcome (mRS score 0 or 1) at 3 months.59

Existing Predictive Scoring Systems

Intraarterial therapy is an invasive and complex procedure that should require a careful patient selection process. As physicians ponder why some patients experience a better outcome than others regardless of recanalization status, it is important to look at all the predictors of outcome that have been assessed. Recently, research groups have begun to develop scales utilizing significant predictors to help physicians select patients for IAT; two of the most recently validated are the HIAT score and the THRIVE score.

The HIAT Score. Researchers from Houston and UCLA developed the HIAT score, which is composed of 3 factors found to be significant and independent predictors of patient outcome subsequent to IAT regardless of patient recanalization status: age, NIHSS score, and admission glucose level.26 Patients treated with IAT at the University of Texas Houston Stroke Center were retrospectively assigned 1 point for each of the following factors: age > 75 years, NIHSS score > 18, and glucose level > 150 mg/dl. The median NIHSS score for good outcome was 16, while the median NIHSS score for poor outcome was 20. Poor outcome in patients treated with IAT was defined as an mRS score of 4–6 at hospital discharge. The researchers report that with increasing HIAT scores (maximum score, 3), there was an increase in poor outcome and mortality. The data were validated using a separate set of patients from UCLA. The HIAT enables interventional neuroradiologists to estimate the chance of poor outcome after IAT—regardless of recanalization status—and therefore aids in selecting patients who will benefit more from IAT treatment.

The THRIVE Score. Patient data from the MERCI and Multi-MERCI trials were analyzed to determine whether specific chronic diseases can be used—along with NIHSS score and age—to create a predictive scale that would indicate likely patient outcome following endovascular stroke treatment with the Merci retriever.20 The investigators who created the THRIVE score report that recanalization status did not significantly differ between the poor and good outcome groups. NIHSS score and age were trichotomized, and specific chronic diseases were assigned point values to make up the THRIVE scoring system (see Table 2).

Two points were given for each level of the trichotomized NIHSS, 1 point for each level of trichotomized age, and 1 point for the presence of each chronic disease (hypertension, DM, and/or atrial fibrillation). Patients with a low THRIVE score (0–2) had good outcomes in 64.7% of cases and a mortality rate of 5.9% at 90 days after onset. Patients with a moderate THRIVE score (3–5) had good outcomes in 43.5% of cases and a mortality rate of 30.1% at 90 days, and patients with a high THRIVE score (6–9) had good outcomes in 10.6% of cases and a mortality rate of 56.4% at 90 days.

Among the patients with successful vessel recanalization, those with a low THRIVE score had good outcomes in 82.6% of cases and a mortality rate of 0% at 90 days; those with a moderate THRIVE score had good outcomes in 60% of cases and a mortality rate of 19.4% at 90 days; those with a high THRIVE score had good outcomes in 18.5% of cases and a mortality rate of 48.5% at 90 days. Among patients without successful vessel recanalization, those with a low THRIVE score had good outcomes in 27.3% of cases and a mortality rate of 18.2% at 90 days; those with a moderate THRIVE score had good outcomes in 6.9% of cases and a mortality rate of 53.3% at 90 days; and those with a high THRIVE score had good outcomes in 0% of cases and a mortality rate of 67.4% at 90 days (Mantel-Haenszel chi-square test).

This analysis shows that among the patients who underwent endovascular stroke treatment in the MERCI and Multi-MERCI trials, the THRIVE score effectively predicts 90-day clinical outcomes. Further validation of this score would make it a very effective tool in the selection of patients for IAT.

Individual Predictors of Futile Recanalization

There exist many suggested factors that might be used to predict which patients are most likely to benefit from IAT; risk factors that have been shown to independently predict negative functional outcomes—some regardless of recanalization status—may be used in weighing whether to treat patients with acute ischemic stroke who are not eligible for IVtPA. Patients whose profiles include a number of these predictive risk factors may need extra consideration before intervention, and some may be better suited for alternative therapy.

The NIHSS Score. The NIHSS score is a marker of stroke severity that is widely used at admission as a surrogate outcome marker in many ischemic stroke studies. As previously mentioned, the authors of the HIAT study found that the median baseline NIHSS score for patients with good outcomes after IAT was 16, while the median baseline NIHSS score for poor outcomes was 20; the rate of recanalization did not differ significantly between the
Improving patient selection for treatment of cerebral ischemia

good and poor outcome groups (p = 0.4).26 The THRIVE score author group trichotomized NIHSS scores (≤ 10, 11–20, and ≥ 21) and concluded that the breakdown of the scale could effectively predict those very likely, moderately likely, and least likely to experience good outcome subsequent to endovascular stroke treatment, respectively.26 Yet another analysis reports that patients who experienced futile recanalization, defined as successful removal of the thrombus without corresponding clinical improvement, had higher median baseline NIHSS scores (19) compared with those with nonfutile recanalization pursuant to IAT (14).29 Multiple groups report that an NIHSS score of < 10 is a predictor of a good clinical outcome for patients treated with IAT.29

Further, investigators also report that NIHSS scores can significantly predict reocclusion after tPA-induced recanalization, indicating that patients who experienced reocclusion presented with higher baseline stroke scale scores.30 Reocclusion is associated with a worse clinical course and poor long-term outcome compared with patients with sustained recanalization. Thus, a patient’s NIHSS score must be factored into the decision of whether to pursue IAT or not to, both to minimize likelihood of futile recanalization and the risk of deleterious recoclusion and maximize chances of actual therapeutic benefit.

Age. There are limited data available regarding the safety and efficacy of IAT specifically in elderly patients, despite the fact that this is the population most likely to experience cerebral ischemia and therefore be considered for this therapy.11,17,23,42,58 Stroke is an age-related disease: per capita, people aged 85–94 years experience a 2-fold higher incidence of stroke compared with people aged 65–74 and a 26-fold higher incidence compared with people aged 45–54. As the elderly population in the US rapidly grows, advances in acute therapies for stroke shown to be effective in the elderly are urgently needed.

A study to identify age-specific aspects of response to IAT analyzed a large group of ischemic stroke patients and compared the outcomes between those patients older than 80 years and those younger than 80 years.4 The 90-day outcomes among the elderly showed lower rates of excellent functional outcome (mRS score < 1, 26% of elderly patients vs 40% of younger patients) and survival (57% vs 80%, respectively), regardless of recanalization status. The authors ultimately report that patients 80 years and older had a higher risk for poor outcome at 1–3 months following IAT, even after adjusting for recanalization status. These results could be related to a higher frequency of prior stroke or TIA, higher frequency of prestroke comorbid conditions and poststroke medical complications, impaired collateral circulation, reduced neuronal reserve, and fewer social supports in the elderly population.

Age brings in to consideration a number of factors. It is posited that diminished neural plasticity in the elderly may lower the chances of recovery following cerebral injury.12,24,56 Patients 80 years of age or older were reported to have more frequent comorbidities, more extensive coronary disease, and a 2- to 4-fold increase in risk for complications following IAT, including death, Q wave myocardial infarction, renal failure, stroke and vascular complications.47 Studies also show that elderly patients have a reduced capacity for developing collateral blood flow and that increased age predicts the absence of collateral circulation to the ischemic region.35,47 The presence of collateral flow is correlated with better outcomes, most likely due to its ability to provide at-risk areas of brain tissue with some blood flow; the independent predictive values of the presence of comorbidities and the presence of collateral flow are discussed later in this paper.

A second group studying IAT in acute cerebral ischemia reported that patients experiencing futile recanalization were older (73 ± 11) as compared with the nonfutile recanalization group (58 ± 15 years); further, age > 70 years was independently and positively associated with futile recanalization.29 Yet another study found that between 2 groups of patients, one composed of patients 80 years of age and older and the other only patients younger than 80 years, outcomes at 90 days post-IAT showed lower rates of excellent functional outcome (mRS score ≤ 1, 26% vs 40%, p = 0.02) and survival (57% vs 80%, p = 0.01) in the older patient group; there were no detectable differences in recanalization (TIMI score 2–3) between the 2 groups.33

Intraarterial thrombolysis can be accomplished in the elderly with recanalization rates and hemorrhage rates equal to those obtained in younger patients. Even with higher mortality rates and lower rates of good functional outcomes than in younger patients, nondisabling outcomes may be achieved in a quarter of the elderly population treated with IAT. These findings suggest that the use of IAT in very elderly patients should not be avoided, but pursued with caution in an effort to treat those patients likely to benefit from it.33

Hyperglycemia. It is widely accepted that high serum glucose concentration at presentation in patients with acute cerebral ischemia often indicates a more serious stroke and, all else being equal, foreshadows a worse outcome. Hyperglycemia occurs in diabetic and nondiabetic acute ischemic stroke patients and it is present in up to 49% of stroke patients without a preexisting diagnosis of DM.24 Although few studies have looked solely at the association between hyperglycemia and futile recanalization, a number of groups have established that a high admission glucose level is associated with worse outcome. The investigators who devised the HIAT and THRIVE scores took these studies into consideration and found admission hyperglycemia or a preexisting diagnosis of DM to be independent predictors of outcome after endovascular treatment of acute ischemic stroke.20,26

One of the many studies that have looked at the correlation between admission hyperglycemia and ultimate outcome found that in acute stroke patients, hyperglycemia was a predictor of poor outcome following recanalization, independent of age, DM diagnosis, and stroke severity.2 The exact cause of poststroke hyperglycemia in nondiabetic patients is not definitively known, but some posit that it may be due to stress caused by the release of cortisol and norepinephrine or impaired glucose metabolism.2,18 Additionally, the cause of the difference in outcome between patients with hyperglycemia at presen-
tation without a history of diabetes versus those with a previous diagnosis is unclear.

A number of correlations exist between hyperglycemia and stroke, including a smaller volume of salvageable penumbra, increased infarct volumes, and reduced efficacy of thrombolytic agents. High glucose levels at admission may counteract the beneficial effects of tPA, regardless of recanalization status. A baseline blood glucose level greater than 140 mg/dl is linked to greater infarct size, worse outcome, and lower degree of neurologic improvement after reperfusion. Leigh et al. report that hyperglycemia (> 150 mg/dl) at admission was greater in patients who had hyperacute worsening (NIHSS score change ≥ 4 points within the first 24 hours) even in the presence of recanalization after IAT (p = 0.004, OR = 6.47). The group also reports that high blood glucose concentration was an independent predictor of in-hospital mortality.

Because of the associated risk of hyperglycemia and poor outcome, glucose monitoring is imperative. Poor glycemic control was associated with unfavorable prognosis in patients with persistent hyperglycemia, patients without a known history of diabetes, and patients with cortical infarction. Early identification of patients with abnormal glucose metabolism or DM is important when considering glycemic control strategies as well as when considering other acute stroke treatment.

Comorbidities. A patient's general state of health prior to stroke onset is another factor that must be used in determining the probability that he or she will experience a positive functional outcome after IAT, as the body's ability to quickly recover from injury is often compromised in patients with other illness. A history of cardiovascular disease, cerebrovascular disease, or neurological deficits may compound the effects of stroke and increase the difficulty of endovascular reperfusion.

The THRIVE scale investigators report that a patient’s history of hypertension, DM, or atrial fibrillation is independently predictive of poor outcome following IAT, regardless of reperfusion status. A history of stroke, coronary artery disease, or congestive heart failure has also been associated with worse outcomes in patients given endovascular therapy for acute cerebral ischemia.

Other authors have investigated the impact of admission cholesterol level on outcome after ischemic stroke thrombolysis in 104 patients who received IVtPA, intraarterial tPA, or mechanical thrombus retrieval. Lower levels of low-density lipoprotein cholesterol, with or without statin treatment, were independently and significantly correlated with a higher risk of symptomatic hemorrhagic transformation after revascularization therapy. Patients who were current smokers and who presented with greater stroke severity also had a greater risk of symptomatic hemorrhagic transformation. Old age, hypertension, hyperlipidemia, and previous coronary heart disease were more prevalent in patients with prior statin use. Restrepo et al. reported that even after controlling for recanalization status, an analysis of a prospectively maintained stroke registry showed that a patient history of hyperlipidemia was negatively associated with excellent functional outcome (mRS score ≤ 1) at 3 months after stroke; the group reports that for every 50 mg/dl increment in a patient’s total cholesterol level, there was a 64% decrease in the odds of excellent functional outcome (OR = 0.36, p = 0.0253). The presence of hyperlipidemia also was associated with a higher NIHSS score at 7 days after stroke or on the day of discharge, and statin use was related to an average 6.5-unit NIHSS score decrease at discharge (p = 0.016). Statin use was not associated with increased frequency of recanalization or symptomatic intracranial hemorrhage.

Another study found a relationship between blood pressure, vessel recanalization, and patient outcome. In most stroke patients, blood pressure is typically elevated; ischemic stroke patients with high blood pressure are more likely to experience dependency, death, or risk of recurrent stroke. Another study that analyzed data obtained in patients after intraarterial therapy noted that in those patients in whom recanalization was achieved, systolic blood pressure measured 12 hours after therapy had declined more than when recanalization failed and thus made better outcome more likely.

Patients who are already vulnerable due to a preexisting health condition are less likely to recover from an injury related to an endovascular procedure, but exactly which conditions make patients especially susceptible to injury have not been extensively studied. Although some studies report contrasting conclusions regarding specific comorbidities and their links to patient outcome following IAT, the individual patient’s medical history, especially regarding current cardiovascular or cerebrovascular issues, must be taken into consideration when determining whether he or she is a good candidate for IAT. Once further analyses are done to reliably relate the presence of a specific comorbidity with a likely outcome of futile recanalization, physicians should screen all patients presenting with ischemic stroke for any proven predictors and take their presence into careful consideration before undertaking IAT. The utmost consideration should be given to the likelihood that a patient will benefit from an endovascular reperfusion strategy before any IAT measures are initiated.

Thrombus Burden. Thrombus size has been shown to affect endovascular interventions and predict poor clinical outcomes and is thus an important factor when considering endovascular stroke intervention. Qureshi et al. modified the TIMI scale to include a 5-point angiographic thrombus burden grading scale in patients with cerebral ischemia; the scores range from 0 (no angiographic characteristics suggesting a thrombus) to 4 (large thrombus present, greatest dimension equivalent to 2 or more vessel diameters). Multiple groups report that large thrombi present in the proximal MCA and the terminal internal carotid artery have demonstrated resistance to mechanical therapy and thrombolysis, thereby complicating and delaying recanalization efforts. As discussed later in this paper, increased length of time to recanalization is often associated with poor outcome, so further delay in time to recanalization must be considered in patients presenting more than 8 hours after onset with large thrombus burdens.
Improving patient selection for treatment of cerebral ischemia

Gralla et al. studied thrombus length and its effect on success of recanalization during mechanical thrombectomy. They report that longer thrombi (20–40 mm) result in a decreased recanalization rate and an increased complication rate in comparison with shorter thrombi (10 mm), a finding that they attributed to thrombus-device interaction. They report that distal dislocation of thrombotic material increased with thrombus length; thromboembolic events into other vessels increased from 0% in the 10-mm thrombus group to 7.4% in the 20-mm thrombus group to 14.8% in the 40-mm thrombus group. They note that these events are clinically significant due to the likelihood that they will worsen neurological status by occluding a previously unaffected vascular territory. Similarly, another group found that the length of basilar artery occlusions was a predictor of clinical outcome independent of recanalization status, likely related to the extent of irreversible brainstem damage, vegetative dysfunction, and/or death in patients with larger thrombi.

Researchers hypothesize that larger thrombi are more clinically significant due to their resistance to thrombolysis. Grade 4 thrombi require longer times for intraarterial therapy and often necessitate larger doses of thrombolytic agents. The rate of successful recanalization did not differ significantly between Grade 4 thrombi and Grades 0–3; however, for patients in whom recanalization was achieved, the time from the diagnostic angiogram to recanalization was significantly longer in those with Grade 4 thrombi (median 115 vs 72 minutes) than those with lower-grade thrombi. After controlling for age, baseline NIHSS score, and artery of involvement, patients with Grade 4 thrombi are 2.4 times more likely to experience a poor clinical outcome and 4 times more likely to die. Patients with Grade 4 thrombi were 2.7 times more likely to be discharged to a nursing home or hospice. These poor outcomes in patients with Grade 4 thrombi may be a result of greater stroke severity (based on the NIHSS score), delay in recanalization, or occlusion of collateral pathways that could create larger infarctions. Because Grade 4 thrombi show resistance to thrombolytic agents, many researchers suggest early aggressive IAT therapy. This clinical decision should be made after considering other cofactors related to the individual patient in question.

**Collateral Circulation.** When cerebral vessel occlusions occur, some areas of neural tissue originally perfused by the occluded artery can be fed by collateral blood flow originating in other parts of the brain, including from large vessels at the circle of Willis or small pial vessels near the surface of the brain. When blood flow to a part of the brain is blocked, these existing arterial connections may be able to compensate for the lack of perfusion in that territory. Collateral flow reduces the expansion of the infarct core and thereby helps to sustain tissue viability until reperfusion is achieved.

Brandt et al. report that collateral blood supply in basilar artery occlusions is, like length of occlusion, an independent predictor of clinical outcome independent of recanalization status. The group posits that existence of collateral blood supply correlates with the number of obstructed perforating arteries and therefore the degree and volume of brainstem ischemia, which is intimately associated with clinical state. They conclude that good collateral flow may restrict the hypoperfused tissue volume in the brainstem and enable survival.

Many researchers have wondered to what extent the presence of collateral vessels can act as a predictor of clinical outcome in ischemic stroke patients treated with thrombolysis. In one study, clinical data for 53 qualified patients who underwent intraarterial thrombolysis for the treatment of acute ischemic stroke were reviewed for age, sex, time to treatment, NIHSS score, and mRS score; site of occlusion, recanalization, and pial collaterals were analyzed on angiograms, and infarct volume was assessed on CT scans. The investigators report that independent of age, site of occlusion, time to treatment, and recanalization, an assessment of pial collateral formation before thrombolysis could predict clinical outcomes and infarct volume in ischemic stroke patients. Those patients with both good pial collaterals and nearly complete recanalization appeared to have the best mRS scores at discharge. Those with poor collateral scores tended to have worse mRS scores, despite recanalization. Even without complete recanalization, if good collaterals were present, there was significantly less infarct growth and a chance for good outcome.

The site of the occlusion may also affect the extent of collateral circulation. Proximal occlusions affect larger areas of brain tissue than distal occlusions do and are therefore associated with poorer outcomes. One group points out an example of a stroke in a particular region that might not receive collateral flow and thus indicates an infarct for which the benefits of IAT must be heavily weighed—a proximal MCA clot that occludes the lenticulostriate arteries supplying the basal ganglia and internal capsule. The lenticulostriate arteries are not collateralized from the cortex, so while transcortical collateral vessels might allow cortex to be salvaged, permanent hemiplegia might still result from infarction of the internal capsule. About one-fourth of patients with proximal MCA occlusions have poor collateral flow measured by sylvian fissure and leptomeningeal convexity vessels on CT angiography and, therefore, have increased risk of poor outcome. However, because most patients demonstrated sufficient collateral vasculature comparable to those without an occlusion, some researchers believe it may be beneficial for patients with diminished collateral circulation to be treated with IAT techniques. In contrast, others believe if little or no collateral vasculature is present on the angiogram, the chance of recanalization may be reduced and risky endovascular procedures may not be warranted. In the case of good collateral vessel formation, neurointerventionalists may feel the need to try more aggressive IAT because there may be salvageable tissue. There is currently no general consensus on what the presence or absence of collateral circulation means with respect to treatment choices for acute ischemic stroke patients.

**Time To Treatment.** Time to treatment plays an important role in neurological worsening; it is generally accepted that the longer the time between symptom onset...
and treatment, the greater the risk of complications. Because IVtPA can only be used within the first few hours following acute stroke, many groups have looked at the effects of later methods of recanalization and the impact that time to treatment has had on outcome.

A recent study concluded that good clinical outcome following angiographically successful reperfusion is significantly time dependent.31 Reperfusion at 310 minutes after symptom onset corresponded to a 10.6% decrease in the probability of a good outcome compared with a time lapse of 280 minutes from symptom onset, and the probability of good clinical outcome decreased as time to revascularization increased. These findings were consistent with the results of animal studies, suggesting an approximately 6-hour time window before irreversible neurological deficit.31,60 As IAT is the only available therapy for a patient at 6 or more hours after stroke onset, the results of these findings must be used when making treatment decisions for patients presenting long after symptoms start. Another study discovered that early treatment proved to be the most important factor for successful endovascular therapy in acute intracranial vertebrobasilar occlusion and was a better predictor of patient outcome than was achievement of recanalization.39 Early intraarterial fibrinolysis treatment (with early defined as ≤ 6 hours from stroke onset) led to a significantly better neurological outcome than delayed treatment (≥ 6 hours from stroke onset). Of the 33 patients who received early treatment, 36% survived with a favorable outcome, 12% survived with an unfavorable outcome, and 52% died. Of the 43 patients who received delayed treatment, only 7% survived with a favorable outcome, 23% survived with an unfavorable outcome, and 70% died. There were 16 patients who were treated more than 10 hours after stroke onset. Of these, 75% died and 25% survived with an unfavorable outcome. This study indicated that rapid initiation of endovascular therapy is an incredibly important factor in determining improved neurological outcome of patients with acute vertebrobasilar occlusion and that endovascular treatment might not be a reasonable choice in patients presenting long outside of the 6- to 8-hour window; the investigators state that the delay in initiation of treatment might be a reason for high mortality rates despite successful recanalization.

Multimodal Imaging. It is hypothesized that multimodal imaging results at presentation can be used to predict which patients are likely to benefit from reperfusion therapies. One study looked at the predictive value of the Alberta Stroke Program Early CT Score (ASPECTS) for patients who would likely benefit from intraarterial pro-urokinase thrombolysis after acute MCA occlusion within 3–6 hours of symptom onset.28 Each patient underwent baseline and 24-hour follow-up noncontrast CT imaging; patients were stratified based on ASPECTS (> 7 or ≤ 7), then randomly assigned to a treatment (intraarterial pro-urokinase) or control group. ASPECTS is a 10-point score that quantifies the presence of ischemia in 10 different regions of the brain; previous validations have dichotomized patients with a score of 0–7 versus those with a score of 8–10 at presentation, with a lower score indicating more extensive ischemic damage and a worse prognosis. Ischemic stroke patients with an ASPECTS of more than 7 who received intraarterial pro-urokinase were 3 times more likely to have a good outcome (defined as mRS score ≤ 2 at 90 days after treatment) than those with a similar ASPECTS in the control group, indicating that patients with good ASPECTS stood to benefit from IAT. However, among patients with an ASPECTS ≤ 7, there was no significant difference between the treatment and control arms of the study, indicating that those patients with extensive ischemia do not show significant improvement with IAT.

Gasparotti et al.24 report the utility of perfusion CT imaging in selecting patients who are likely to benefit from IAT following acute ischemic stroke. The group reports that a multiparametric assessment of perfusion deficits on cerebral blood flow, cerebral blood volume, and time-to-peak maps (particularly the infarct core size), is a reliable tool for predicting clinical outcome after IAT. They posit that the size of the infarct core based on perfusion CT is a more relevant determinant of the severity of clinical outcome than penumbra and total perfusion deficit. Gasparotti et al. conclude that their results prompt speculation that some patients with stroke experiencing little or no improvement despite achieving recanalization might have a larger core size, which is easily detected with perfusion CT.

Another group analyzed the utility of MRA-DWI mismatch at patient presentation in predicting those individuals who were likely to benefit from reperfusion.37 The authors suggest that the presence of an occlusion or intracranial vessel stenosis on MR angiography and with a small DW imaging lesion (collectively known as the “MRA-DWI mismatch”) would be better suited for IAT. The study showed that those 44% of patients who had an MRA-DWI mismatch at baseline had an overall increased rate of a favorable clinical response after reperfusion, while those patients without mismatch experienced less benefit from IAT. The authors conclude that baseline MR angiography and DW imaging may be used to predict whether a patient is a good candidate for IAT.

Using a combination of MR imaging sequences enables practitioners to rapidly assess the ischemic infarct core (via DW imaging), visualize the underlying arterial pathology (via MR angiography), and visualize the area of tissue at risk (PWI > DWI mismatch).10 One paper reports the utility of pretreatment MR imaging in predicting those patients who would likely benefit from reperfusion therapies in extended time windows (between 3 and 6 hours after symptom onset).1 It is proposed that a diffusion-perfusion mismatch be used as a surrogate for indicating the ischemic penumbra and that those patients with a mismatch are more likely to benefit from IAT. Presence of a volumetric difference between a larger PW imaging lesion and a smaller DW imaging lesion is thought to represent the hypoperfused but potentially salvageable ischemic penumbra. Davis et al.16 further specify the concept of PWI-DWI mismatch—a pure subtraction of the two images is oversimplified. They state that some areas of apparent lesions on PW images often include benign oligemia. Further, lesions shown on DW imaging—generally accepted to indi-
Improving patient selection for treatment of cerebral ischemia

cate irreversibly damaged tissue—may sometimes include areas salvageable with rapid reperfusion.

Several studies have been initiated to test the theory of a time-sensitive salvageable penumbra visualized with neuroimaging techniques: Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET),45 Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution (DEFUSE),46 Desmoteplase in Acute Ischemic Stroke (DIAS),15 Mechanical Retrieval and ReCanalization of Stroke Clots Using Embolectomy (MR RESCUE), and ReoPro Retavase Reperfusion of Stroke Safety Study—Imaging Evaluation (ROSIE).19 There currently is no accepted standard of imaging used to determine which patients might benefit most from IAT, but it is clear that most modalities have significant potential to help a physician decide whether the extent of a patient’s injury would preclude benefit from IAT.

Discussion

Despite the improvements that IAT has demonstrated in better patient functional outcome, this therapeutic method does not come without costs. Intraarterial therapy carries a significant risk for complications during or after the procedure, including vessel spasm, vessel rupture, vessel perforation, or the formation of new distal emboli derived from particles of the original thrombus.14 Before a patient is treated with IAT, it is imperative that clinicians thoroughly examine predictors for the individual patient’s clinical outcomes to avoid unnecessarily aggressive therapy.

In addition to risks inherent to the therapeutic procedure and devices, there is also a clinical risk of futile recanalization, or the absence of clinical benefit from recanalization following endovascular treatment of acute ischemic stroke. In a recent multicenter study28 of 270 patients undergoing intraarterial thrombolysis, complete recanalization was observed in 96 (38%) of 254 patients that were eligible.3 The occurrence of unfavorable outcome was defined by an mRS score greater than 3 at 1–3 months after treatment despite a complete angiographic recanalization. Of all the patients in whom complete recanalization was achieved, favorable outcome was observed in 49 (51%), while 47 patients (49%) had futile recanalization and did not experience therapeutic benefit. Another study found similar results, indicating that even with successful recanalization of blood vessels, only 40%–50% of these patients have positive functional outcomes.26

It is also necessary to consider the demand for and availability of trained specialists when considering IAT for a patient. Intravenous tPA is the first line of treatment for acute stroke patients within 3 hours of occlusion and is preferred over IAT because it is effective, safe, relatively inexpensive, and does not require a highly specialized physician; for these reasons, tPA is sometimes the only therapy offered to acute stroke patients at smaller health centers and hospitals with limited staff and technology.14 Intraarterial therapy, the second line of attack in patients with acute cerebral ischemia, may only be administered at comprehensive stroke centers appropriately staffed with interventional neuroradiologists and other trained stroke specialists. As a result, many smaller stroke centers must either offer only IVtPA to patients presenting within 3 hours of stroke onset or rush patients to specialized hospitals that are able to provide IAT.

Significant financial burden is another facet of IAT that makes it imperative for physicians to consider whether a patient is truly a good candidate for treatment. One study examined the cost-effectiveness of mechanical therapy compared with standard medical therapy by comparing health benefits and costs.45 Health and quality-of-life factors were measured in quality-adjusted life years (QALYs) and cost of hospitalization, rehabilitation, and long-term care. The authors found an incremental cost-effectiveness ratio (ICER) of $12,120 per QALY gained, which is considered cost-effective (ICER < $50,000 per QALY gained). Intraarterial therapy was found to be only borderline cost-effective in patients older than 82 years. This evidence indicates that endovascular mechanical thrombectomy appears to be cost-effective, but it is still very expensive and controlled randomized trials are needed to validate this hypothesis.

Through our literature analysis we have found that the mentioned predictors may be markers of stroke severity and directly correlate with treatment. It is evident that the presence of these predictors in combination with aggressive treatment options, such as endovascular therapy, could lead to more serious complications, including reperfusion injury. Although there are many factors related to outcome after IAT, there is abundant evidence supporting the relationship between the mentioned predictors and futile recanalization.

Many patient factors are, understandably, indicators of likely poor outcome altogether and perhaps are arguably not linked specifically to outcome following IAT. In patients with comorbidities such as high blood pressure or vascular disease, increased risk of hemorrhage during IAT points to a greater likelihood of poor outcome of intravascular therapy. Patients who are older and therefore less likely to recover from negative effects of treatment may be better off without risky intervention. Patients with high NIHSS scores, remarkable neuroimaging results, or a long time to treatment may have little salvageable tissue left and may therefore not be able to benefit from IAT. Reperfusion injury following a longstanding occlusion can occur. Perhaps in some patients, necrotic tissue flow through the brain days after a clot has set in will be significantly more detrimental than the treatment is helpful. It is imperative that practitioners consider these factors before deciding to treat acute ischemic stroke patients.

Application of our center’s data to the HIAT and THRIVE scores verifies that these groups who have put together predictive scoring systems for patient outcome subsequent to IAT are justified in doing so. The THRIVE score proves to break down predictive factors and assign correct weight to each, but both scales indicate that some stroke patients experience much more risk than benefit from IAT. Our univariate analysis of potential predictive factors of patient outcome indicates that the HIAT and THRIVE scoring systems’ inclusion of age, history of hypertension, and admission NIHSS scores are applicable to our population as well. Additionally, our finding that patients with a history of tobacco use may have less to
gain from IAT indicates that future comprehensive predictive models should include this factor in their analyses. In light of the risks, costs, and requirements of IAT, physicians must assess all factors to make the best decision for the patient. If the stroke victim is likely to experience futile recanalization, it may be unwise to subject him or her to the costs and risks inherent to IAT. Thus, it is imperative that clinicians understand and consider possible predictors of long-term patient outcome following recanalization to decide whether to administer IAT.

Conclusions

Intraarterial therapy has great potential benefit, but the unique health profile of the individual patient must be taken into account before deciding to undertake IAT. Recently developed scoring systems like the HIAT and THRIVE are necessary tools for clinicians to better select patients for IAT. An analysis of a set of patients from our center indicates that the THRIVE score may be the better of the existing scales for use in assisting in the decision of whether to treat an individual patient with IAT after acute stroke. Furthermore, it is imperative that physicians and policymakers also consider factors such as the high monetary cost and required specialized workforce needed to implement IAT.

As it is evident that practitioners need a way to consistently select patients for whom IAT is likely to benefit rather than treating anyone with acute ischemic stroke, further research and validation of existing studies must be done to develop a general score incorporating all significant predictors. While the HIAT and THRIVE scales prove to be useful, each is missing information that the other proclaims important. Furthermore, there are predictors of outcome that other studies have found that are not included in either of these predictive scales. Thus, any existing databases of IAT patients should be used to externally validate or refute both of these scores, in addition to being checked for additionally independent and significant predictors of outcome, such as multimodal imaging results, presence of collateral vessels, time to treatment, and thrombus burden.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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Improving patient selection for treatment of cerebral ischemia

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Neurosurg Focus / Volume 30 / June 2011

11

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