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EDITORIAL

Teaching Lessons by MR CLEAN

L. Pierot, V. Mendes Pereira, C. Cognard, and R. von Kummer

After centuries of therapeutic nihilism for patients with ischemic stroke and 2 decades of systemic thrombolytic therapy with modest effects, there is hope that increasing arterial recanalization rates with endovascular treatment (EVT) can improve clinical and functional outcomes. Given that data from 3 previous randomized trials (SYNTHESIS Expansion, Interventional Management of Stroke III [IMS III], and Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy [MR-RESCUE]) failed to demonstrate a beneficial clinical effect, the positive outcomes from the Multicenter Randomized Clinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands (MR CLEAN) have renewed the enthusiasm and hope among physicians treating stroke.^{1–4} Initial data from additional trials (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]) provide further evidence supporting the MR CLEAN results.^{5,6} It appears that the new-generation interventional devices could enable highly effective stroke treatment in a time window broader than before, making restrictions of IV therapy alone either clinically irrelevant or applying to a very defined patient population.

Why Is the MR CLEAN Outcome Positive?

MR CLEAN was designed to compare EVT plus usual stroke care (intervention) versus usual stroke care alone (control) in 500 patients with proved occlusions of proximal major arteries of the anterior cerebral circulation. Usual stroke care included treatment with IV-rtPA in 90.6% of the control patients and 87.1% in intervention patients. All primary and secondary end point results statistically favored EVT, especially in a population in which poor prognosis is seen with usual stroke care alone. On the basis of the imaging data, the absence of arterial occlusion at the target site on

24-hour CTA was significantly higher with EVT compared with usual stroke care alone (75.4% versus 32.9%; OR, 6.27). Compared with another large prospective EVT/stent retriever series such as the Solitaire Thrombectomy for Acute Revascularization (STAR) (79.2%), the successful reperfusion rate on DSA (TICI 2b or 3) was lower in MR CLEAN (58.7%).⁷ In both trials, TICI was independently evaluated by a core laboratory, but as mentioned by the MR CLEAN authors, the differentiation between 2a and 2b was not always easy, particularly in the absence of a lateral DSA view. In such cases, a conservative approach was taken and recanalization was graded as TICI 2a. In addition, center experience may be an important factor to consider. STAR was conducted in highly experienced neurointerventional centers, whereas MR CLEAN was conducted in 16 Dutch centers with at least 1 member of the intervention team having completed at least 5 procedures with a particular type of device.

Most important, MR CLEAN results demonstrated an increased rate of functional independence in the EVT group (32.6%) compared with the usual care group (19.1%), with an absolute difference of 13.5%. Compared with previous randomized trials, the percentage of patients with favorable clinical outcomes in MR CLEAN is relatively low (40.8% in IMS III and 42.0% in SYNTHESIS) and even lower than that in the placebo group in the European Cooperative Acute Stroke Study (ECASS III) (45%).⁸ It can be presumed that some patients who were enrolled into previous trials such as ECASS-III, IMS-III, and SYNTHESIS had spontaneous good clinical outcomes because they did not require confirmation of large-vessel occlusion (LVO) with baseline imaging. However, compared with EVT/stent-retriever studies requiring baseline vessel imaging, the rate of functional independence reported in MR CLEAN is low (SWIFT, 37%; STAR, 57.9%; Thrombectomy Revascularization of Large Vessel Occlusions in Acute Ischemic Stroke 2 [TREVO 2], 40%; North American Solitaire Stent-Retriever Acute Stroke Registry [NASA Registry], 42%).^{7,9–11}

The MR CLEAN patient population primarily comprised patients who had failed IV-rtPA (ie, IV-rtPA-treated patients without clinical improvement after receiving only the full dose administered during 1 hour). Most of the centers initiated rtPA after plain CT and subsequently performed CTA only when it had been determined that the patient was not clinically improving. Given that close to 90% of patients in both arms received IV-rtPA, the treatment response of this particular patient population can per se explain the poor outcome of the usual treatment arm. The MR CLEAN population is different in comparison with those in previous and upcoming trials. In terms of workflow metrics, there was a long delay between symptom onset and groin puncture in MR CLEAN (260 minutes compared with 208 minutes in IMS III and 225 minutes in SYNTHESIS). Initiation of IV treatment was not delayed in MR CLEAN (87 minutes) compared with IMS III (121 minutes) and SYNTHESIS (165 minutes).

Another contributing factor is the screening of consecutive eligible patients into the MR CLEAN trial. The Dutch health system allowed EVT for ischemic stroke only inside the MR CLEAN trial. This factor enabled high recruitment rates and avoided the “cherry picking” of presumably easy-to-treat patients. MR CLEAN was thus a “real life” study in a small country with short

distances, including all centers irrespective of their experience with ischemic stroke treatment.

The MR CLEAN investigators did not put their patients at additional risk. Safety results demonstrated that new ischemic strokes in different vascular territories occurred in the EVT treatment group; however, mortality did not increase, while functional outcome at 3 months improved.

In summary, data from the MR CLEAN trial significantly favored the EVT treatment arm in achieving a significant decrease of the median modified Rankin Scale score from 4 (severe disability) to 3 (moderate disability) due to several factors: 1) the inclusion of patients who failed IV-rtPA treatment, 2) excellent trial execution without allowing EVT outside the trial setting, and 3) safe implementation of EVT by the participating centers. MR CLEAN probably gives us a more realistic picture of clinical outcome after medical treatment in patients with large-vessel occlusion and failed IV treatment.

Role of the EVT Technique in MR CLEAN

Since the implementation of EVT in ischemic stroke by Zeumer et al,¹² several techniques have been developed, from intra-arterial (IA) administration of thrombolytics to mechanical thrombectomy with stent retrievers and aspiration devices.¹³ Data from previous randomized studies demonstrate that stent retrievers are superior to other clot-retriever devices (eg, Merci retriever; Concentric Medical, Mountain View, California) in terms of recanalization, mortality, and clinical outcome.^{9,10} IMS III, MR-RESCUE, and SYNTHESIS included heterogeneous EVT techniques that significantly impacted procedure times and revascularization results.^{14,15} MR CLEAN allowed only devices that had received US Food and Drug Administration approval or a Conformité Européenne marking. In contrast to the IMS III, MR RESCUE, and SYNTHESIS trials, 190 of the 196 (96.9%) patients who actually received EVT were treated with stent retrievers. Twenty-four percent received IA thrombolytics in addition. Additional information on procedural techniques such as the use of distal access catheters or guide catheters with balloon occlusion of the internal carotid artery was not reported. In contrast to other trial protocols, patients with internal carotid artery occlusion were included and treated with cervical carotid stent placement ($n = 30$, 12.9%). The results suggest that the use of stent retrievers was the main component of the success of the trial. MR CLEAN, however, was not a trial testing the efficacy of stent retrievers in the treatment of ischemic stroke, but of EVT in general. The therapeutic impact of other components (anesthesia, proximal-versus-distal access, aspiration, IA thrombolytics before or after EVT) needs to be assessed.

What Can We Learn from Subgroup Analyses?

Several subgroup analyses have been presented in the initial publication of the MR CLEAN results. Data suggest that endovascular treatment with stent retrievers has a relatively similar efficacy regardless of initial NIHSS values, suggesting that the severity of acute ischemic stroke need not be taken into account when considering EVT. However, it is not logical to perform EVT in patients with initial low NIHSS scores and spontaneous good prognosis. Indeed, the median NIHSS score was 17 in the interventional arm of MR CLEAN and 18 in the

medical arm, making it unlikely that many patients with low NIHSS scores were included. A detailed analysis of the outcomes from patients with very low baseline NIHSS scores and extended ischemic lesions on brain imaging is required and would be interesting.

The question of revascularization in patients older than 80 years is still controversial. Subgroup analysis in the NASA registry showed that being older than 80 years of age is predictive of poor clinical outcomes (mRS 0–2 in 27.3%) and greater mortality (43.9%) compared with younger patients (mRS 0–2, 45.4%; mortality, 27.3%).¹⁶ In MR CLEAN, the patient age range was 23–96 years, and 81/500 patients were older than 80 years (16.2%). In this subgroup of elderly patients, there is clearly a great benefit of EVT (odds ratio, 3.24 versus 1.60 in patients younger than 80).

As previously demonstrated, there is a very limited benefit of EVT in patients with a low ASPECTS (OR, 1.09 in patients with ASPECTS 0–4, but 1.97 and 1.61 with ASPECTS 5–7 and 8–10, respectively); this criterion should probably be a contraindication to EVT.¹⁷

The data also reveal a benefit of EVT when there is an associated extracranial ICA occlusion (OR, 1.43 versus 1.85 when absent). A precise analysis of the strategy of treatment in tandem lesions is important to determine the best approach. Finally, the data also established a high benefit of EVT in case of ICA terminus occlusion (OR, 2.43 versus 1.61 when absent).

How to Improve the EVT Results?

Numerous analyses have shown that reducing the delay for recanalization is essential if we want to improve the clinical outcome of patients with ischemic stroke.¹⁸ In MR CLEAN, the median time from stroke onset to groin puncture (not to recanalization) was relatively long, exceeding the 260-minute time window for which IV-rtPA is approved. This suggests that ischemic stroke can be effectively treated beyond 3 or 4.5 hours; a subgroup analysis on the impact of time to intervention on clinical outcomes would be of value. Intervention with EVT should be based on clinical examination and brain and vessel imaging. Every management step has to be carefully analyzed to reduce the time from stroke onset to EVT. Delaying endovascular intervention until IV thrombolysis fails does not make sense and should not be part of the decision-making process; further studies should clarify whether IV-rtPA improves the efficacy of EVT. Several technical questions concerning the use of EVT also need to be answered, including how to reduce the rate of procedural complications (11.2% in MR CLEAN), such as embolization to new territories (8.6%) and vessel dissection or perforation (2.6%); determining the type of anesthesia (general anesthesia or conscious sedation) to be used; the systemic use of balloon-guide catheters; distal clot aspiration; and so forth.¹⁹ Finally, considerations to modify the design of the stent retrievers to reduce the risk of arterial dissection or rupture should also be evaluated.

Continuous work is also needed to improve the selection of patients to be treated with mechanical thrombectomy. A precise analysis should be conducted to determine the severity of the stroke to be treated. Should patients with mild or moderate symp-

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.

Disclosures: Laurent Pierot—RELATED: Consulting Fee or Honorarium: Codman, Covidien/ev3, and MicroVention; UNRELATED: Consultancy: Sequent. Vitor Mendes Pereira—RELATED: Consulting Fee or Honorarium: Covidien, Comments: Principal Investigator for the STAR trial, co-Principal Investigator for the SWIFT PRIME trial, Steering Committee of the Trevo and Medical Management versus Medical Management Alone in Wake Up and Late Presenting Strokes trial. Christophe Cognard—UNRELATED: Consultancy: Codman, Covidien/ev3, MicroVention, Sequent, and Stryker. Rüdiger von Kummer—RELATED: Consulting Fee or Honorarium: Lundbeck, Covidien, Penumbra, and Boehringer Ingelheim; Support for Travel to Meetings for the Study or Other Purposes: Lundbeck, Covidien, Penumbra, and Boehringer Ingelheim; Fees for Participation in Review Activities (such as data monitoring boards, statistical analysis, end point committees, and the like): Lundbeck; UNRELATED: Board Membership: Lundbeck, Covidien, Penumbra, and Boehringer Ingelheim; Payment for Lectures (including service on Speakers Bureaus): Lundbeck, Penumbra.

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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-