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Comeback Victory

V. Mendes Pereira and T. Krings

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toms be treated? On the contrary, is mechanical thrombectomy indicated in patients with severe stroke? It will also be important to determine whether mechanical thrombectomy is indicated regardless of the patient's age (see above). The role of imaging in patient selection will have also to be carefully evaluated.

Will MR CLEAN Results Affect the Management of Patients with Ischemic Stroke?

A single trial with a positive outcome is certainly not sufficient to claim that EVT is now the first-line treatment for ischemic stroke. Positive data from 3 additional trials (ESCAPE, EXTEND-IA, and SWIFT PRIME) are now available. On the basis of this evidence, it is likely that EVT will rapidly become the first-line treatment in patients with ischemic stroke with LVO. This will tremendously impact the health care system, because it will be necessary to offer this demanding treatment by well-trained interventional neuroradiologists to all patients without delay.[20] This means early identification of patients with ischemic stroke who will benefit from EVT, the establishment of stroke centers offering this service 24 hours/7 days, and enabling training in the EVT of cerebral arteries.

MR CLEAN has shown the value of EVT initiated within 6 hours of ischemic stroke onset caused by LVO of the anterior circulation. According to the clinical severity of ischemic stroke of the posterior circulation and recent data from a registry showing high recanalization rates in patients with basilar artery occlusion, continued evaluation in this group of patients seems important.[21] Indeed further trials will be necessary to precisely define the arterial occlusion type, brain pathology, and finally the time window in which EVT is indicated for patients with anterior or posterior circulation stroke and the management of patients with wake-up stroke.

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EDITORIAL

Comeback Victory

V. Mendes Pereira and T. Krings

The International Stroke Conference (ISC) 2015, in Nashville, Tennessee, was a memorable meeting. During a crowded plenary session, we witnessed the presentation of 4 randomized con-

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trolled trials (RCTs) that will change acute ischemic stroke (AIS) treatment, favoring an endovascular approach: Multicenter Randomized Clinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands (MR CLEAN), Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke (ESCAPE), Extending the Time for Thrombolysis in Emergency Neurological Deficits–Intra-Arterial (EXTEND-IA), and Solitaire FR With the Intention For Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke (SWIFT PRIME).[1-4] It was maybe even more memorable, given that only 2 years ago, in a similarly crowded session at the same conference, the presentation and simultaneous publication of 3 other RCTs, Interventional Management of Stroke III (IMS III),[5] SYNTHESIS,[6] and Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE),[7] led to completely different results, despite handling seemingly the same problem: whether the addition of intra-arterial therapies to the established intravenous treatment leads to improved patient outcome. Two years ago, these 3 studies were a serious blow at a time of huge excitement in the interventional/endovascular community because we had started to experience the beneficial effects of the new-generation devices, the stent retrievers, and were finally able to move away from the kitchen sink approach to stroke treatment.

However at the ISC 2013, in Honolulu, Hawaii, there was also a silver lining: the Solitaire FR Thrombectomy for Acute Revascularization (STAR) trial, which was subsequently published in *Stroke*, demonstrated positive results for mechanical thrombectomy.[8] That study pooled data from high-volume stroke centers that had documented experience with stent retrievers. Moreover, this study focused on patient selection (including documentation of the vascular occlusion), procedure standardization, and revascularization results (successful recanalization reported in the modified TICI score). In this study, good clinical outcomes at 3 months (mRS 0–2) were obtained in 57.9%, final revascularization rates were 88.1% (modified TICI 2b or 3), mortality was 6.9%, and the symptomatic hemorrhagic rate was 1.5%. Some critiques remarked that these results were "too good to be true," though 2 previous studies, Solitaire FR With the Intention for Thrombectomy (SWIFT)[9] and Thrombectomy Revascularization of Large Vessel Occlusions in Acute Ischemic Stroke (TREVO 2),[10] had demonstrated that stent retrievers do represent a breakthrough in the endovascular treatment of AIS. For most interventionalists, these studies showed the potential of this new generation of mechanical thrombectomy, which was the technology used in the recently presented RCTs.

Despite the negative results of the 2013 RCTs, it took only little more than 2 years to overcome the skepticism around the endovascular treatment of AIS. This change was made possible due to the personal effort of leaders in the field of stroke; organized effort of professional societies; trial designs, execution, and center and patient selection; and standardized outcome measures. The lessons learned from previous trials with negative results were understood, and effort was made not to replicate them. Patient inclusion was based on well-defined parenchymal and angiographic imaging criteria and was consecutive rather than sporadic. In addition, center/team/operator selection was based on experience and workflow capacity, and the use of next-generation technology was a common criterion among all those new trials. Some of them, targeted to select the best possible potential population for an AIS study, used advanced mismatch perfusion imaging. However, their results presented some variances, and they should be analyzed from different perspectives to get the right message from each one.

The first of the 4 published trials was the MR CLEAN study,[2] a Dutch trial that, despite all uncertainty from the stroke community, demonstrated that intra-arterial treatment for AIS caused by an anterior circulation occlusion up to 6 hours after stroke onset is safe and clinically effective. They enrolled 500 patients in 2 randomized and controlled arms: intervention and control. The release of the MR CLEAN results generated an "on hold" response in all other trials as recommended by their leadership or data and safety monitoring boards until an unplanned interim analysis was conducted on their own populations. MR CLEAN had a major impact not only because it was the first study with positive findings but also because the authors had wisely chosen the best population for the question at hand and answered it in a "real world" scenario. In the favor of the trial, they had a structured health system, confined geography, and committed centers and health policy makers (allowing reimbursement only under the auspices of the trial). Thus, they enrolled patients fast, including patients with salvageable brain (median ASPECTS scores of 9 in both arms) with a proved arterial occlusion. Additionally, they used stent retrievers in 97% of patients. However, their final recanalization results (58.7%) were not that impressive, and neither were the clinical outcomes in both arms (32.6%, interventional; 19.1%, control). They also reported 9% of emboli to new territories on DSA following stent thrombectomy, a rate not reported in any previous study using these new devices, to our knowledge.

The endovascular results suggest that a learning curve effect might have been present because the study started in 2010, at the beginning of the use of stent retrievers in Europe.[11] The advantage of this study becomes apparent when looking at the trial execution: When MR CLEAN was designed and executed, the consensus was not to consider a patient a potential candidate for endovascular treatment of AIS without full IV rtPA treatment. Thus, patients included in this trial were the "failed IV rtPA" population, with a proximal occlusion detected after intravenous treatment. This explains the rather poor clinical outcomes in the control arm along with the fact that they had long needle-to-puncture times in the interventional arm as well. This workflow is reflected on the reported times of the study: The authors were extremely fast at initiating the IV rtPA (85–87 minutes from stroke onset) but performed randomization only at a median time of 111–119 minutes after IV therapy started. This aspect does not disparage the study; it just explains why the outcome results are different (at a superficial sight) compared with other trials. For future meta-analyses and subset studies, note that this patient population was different from the ones evaluated in IMS III, SYNTHESIS, ESCAPE, or SWIFT PRIME.

The second recently published trial, ESCAPE,[1] was a well-designed and executed trial focused on sequential (or consecutive) patient randomization, stringent imaging-selection criteria (ASPECTS score, leptomeningeal collateral evaluation, and site

occlusion imaging), quick workflow with targeted times after stroke onset, and next-generation technology. The authors randomized 316 patients in 2 arms (endovascular intervention versus standard of care control) in a therapeutic window of 12 hours. The trial was stopped following interim analysis because of the overwhelming benefit of endovascular treatment. Due to the optimized workflow, the mean time between CT and the onset of endovascular treatment was 51 minutes and the mean time from CT to recanalization was 84 minutes. Reperfusion (TICI 2b or 3) was achieved in 72.4%. Good clinical outcomes (mRS 0–2) were achieved in 53% of patients treated by endovascular means compared with 29.6% in the control arm. Absolute reduction in mortality was 8.6 ($R = 0.4$), and the number of treated patients needed to achieve independence was 4. Despite inclusion being permitted for up to 12 hours, >75.3% of included patients were IV-rtPA candidates (also <4.5 hours).

SWIFT PRIME was the third trial (in order of the number of patients reported) and was also put on hold for unplanned interim analysis on release of the MR CLEAN results and was subsequently stopped. This study included 196 patients in 2 arms: IV rtPA alone versus IV rtPA associated with the Solitaire stent retriever (Covidien, Irvine, California). The focus of this trial was workflow performance targets and patient selection based on imaging. The latter was initially based on perfusion mismatch criteria, but after one-third of patients were included, the steering committee decided to change to parenchymal and site occlusion imaging criteria. Good clinical outcomes (mRS 0–2) were achieved in 60.2% of patients treated in the interventional arm compared with 35.5% in the control arm. In the endovascular arm, successful reperfusion rates were 88%, with a substantial amount being TICI 3 (68.7%). This outcome probably reflects the experience of the selected centers and a standard endovascular protocol at all participating sites. The symptomatic hemorrhagic rate was 1%, and mortality was 9.2% (intra-arterial) versus 12.4% (controls). The STAR trial, which had very similar patient and center inclusion criteria, arrived at very similar results for intra-arterial treatment.[8]

The Australian/New Zealand EXTEND-IA trial[3] included 70 patients until October 2014. The authors selected candidate patients by using mismatch perfusion imaging randomized into medical therapy alone versus a combined intravenous/intra-arterial approach with mechanical thrombectomy using a stent retriever. They reported reperfusion (TICI 2b/3) rates of 86% in the intra-arterial treatment arm that were associated with a good clinical outcome in 72%, compared with good clinical outcome rates of 39% in the control arm. Despite the small number of selected patients, this difference was statistically significant and justified stopping the trial. Mortality and symptomatic hemorrhagic rates were 3% and 0% in the interventional arm compared with 7% and 2% in the control arm.

These trials have the following in common: efficient trial execution, patient selection based on imaging, and results that overwhelmingly favored intra-arterial treatment, which led to the early end of the trials with <50% of the initially planned patients included. The higher estimated number of patients stems presumably from pessimism about endovascular treatment for AIS that prevailed during the design of these studies following the 2013 initial results, leading to more conservative expectations. With increasing imaging complexity (from ESCAPE to SWIFT PRIME and EXTEND-IA) and thus more granular patient selection, the rate of good clinical outcomes increased. This result may suggest the value of selection criteria based on advanced imaging for patients with AIS. However, the more we "cherry pick" our patients in a real-world scenario, the fewer patients overall will be treated by endovascular means and more patients with potentially treatable strokes may remain untreated. Future studies and guidelines will determine how to innovate for imaging to determine acute stroke treatment.

Determination of imaging criteria is only one of the unanswered questions related to the extent of the investigation: Is there an age limit? How far can we stretch the time limit? How do we treat associated vascular lesions (such as carotid stenosis)? In addition to the pure procedural questions, we must answer system-wide questions: How can we ensure standards of training? How do we change prehospital care guidelines concerning patient transfer? What is the cost per quality-adjusted life year or treatment that society can pay? Should this treatment become "more available" to the detriment of quality? Obviously a number of discussions are needed.

Regarding the latter question, one can envision 2 antithetical scenarios: first, with a nonstroke clinician seeing the patient and a general nonspecialized radiologist reading a basic head CT, thus making treatment decisions performed by a non-neurointerventionally trained team. In the other, the stroke-specialized neurology team and the diagnostic neuroradiology team make a decision based on advanced imaging for a neurointerventionally trained group in an institution prepared to welcome patients with AIS and offer each patient the workflow, revascularization rates, clinical outcomes, and safety targets described by the most recent RCTs. The questions to ask ourselves, our professional societies, the policy makers, and our health system are related to these 2 scenarios: What are the minimum requirements we are willing to accept? How many centers do we need? What are the available resources, and how can we best reach our goal of offering the best care to as many patients as possible?

Disclosures: V. Mendes Pereira—*RELATED*: Principal Investigator for the STAR trial and Co-Principal Investigator for SWIFT PRIME, sponsored trials by Covidien.

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