Acute Stroke Therapy at the Crossroads

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CLINICAL DECISION MAKING IS BASED ON A MIX OF SCIentific data, experience, training, and other influences, such as reimbursement, allure of new technology, current opinion, and bias. Acute ischemic stroke care has reached a critical juncture: clinical practice, particularly the use of endovascular therapy, is starting down a road containing little scientific evidence of clinical efficacy, while the conduct of clinical trials to provide such critical data is impeded.

Intravenous tissue plasminogen activator (IV t-PA) is the only treatment approved by the Food and Drug Administration (FDA) that was proven clinically effective in multiple randomized clinical trials for acute ischemic stroke.[1] The effectiveness of t-PA is time-dependent; treatment beyond 4.5 hours from stroke onset does not result in improved clinical outcome.[1] By reducing long-term disability, IV t-PA is also highly cost-effective.[2] No other treatment for acute ischemic stroke has shown greater clinical efficacy than IV t-PA.

The development of endovascular treatment for acute ischemic stroke paralleled the clinical testing of IV t-PA in 1980 through the 1990s.[3] Initially, treatment consisted of endovascular administration of fibrinolytic medications at the site of vascular occlusion and often beyond the 3-hour FDA-approved time window for IV t-PA. PROACT II (Prolyse in Acute Cerebral Thromboembolism) is the only randomized trial in which an intra-arterial fibrinolytic (prourokinase) demonstrated predefined better clinical efficacy and improved recanalization compared with control therapy (heparin) in a 0- to 6-hour time window.[4]

The past 10 years have seen a substantial expansion in endovascular technology designed to remove intra-arterial thrombus in patients with acute stroke. Two devices, the Merci Concentric Retriever (2004) and the Penumbra aspiration system (2007), were cleared by the FDA via the 510k pathway for "removal of thrombus" within 8 hours of stroke onset.[3] FDA clearance was based on single-group, nonrandomized trials comparing device treatment with historical controls from PROACT II. In these single-group trials, recanalization rates were higher than those reported in studies of IV t-PA, rates of symptomatic intracerebral hemorrhage were similar, but the rates of good functional outcomes at 3 months were worse than rates in the IV t-PA trials. Poorer outcomes were explained in part by greater stroke severity and later time to treatment. Thus, these devices were not approved by the FDA as clinically effective treatments for acute stroke but were cleared for use as devices to remove thrombus in acute stroke.

Even though no device has proven clinically effective for treatment of acute ischemic stroke, a substantial proportion of the stroke interventional community in the United States is seemingly unwilling to enroll patients into ongoing acute interventional randomized trials. These clinicians apparently consider that endovascular therapy using clot removal devices leads to better clinical outcomes than IV t-PA, or in later time periods, than standard therapy. Their primary rationale may be the radiographically compelling appearance of more rapid recanalization using devices as compared with IV t-PA. These physicians may view recanalization as a surrogate, and essentially equivalent, end point of clinical effectiveness. However, there are many examples of therapies that were deemed successful based on a surrogate measure only later to fail when judged by clinical efficacy.

Failed surrogate end points in trials of cerebrovascular disease include extracranial-intracranial bypass for stroke prevention in patients with symptomatic carotid occlusion,[5,6] recombinant factor VIIa to slow and stop bleeding in patients with intracerebral hemorrhage,[7] and intracranial stenting for stroke prevention in patients with symptomatic high-grade intracranial artery stenosis.[8] In each of these studies, the device or medication accomplished its biologic purpose (restoring blood flow to brain areas that had impaired perfusion, slowing bleeding, or reopening a high-grade stenosis), but clinical efficacy was not proven in phase 3 trials.

The Carotid Occlusion Surgery Study (COSS) reported in this issue of *JAMA*[5] joins the list of stroke trials in which a successful outcome as measured by an important bio-

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logic marker of brain perfusion—improved oxygen extraction ratio after the bypass procedure—was not reflected in improved clinical outcome at 2 years. The pretrial assumptions regarding the 30-day postoperative stroke rate and the 2-year stroke rate in the surgical group were fairly accurate, but the 2-year stroke rate in the medical group was much lower than expected, possibly reflecting improvements in medical prevention of stroke during the conduct of the trial. The authors note that the COSS trial "reaffirm[s] the hazard of using even the most carefully studied historical controls to infer therapeutic efficacy and the necessity of performing randomized controlled trials to establish clinical benefit."

One consistent theme from the trials of endovascular therapy is that clinical outcomes after revascularization are highly dependent on the time from stroke onset to revascularization, as it is for IV t-PA. The single group IMS (Interventional Management of Stroke) I and II trials,[9,10] Penumbra Trial,[11] and French RECANALISE study[12] demonstrated a strong relationship between time to revascularization and good functional outcome at 3 months. In IMS I and II, revascularization beyond 6 hours resulted in similar outcomes as compared with no revascularization. Retrospective series also suggest poorer outcomes in patients treated endovascularly under general anesthesia, a finding that requires further investigation.[13] Thus, recanalization is an excellent surrogate end point in the first hours after stroke onset but is a poor surrogate at later time intervals and does not capture the entire effect of the endovascular procedure.

Intravenous t-PA for acute stroke is an example of the power of reimbursement to change clinical practice. Despite strong clinical evidence, use of IV t-PA for acute stroke languished at about 1% to 2% of all ischemic strokes from the time of FDA approval in 1996 through 2005.[14] After a new hospital diagnosis related group specific for patients with stroke treated with IV t-PA was instituted by CMS in 2005, use of IV t-PA at US hospitals in the Premier database increased from 2.4% of ischemic strokes in 2005 to 4.5% in 2009.[14] Similarly, increased reimbursement for use of endovascular procedures has been associated with the increasing use of acute stroke devices in US hospitals, despite the lack of clinical effectiveness.[15] Reimbursement for devices and procedures that lack evidence for clinical efficacy greatly increases their use by physicians and hospitals as well as the cost of health care in the United States.[16]

Reimbursement for procedures and devices in routine clinical practice, without evidence of clinical effectiveness, also affects enrollment into randomized trials in which clinical efficacy can be clarified. The decision by CMS to reimburse for treatment of patients with symptomatic intracranial stenoses only in the setting of a randomized clinical trial (SAMMPRIS) greatly facilitated recruitment and led to relatively rapid conclusion of the trial.[8] By contrast, recruitment into randomized trials of endovascular therapy for acute ischemic stroke vs standard care (IV t-PA) such as IMS III (NCT00359424)[17] and MR Rescue (NCT00389467)[18] has been slow in the United States because the same devices are reimbursed in the United States as part of routine clinical practice. The monthly recruitment rate at US sites in IMS III (0.14 per site per month) is lower than the rate at sites in Canada (0.16), Australia (0.32), and Europe (0.82) where financial support for health care is allocated differently.

Clinical science and reimbursement for delivery of clinical stroke care must be balanced and aligned. Physicians who provide care for patients with stroke must recognize the current lack of evidence for clinical efficacy of endovascular therapy and enroll patients in randomized trials. The review process of the FDA and CMS must be harmonized and should require higher standards of evidence for clinical efficacy prior to clearance or approval of devices for stroke and subsequent reimbursement. Long-term and ongoing reimbursement should be predicated on evidence for equivalent or superior clinical efficacy, and cost-effectiveness should be an important consideration for clinically equivalent therapies. For example, if IV t-PA is clinically equivalent to endovascular therapy, society will have to weigh the substantially increased costs for equal clinical benefit. If these devices produce better clinical outcomes, appropriate reimbursement, even for more expensive endovascular interventions, should be promptly instituted so appropriate changes in delivery of care for patients with acute stroke can be expedited.

Conflict of Interest Disclosures: Both authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Genentech is a supplier of alteplase for the National Institute of Neurological Disorders and Stroke (NINDS)–funded IMS III and CLEARER trials. Dr Broderick reported having received consulting fees from Genentech. EKOS Corporation supplies catheter devices for the ongoing IMS III clinical trial. Concentric supplied devices for the IMS III trial up until 2009. Johnson and Johnson supplied catheters for the IMS III trial until 2009. Schering Plough supplies drug for the ongoing CLEARER Trial. Dr Broderick reported receiving consulting fees as a member of the data and safety monitoring board for the NEST III trial. Consulting fees and honoraria for Dr Broderick are placed in an educational/research stroke fund within the Department of Neurology. Dr Meyers is the external interventional safety monitor for the IMS III trial (NINDS U01 NS052220 and U01 NS054630).
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Financial Incentives and the Art of Payment Reform

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During the past 2 decades, physicians have expanded the scope of care provided in their offices to encompass a variety of services including advanced imaging that were traditionally performed in hospital-based settings. In this issue of *JAMA*, Shah and colleagues[1] describe a well-recognized consequence of this shift; namely, that physicians who provide and bill for a service, in this case cardiac stress imaging, tend to do more of it. The authors explored this relationship by linking physician billing patterns to the routine use of cardiac stress imaging after coronary revascularization—a practice with little supporting evidence.[2] The main finding was that the use of cardiac stress imaging for this typically discretionary indication was more common among patients evaluated by physicians who billed for the service, particularly physicians whose billing included technical fees in addition to professional fees. At first glance, the solution would appear clear—dampen the incentive to do more by additional regulatory and administrative levers and unnecessary services will be reduced.

At issue here is the oft-debated controversy surrounding physician self-referral and its associated financial incentives, which are governed by the Stark laws. Implemented in the 1990s, these laws were designed to remove the financial conflicts of interest from physician decision making for clinical laboratory tests (Stark I) and a variety of other ancillary services, including imaging (Stark II).[3] To preserve the potential efficiency advantages of legitimate business arrangements, however, numerous exceptions were established. The most commonly cited of these is the "in-office ancillary services exception," which permits self-referral to a physician-owned entity for certain services performed in the office. Although office-based care was initially designed for simple services, such as laboratory tests and chest radiography, this care setting has evolved to include expensive, high-end services, such as magnetic resonance imaging, computed tomography, and cardiac stress imaging. The financial benefits of such arrangements are clear as evidenced by their popularity—almost 1 in 5 physician practices report owning or leasing equipment for advanced imaging.[4]

As a result of such data, there are concerns that these exceptions have made the Stark laws ineffective at constraining imaging use, which increased by 70% during the last decade.[5] Increased use of imaging was particularly fast-paced among cardiologists—a group in which payments for imaging increased by approximately 200% over the same period.[6] However, these numbers must be viewed cautiously. Such trends occurred in the setting of considerable transitions in cardiac care from inpatient to outpatient settings,[7] and more importantly have been linked to substantial declines in mortality related to coronary disease.[8] Thus, it is uncertain whether the observed increase in imaging utilization is en-

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