CORRESPONDENCE

Endovascular Treatment for Acute Ischemic Stroke

TO THE EDITOR: In the Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE) trial, reported by Kidwell et al. (March 7 issue),[1] 22 participating centers enrolled 118 patients during the period from 2004 through 2011. Thus, on average, each participating center enrolled 1 patient every 16 months. This extremely low rate may suggest that inclusion in the trial was selective and not representative of patients with stroke in general. This notion is supported by the poor outcomes reported for both forms of treatment in the study. A good clinical outcome, defined as a 90-day score of 2 or less on the modified Rankin scale (ranging from 0 [no symptoms] to 6 [death]), was achieved in 44% of the patients in the Local versus Systemic Thrombolysis for Acute Ischemic Stroke (SYNTHESIS Expansion) trial reported by Ciccone et al.[2] and in 42% of the patients in the Interventional Management of Stroke (IMS) III trial reported by Broderick et al.[3] in the same issue. However, the corresponding proportion in the MR RESCUE study was only 19%. Assessment of a diagnostic tool with ineffective treatment methods will make even a very valuable diagnostic tool appear to be useless.[4] Accordingly, when the value of perfusion imaging is addressed in a population in which neither of the treatment methods under study appears to work, the validity of the entire study may be questionable. Unfortunately, neither the authors of the MR RESCUE study nor Chimowitz,[5] in the corresponding editorial, addresses this threat to the generalizability of the results.

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Dr. Andersson reports receiving consulting fees from Covidien and Neuravi. No other potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: In these three randomized trials of endovascular treatments for acute ischemic stroke, limited information was provided about anesthetic management. For example, results were not adjusted for the use of sedation, anesthesia, or both.

We recently performed a survey in France that showed that the use of sedation or general anesthesia appears to be a prevailing practice during endovascular procedures for stroke (unpublished data). Recent studies have reported worse outcomes in patients who received general anesthesia for endovascular procedures. The basis for this

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association remains unclear, especially because of the nonrandomized nature of the published studies.[1-4] A nonexhaustive list of hypotheses includes delays in treatment, risks related to intubation, hemodynamic changes, or specific effects of anesthetic drugs that could interfere with in situ fibrinolytic agents.[5] Until prospective, randomized studies that address the effect of anesthetic agents in acute ischemic stroke are undertaken, we suggest that trials that evaluate endovascular strategies should standardize and report the regimens of these agents to allow secondary analyses.

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TO THE EDITOR: Two of the reasons for the failure to prove the efficacy of endovascular treatment in these three randomized trials are the use of first-generation devices and the delayed (in the studies by Broderick et al. and Ciccone et al.) or absent (in the study by Kidwell et al.) introduction of new techniques in the study protocols. Recent randomized studies have clearly shown that stent retrievers were more efficacious than the Merci device.[1,2] Stent retrievers were used in 4 patients in the IMS III trial and in 23 patients in the SYNTHESIS Expansion trial; they were not allowed in MR RESCUE.

Furthermore, the large proportion of patients in whom there was a very long time from the start of intravenous thrombolysis to groin puncture indicates that the best clinical pathways were not used in several study sites. In addition, cross-sectional angiography before random assignment of patients to intravenous or interventional treatment should be mandatory.

In summary, we think that in all three trials, intravenous thrombolysis was not compared with best endovascular treatment. Further randomized, controlled trials should be based on modern concepts of imaging in patients with stroke and should continuously incorporate new devices.

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Drs. Arnold, Schroth, and Gralla report receiving lecture fees from Covidien. Dr. Arnold also reports receiving lecture and advisory board fees from Boehringer Ingelheim and Bayer Schering, and Dr. Gralla reports receiving consulting fees from Covidien as the global principal investigator for the Solitaire FR Thrombectomy for Acute Revascularization trial of the Solitaire FR revascularization device in stroke. No other potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: Kidwell et al. completed a rigorous, randomized evaluation of imaging-based treatment selection. However, their conclusion that penumbral-imaging selection did not identify a subpopulation of patients who would have a favorable response to endovascular therapy for stroke conflicts with previous findings.[1-3] The MR RESCUE trial did show significantly better outcomes in patients with a favorable penumbral pattern when recanalization occurred; these findings were consistent with those of previous studies, despite relatively large infarcts at baseline and a complex "penumbral selection" method. Interpretation of these data and the apparent response to recanalization in the nonpenumbral group is hampered by a lack of reported baseline characteristics for these subgroups. In addition, the key cofactors of reperfusion and recanaliza-

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tion were assessed late (at 7 days) when spontaneous recanalization was common and perhaps nonnutritional. Early recanalization holds the key to improved outcomes, and the low rate (27%) of good-quality postprocedural revascularization in MR RESCUE (a score of 2b to 3 on the Thrombolysis in Cerebral Infarction [TICI] scale, which ranges from 0 [no perfusion] to 3 [full perfusion]) is in stark contrast to results achieved with newer devices.[4] Ongoing studies such as Extending the Time for Thrombolysis in Emergency Neurological Deficits — Intra-Arterial (EXTEND-IA) (ClinicalTrials.gov number, NCT01492725) and Solitaire FR as Primary Treatment for Acute Ischemic Stroke (SWIFT PRIME) (NCT01657461) are using penumbral-imaging selection with more effective devices, and we await the results with interest.

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TO THE EDITOR: Broderick et al. and Ciccone et al. described studies comparing intravenous tissue plasminogen activator (t-PA) alone with intravenous t-PA plus endovascular treatment for acute ischemic stroke, and they found no advantage with endovascular treatment. These studies include patients with both large and small distal-vessel occlusions who probably benefit from different treatment approaches. Stent-based thrombectomy, the state-of-the-art endovascular approach, was used in only a handful of patients. Because of these limitations, both studies should be viewed with caution.

Intravenous t-PA improves outcomes in patients with mild-to-moderate stroke by recanalizing small-to-midsize arteries; however, its efficacy in recanalizing major large-vessel strokes is limited. Outcomes with early endovascular techniques — intraarterial thrombolysis and mechanical thrombectomy — were limited by long procedure times.

The newest stent-based thrombectomy devices allow unprecedented rapid complete recanalization rates (Thrombolysis in Myocardial Infarction risk score, 3 on a scale of 0 to 3, with 0 indicating no flow and 3 normal flow; TICI score, 2b to 3) in occlusions of the proximal middle cerebral artery. We found that stent-based thrombectomy provides superior outcomes as compared with intravenous t-PA in these patients,[1] with good functional outcome (a score of 0 to 2 on the modified Rankin scale, which ranges from 0 to 6, with higher scores indicating greater disability) in the majority of patients.[2] The SWIFT study also showed superior results with current devices as compared with the Merci device.[3] Rapid recanalization with stent-based thrombectomy appears to improve outcomes.

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DR. BRODERICK AND COLLEAGUES REPLY: The IMS III trial was designed to test the approach of endovascular therapy after intravenous t-PA as compared with intravenous t-PA alone because we anticipated the rapid evolution of Food and Drug Administration (FDA)–cleared endovascular

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technology for clot removal during the course of the trial, which did occur. Unfortunately, our trial was halted prematurely for futility after only a handful of patients had been treated with the trial-approved Solitaire stent-retriever device, and we agree that the trial cannot address the efficacy and safety of the devices. However, many interventionalists did not participate in our study because they believed that the older endovascular approaches were superior to intravenous t-PA alone, which the trial did not show. Randomized trials of the new endovascular technology as compared with intravenous t-PA alone, including SWIFT PRIME and Assess the Penumbra System in the Treatment of Acute Stroke (THERAPY; NCT01429350), are ongoing.

We agree with the importance of vascular imaging before treatment in clinical trials of endovascular therapy. When our study began in 2006, few centers used computed tomographic (CT) angiography as part of the standard evaluation of patients with acute stroke.[1] For this reason, we used a score of 10 or more on the National Institutes of Health Stroke Scale (ranging from 0 [no neurologic deficit] to 42 [maximum possible deficit]) to identify patients with a high likelihood of an intracranial artery occlusion on angiography after intravenous t-PA. The use of CT angiography as a diagnostic tool dramatically increased during the trial, and we incorporated its use so that nearly half the trial patients underwent vascular imaging before treatment. In a prespecified analysis, we found no significant difference in outcomes in patients with a pretreatment occlusion of the internal carotid artery, proximal middle cerebral artery, or basilar artery.

Our study, which included many of the most experienced sites in the world with regard to endovascular therapy, emphasized rapid therapy in its design, but it still had a longer time to the start of endovascular therapy than the smaller, single-group IMS I[2] and II[3] trials. We agree that minimization of the time to the start of endovascular therapy will be critical to show its efficacy, and we recommend critical examination of the delivery of stroke care in the United States, in which patients are commonly treated with intravenous t-PA at a community hospital and then are transported to a tertiary center for additional endovascular therapy.

We agree with Gakuba and colleagues about the role of general anesthesia in endovascular therapy.

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Since publication of their article, the authors report no further potential conflict of interest.

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DRS. CICCONE AND VALVASSORI REPLY: We were glad to contribute to the evidence on the efficacy of endovascular treatment for stroke. The SYNTHESIS Expansion investigators have worked with great enthusiasm, even though the results were different from what was expected. We expected to confirm the common perception of the superiority of endovascular treatment over intravenous t-PA. Our findings confirm the importance of conducting randomized, controlled trials in this area. The comparative trials of old- and new-generation retrievers for thrombectomy revascularization (Trevo vs. Merci and Solitaire vs. Merci) described by Arnold et al. favor this erroneous perception. If endovascular therapy is intended to be stent-based thrombectomy with devices such as Trevo and Solitaire, then the first step in showing the efficacy of endovascular therapy, in our view, would be to show, with a well-designed, randomized, controlled trial, that stent retrievers are superior to intravenous t-PA in patients with large-vessel stroke. Unfortunately, the studies cited by Cohen and Leker which favored thrombectomy were not randomized, controlled trials and as such have many types of bias, as described by Mullen et al. in their systematic review.[1]

The investigators in our trial aimed to produce evidence that would support the diffusion of endovascular treatment to reduce the stroke burden nationwide, not in a subgroup of patients with ischemic stroke. We were not interested in a specific device; our study pragmatically allowed the use of the devices that were available on the

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market at the time of the study and, inevitably, its results are related to the devices available when it was conducted.

The invitation by Gakuba et al. to perform a subgroup analysis involving patients who received anesthesia should be considered with caution: different institutions have different treatment protocols that are not always related to the clinical status of the patients. In some centers, patients in critical condition are more likely to undergo intubation; thus, bias is introduced in the analyses.

The same difficulties could be encountered in evaluating the subgroup of patients in whom stent retrievers were used in our trial: they were used mostly in the last part of the trial and only in a few centers. Even if the results seem slightly more encouraging in this subgroup, the numbers are definitely too small to draw conclusions.

Overall, we are in agreement with the accompanying editorial by Chimowitz, and we think that these three trials are not the end of trials of endovascular therapy but are rather a stimulus for new randomized, controlled trials of the use of the endovascular approach.

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Since publication of their article, the authors report no further potential conflict of interest.

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DR. KIDWELL AND COLLEAGUES REPLY: With regard to recruitment and possible selection bias: the average recruitment rate per site was 1 patient every 8 months, since not all sites were active throughout the trial. There is as much, if not more, reason to be concerned about selection bias toward milder cases of stroke in other studies, including the Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evaluation (DEFUSE 2) trial[1] and the study of tenecteplase reported by Parsons et al.[2] In the latter study, 2768 patients were screened and 75 were enrolled. The rate of good outcomes in the MR RESCUE trial cannot be directly compared with those of the IMS III and SYNTHESIS Expansion trials, which had shorter enrollment time windows and differing inclusion and exclusion criteria. We agree that the issue of generalizability for all imaging-based studies requires further scrutiny.

We agree with the concern raised regarding the potential effect of anesthesia management on outcome. We did collect information on anesthesia management in MR RESCUE, since there was reluctance from the endovascular community (endovascular surgeons, anesthesiologists, and interventional radiologists and neurologists) to adopt a single standard approach when our trial was conducted.

Our trial continuously updated the protocol to include newly available devices coincident with FDA clearances throughout the trial; stent retrievers entered practice only as enrollment was being completed. We concur that the results reflect the performance of first-generation neurothrombectomy technology.

With regard to the letter by Campbell et al.: we do not agree that our trial results conflict with previous findings. The Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET) was a negative study that did not include a sufficient number of patients with a nonpenumbral pattern to test the imaging-selection hypothesis; therefore, no strong conclusions can be drawn from this study regarding penumbral-imaging selection.[3] Similarly, the DEFUSE[4] and DEFUSE 2[1] trials lacked control groups; no conclusions can be made definitively regarding the interaction of imaging selection and treatment for acute stroke versus control. We agree that early recanalization is likely to have the most benefit in patients with acute stroke.

In conclusion, as stated previously, we strongly endorse further randomized, controlled trials with new-generation devices to test both the efficacy of endovascular approaches to treatment for stroke and the full spectrum of the imaging-selection hypothesis. We have substantial concerns about studies that select for enrollment a priori only patients with penumbra-imaging patterns. Without definitive proof of the hypothesis of penumbral-imaging selection, these studies could lead to misleading conclusions not only about imaging selection, but also about the criteria regarding which patients may benefit.

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Antibiotics for Uncomplicated Severe Malnutrition

TO THE EDITOR: Trehan et al. (Jan. 31 issue)[1] found that amoxicillin or cefdinir improved recovery from severe malnutrition among children in Malawi. The hypothesized reasons for their effectiveness include an underlying immunodeficiency related to malnutrition.[1,2] However, although a major cause of immunodeficiency in Malawi is the human immunodeficiency virus (HIV), 68% of enrolled children were not tested for HIV; among those tested, 22% had HIV infection. Children known to be infected with HIV had the highest risk of treatment failure or death. Malnutrition is a well-known condition in children with HIV disease; outpatient therapeutic programs are important venues for the identification of infected children.[3] Unfortunately, incomplete ascertainment of HIV status and inadequate management of infection in children, including trimethoprim–sulfamethoxazole prophylaxis, antiretroviral therapy (ART), or both, may confound the interpretation of the trial findings. The proper management of HIV infection could modify the effect of amoxicillin and cefdinir, and ART can improve weight gain and be lifesaving in infected children.[2] Offering HIV testing (and referral for HIV care for those infected) is an internationally accepted practice in clinical trials and is consistent with Malawi's national HIV testing and treatment guidelines.[3,4] It would, therefore, be helpful to know why testing was not performed.

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TO THE EDITOR: Trehan et al. concluded that antibiotics should be used routinely with ready-to-use therapeutic food (RUTF) for severe malnutrition in outpatients, irrespective of concomitant infectious disease. Augmentation of RUTF is sorely needed,[1] but we question the magnitude of the benefit and suggest that it be weighed against alternative interventions and the likely costs of increased antibiotic resistance.

The researchers reported that adding a 7-day antibiotic course to RUTFs resulted in significant reductions in mortality and increases in recovery rates. Careful analysis of the findings, however, shows that among survivors, the differential in the rate of treatment failure between the antibiotic treatment groups and the placebo group was less than 1%. In addition, the study fails to take into account infections, breast-feeding, and status with regard to HIV and AIDS.

Given the high prevalence of moderate and re-

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