



## EDITORIAL

### Endovascular treatment for acute ischaemic stroke: in search of evidence<sup>☆</sup>

### Tratamiento endovascular del ictus isquémico agudo: en busca de la evidencia

J.A. Matias-Guiu\*, L. López-Ibor

*Servicio de Neurología y Neurorradiología Intervencionista, Hospital Clínico San Carlos, Madrid, Spain*

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#### Introduction

Ischaemic stroke is one of the main causes of morbidity and mortality in our setting. There have been significant advances in the treatment of these strokes in recent years, owing to the organisation of stroke units and use of intravenous fibrinolytic therapy with alteplase.<sup>1</sup> Despite the fact that these measures have greatly improved patient prognoses, morbidity and mortality rates related to ischaemic stroke remain high. Current evidence indicates that achieving recanalisation and reperfusion of the affected vascular territory is linked to better outcomes.<sup>2</sup> This being the case, current research into acute stroke treatment has focused mainly on 2 goals: firstly, increasing the percentage of candidates for revascularisation treatment within the patient total; and secondly, achieving higher recanalisation rates. With this in mind, endovascular treatment is a promising tool<sup>3</sup> that, according to some researchers, may deliver significant benefits. It is associated with a higher recanalisation rate than that of fibrinolytic therapy. Nevertheless, a large part of the current results come from observational studies, meaning that trials with a higher level of evidence are required to confirm such hypotheses. Three

such clinical trials addressing these topics have recently been published: International Management of Stroke III (IMS-III), Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE) and Local versus Systemic Thrombolysis for Acute Ischaemic Stroke (SYNTHESIS Expansion).

#### International Management of Stroke III<sup>4</sup>

Considering that the recanalisation rate for intravenous fibrinolytic therapy is sub-optimal in some situations, but that time to start of treatment is greater in endovascular therapy, researchers have proposed combined treatment, or bridging therapy. This approach may be more beneficial since it combines the advantages associated with each treatment: early treatment onset for intravenous fibrinolysis and a better recanalisation rate for intra-arterial therapy. To test this hypothesis, the IMS-III trial included randomised patients whose NIHSS score was higher than 10 and who had received intravenous fibrinolytic therapy within 3 hours of symptom onset. For every 2 patients receiving additional endovascular therapy, 1 patient was treated with intravenous fibrinolysis only. The study was stopped due to futility after 656 patients had been included over 6 years. The patient group undergoing endovascular treatment received a dose lower than the standard dose (0.6 mg/kg) during most of the recruitment period. Angiographies were performed following treatment. Doctors employed endovascular treatment when occlusion was present, selecting from among the

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\* Corresponding author.

E-mail address: [jordimatiasguiu@hotmail.com](mailto:jordimatiasguiu@hotmail.com)  
(J.A. Matias-Guiu).

MERCI retriever, intra-arterial tPA, the Penumbra system, or the EKOS device according to their criteria. A CT angiography was performed prior to treatment in 306 patients. In such cases, the presence of occlusion warranted including the patient in the study, but this was not mandatory and it was not part of the study protocol. Patients whose Alberta Stroke Programme Early CT score (ASPECTS) was less than or equal to 4 were excluded; 42% had an ASPECTS between 5 and 7, and 58%, between 8 and 10. Researchers found no statistically significant differences between the clinical trial's 2 study groups with regard to mortality and percentage of functional independence (score of 2 or less on the modified Rankin scale). Nor were differences statistically significant in an analysis of patient subgroups categorised according to stroke severity (NIHSS 8–19 or NIHSS >19).

### Mechanical retrieval and recanalization of stroke clots using embolectomy<sup>5</sup>

This study tested the hypothesis that neuroimaging tests would be able to identify patients who would benefit from endovascular treatment in the first 8 hours following stroke, with the understanding that this treatment would be useful in patients with established penumbral mismatch and futile in patients with a non-penumbral imaging pattern. Over 8 years, the study included 118 patients with ischaemic stroke of the anterior circulation and NIHSS scores between 6 and 29. Patients were randomly assigned to undergo either endovascular therapy (using the MERCI device or Penumbra system) or standard treatment; groups were stratified according to whether or not the penumbral pattern was favourable. Favourable pattern was defined as those in which the infarct measured less than 90 mL or occupied less than 70% of the vascular territory; this was the case in 58% of the patients. Patients were first selected using diffusion–perfusion MRI and MRA, although in 2009 the protocol was expanded to include selection with perfusion CT and CT angiography. The study also included patients who had already been treated with intravenous rtPA. The recanalisation rate (TICI 2a-3) in the treatment group was 67%, with 27% of the patients achieving optimal reperfusion (TICI 2b-3). No statistically significant differences could be detected between patients with and patients without endovascular treatment, regardless of whether their penumbral patterns were favourable.

### Local versus systemic thrombolysis for acute ischaemic stroke (SYNTHESIS Expansion)<sup>6</sup>

This study randomly selected 362 patients over 4 years and assigned them to 1 of 2 treatment groups: endovascular treatment within 4.5 hours of onset or intravenous fibrinolytic therapy within 6 hours of onset. Endovascular treatment was mainly performed using intravenous rtPA, although interventionists could also opt for using mechanical devices, as occurred in 56 cases. The trial protocol also included the uncertainty principle, and recruited patients therefore included some individuals whose best treatment

option was unclear. Performing CT angiography, MR angiography or a Doppler scan to detect occlusion was not a requirement for including patients, but these scans could be completed. The inclusion criteria did not include a minimum NIHSS score; as a result, the median NIHSS (13) was lower than in the 2 studies described previously (16–17). At 3 months, 30.4% of patients in the endovascular treatment group had reached scores of 0 to 1 on the modified Rankin scale, compared to 34.8% of patients in the intravenous fibrinolytic therapy group. ( $P = .37$ ). There were no statistically significant differences in mortality between groups (14.4% vs. 9.9%;  $P = .22$ ). Although time from symptom onset to random assignment was similar in both groups, time to start treatment was longer in the endovascular group (3 h 45 min vs. 2 h 45 min;  $P < .001$ ).

### Discussion

The main conclusion from all 3 clinical trials is that none was able to demonstrate that endovascular treatment was superior to intravenous fibrinolysis or standard treatment in any of the 3 contemplated scenarios: bridging therapy, direct comparison, or selecting patients according to diffusion–perfusion MRI or perfusion CT results at 4.5 hours after onset of symptoms. This indicates that intravenous fibrinolysis with rtPA should remain the first line of treatment for patients in the first 4.5 hours after ischaemic stroke. Nevertheless, these studies also provide other relevant conclusions.

The IMS-III and SYNTHESIS Expansion studies did not use CT angiography or MR angiography to detect occlusion as a requirement for inclusion in the study. This meant that of the 434 patients included in the endovascular treatment group in the IMS-III trial, 80 (18.5%) did not undergo endovascular treatment because the angiogram did not show a visible thrombus, even though CT angiography was used in nearly half of the sample. These data indicate that it is a good idea to use imaging tests to confirm large-vessel occlusion before proposing endovascular treatment; this type of treatment is more beneficial in cases with large-vessel occlusion, which show poorer results following recanalisation with intravenous rtPA.<sup>7</sup>

Meanwhile, endovascular treatments vary greatly within single studies and among different studies. This situation might seem beneficial, since interventionists have access to a number of different treatment types and devices and can tailor treatment to each patient. However, it does make it more difficult to extrapolate results. Use of intra-arterial rtPA was frequent in both the IMS-III and SYNTHESIS Expansion trials. Intra-arterial rtPA was administered to 266 patients in the first study, while 68 received other treatments. In the second study, 109 patients were treated with intra-arterial rtPA, and a mechanical device was also employed in 56. This is especially important when we consider that the percentage of recanalisation by means of mechanical devices seems higher than that with intra-arterial pharmacological fibrinolysis.<sup>8</sup> The low rate of stentriever use in these clinical trials (4 cases in IMS-III, 23 in SYNTHESIS Expansion) also raises the question of whether results might have been different if these devices had been more widely used.

The recanalisation rates obtained in these 3 clinical trials were lower than rates in other studies using stentrievors, and in fact also lower than rates in other studies using the same devices.<sup>9–11</sup> In the MR RESCUE trial, recanalisation was also evaluated at the 7-day point. Researchers found that recanalisation was associated with a better prognosis regardless of the penumbral pattern being favourable or unfavourable.

These studies also highlight some of the limitations of endovascular therapy. For example, the mean time to start endovascular therapy was 2 hours 4 minutes in the MR RESCUE study and 1 hour longer than the time to start intravenous fibrinolysis in the SYNTHESIS study. This delay, added to the growing evidence that intravenous fibrinolytic treatment can be performed safely prior to endovascular therapy, is a factor that probably supports using bridging therapy rather than continuing to compare the two treatments.

One of the difficulties mentioned by the authors has to do with recruitment. The fact that endovascular therapy is seeing increasing use means that many patients treated with this technique are not included in clinical trials. In fact, the SYNTHESIS Expansion trial protocol employs the 'uncertainty principle' when including patients, which may constitute a selection bias. This may be one reason why patients with vertebrobasilar stroke are rarely seen in these studies (6 patients in IMS-III, 29 in SYNTHESIS Expansion).

Another important consideration is which treatment is indicated for which patients. Intravenous fibrinolysis in acute ischaemic stroke has proved its utility despite heterogeneous patient characteristics including presence or absence of arterial occlusion, different aetiologies, etc. Since the success of endovascular treatment is probably more closely linked to achieving recanalisation and to factors related to the technique, patient selection criteria for this technique should probably be stricter. Factors such as aetiology or the location of the occlusion (carotid T occlusion, tandem lesions, anterior or posterior circulation, etc.) may be more relevant to treatment success.<sup>12</sup> If this were not the case, a large number of patients would probably have to be treated before the therapy could be proved beneficial.

## Conclusions

Intravenous fibrinolysis remains the treatment of choice in ischaemic stroke. Detecting arterial occlusion by means of CT angiography or MRA seems to be necessary to the process of selecting patients who are candidates for endovascular therapy. Use of bridging therapy may reduce the time delays before revascularising treatment can be provided. However, doctors need new clinical trials able to demonstrate the role that endovascular therapy should play in acute stroke and

which include descriptions of patient groups in which this treatment approach may be beneficial. Today, the debate revolves around which decision should be made for each individual patient after reviewing the overall results from completed clinical trials. Until new clinical trials are able to better define the patient groups likely to benefit from endovascular therapy, it seems wise to employ this treatment in selected patients, even when we consider the lack of evidence from randomised clinical trials.

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