Emerging Therapies

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Devices, Drugs, and the Food and Drug Administration
Increasing Implications for Ischemic Stroke

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The approval process at the Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has been of little interest previously to stroke neurologists, but an increasing number of devices are being approved for stroke prevention (carotid stents, patent foramen ovale closure) and now also for acute ischemic stroke intervention. Felten et al provide a review of the CDRH approval process and give their perspective concerning the recent approval of the Concentric Merci Retriever in acute ischemic stroke. Drs Becker and Brott were members of the FDA advisory panel that reviewed the MERCI (Mechanical Embolus Removal in Cerebral Ischemia) Trial and approval application. Despite concerns raised by the advisory panel, the Merci device was ultimately approved by CDRH. It is not our purpose to arbitrate the specific concerns raised by the advisory panel or to question the CDRH decision; readers can judge the strength of the evidence for themselves. However, we do wish to consider some of the implications of this decision for patient care and stroke clinical research.

The Merci Retriever was approved for clot removal in brain arteries and not as a therapeutic modality for acute ischemic stroke. This distinction is critically important. The MERCI Trial relied on historical controls (mostly data from PROlyse in Acute Cerebral Thromboembolism [PROACT II]) for demonstration of safety, recanalization efficacy, and clinical outcome. Although not the primary end point, it is useful to summarize clinical outcomes in the MERCI Trial. The median baseline National Institutes of Health (NIH) Stroke Scale score was 17 in the PROACT II controls and 19 in the MERCI patients, implying that the MERCI patients had more severe strokes. This could partly reflect the inclusion of patients with internal carotid and vertebral basilar occlusions in MERCI. The overall 90-day favorable outcome in MERCI, defined as a modified Rankin score of ≤2, was 31%, which is not significantly better than the rate in the middle cerebral artery controls in PROACT II (25%). In patients who recanalized, the favorable outcome was 53%. The 24-hour symptomatic brain hemorrhage rate was 8%, very similar to the 10% rate in PROACT II, in which patients received intra-arterial (IA) prourokinase. The 90-day mortality rate was 27% in the PROACT II controls and 40% in the MERCI Trial. The conclusions we draw from MERCI are that despite the 54% partial or complete immediate recanalization rate (63% at 1 hour in PROACT II), there was no overall evidence of improved patient outcome at 90 days. There was a suggestion of improved outcome in patients who recanalized. The symptomatic brain hemorrhage rate was similar to patients given an IA thrombolytic agent, and the 90-day mortality was higher in the MERCI trial.

Although these results could reflect case mix and insufficient sample size, it also reinforces that safely re-establishing brain reperfusion alone does not guarantee meaningful clinical improvement in patients with acute stroke. Additionally, establishment of clinical efficacy for reperfusion therapy beyond 3 hours from stroke onset with either device, drug or both, will require a randomized, controlled trial stratified by stroke severity and site of occlusion that also includes patients still capable of responding to reperfusion therapy (ie, patients with ischemic but still salvageable tissue, the ischemic penumbra). Reperfusing irreversibly injured brain tissue will not improve outcome and may lead to an increased risk of hemorrhage. If the Merci Retriever can be used in conjunction with advanced imaging technology that can identify the ischemic penumbra, then it is possible that clinical efficacy could be established beyond 3 hours. Such a trial, Magnetic Resonance and REcanalization of Stroke Clots Using Embolectomy (MR RESCUE), is ongoing, and it will be interesting to see how rapidly patient recruitment occurs.

The approval of the Concentric Merci Retriever for use in ischemic stroke highlights important differences in the FDA approval process between CDRH and the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER). Although the 3 pillars of approval are safety, mechanism of action, and clinical

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efficacy, each FDA center weighs these quite differently. Concerns about the FDA device approval process were first raised by the Temple Report of 1993. After a device is approved by CDER nor CBER has approved pharmacological agents similar to the CDHR process for devices (eg, approving a thrombolytic agent based on demonstrated safe and effective recanalization). This important emerging issue was addressed recently by an FDA advisory panel on the design of clinical trials for endovascular devices to treat and prevent acute ischemic stroke and the Stroke Therapy Academic Industry Roundtable (STAIR) IV conference. We also suggest that “mechanistic approval” of either a device or a drug should be provisional and lead to only limited reimbursement by CMS. Full reimbursement by CMS for a device, just as for a drug, should be linked to unequivocal demonstration of clinical efficacy. Furthermore, in our opinion, there is no justification for CDRH, CDER, and CBER to grant approval using differing standards of clinical efficacy. The highest level of evidence for clinical efficacy for a device or a drug remains a randomized, controlled, adequately powered clinical trial. Less strict alternatives, such as historical controls, objective performance criteria, and validated surrogate end points, should be considered by CDRH, CDER, and CBER, but the circumstances under which such alternatives might be acceptable for approval should be standardized across FDA centers.

Although NIH, CDRH, and CMS have collaborated in studies such as Carotid Revascularization Endarterectomy Versus Stent Trial to fulfill premarket reimbursement and to provide proof of clinical efficacy requirements, such collaboration remains the exception rather than the rule with devices. We suggest that the path to approval at CDER and CBER may be too inflexible and may discourage pharmaceutical participation in stroke research. We believe that the evolution of new stroke therapies requires a similar evolution in the FDA device and drug approval process. A more homogeneous and consistent approach across FDA centers would help advance the care of patients with stroke and other serious and life-threatening conditions.

**References**


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