The eJournal of the European Society of
Minimally Invasive Neurological Therapy

The ESMINT and ESNR statement regarding trials evaluating the endovascular treatment at the acute stage of ischemic stroke

EJMINT Original Article, 2013: **1335000120** (29th August 2013)

Laurent Pierot, Michael Söderman, Martin Bendszus, Philip M White, Mario Muto, Francis Turjman, Salvatore Mangiafico, Jan Gralla, Jens Fiehler, István Szikora, Christophe Cognard

Keywords: Interventional, endovascular treatment, acute ischemic stroke, randomised clinical trials

Abbreviations

EVT	endovascular treatment
AIS	acute ischemic stroke
ESMINT	European Society of Minimally Invasive Neurological Therapies
ESNR	European Society of Neuroradiology
IA	intra-arterial
RCTs	randomised clinical trials

The recent, simultaneous publications of the neutral results of three randomised studies (Synthesis, IMS III, and MR-Rescue) comparing IV thrombolysis therapy to the endovascular treatment (EVT) of acute ischemic stroke (AIS) has been followed by several editorials pointing out their limitations and drawbacks [1-6]. The two European Societies dealing with Interventional Neuroradiology (ESMINT and ESNR) have, in a working group dedicated to acute stroke treatment, analysed the results of these studies leading to the recent publication: “Statement of ESMINT and ESNR regarding trials evaluating the endovascular treatment at the acute stage of ischemic stroke” in Neuroradiology [7]. The same group has already published documents regarding the definition of rules regarding trials evaluating the EVT of AIS [8-9].

Medical treatment as well as EVT of AIS has very rapidly evolved over the last 20 years. If no drugs to date have demonstrated any efficacy in the protection of ischemic brain, the efficacy of IV thrombolysis (with rTPA) was, after several negative randomized clinical trials (RCTs), initially demonstrated in the

Laurent Pierot — Department of Neuroradiology, Hôpital Maison-Blanche, Université Reims-Champagne-Ardenne, Reims, France (lpierot@gmail.com)

Michael Söderman — Department of Neuroradiology, Karolinska University Hospital, Stockholm, Sweden (michael.soderman@karolinska.se)

Martin Bendszus — Department of Neuroradiology, University of Heidelberg, Heidelberg, Germany (Martin.Bendszus@med.uni-heidelberg.de)

Philip M White — Newcastle University Stroke Research Group, Institute for Ageing and Health, Newcastle upon Tyne, UK (phil.white@newcastle.ac.uk)

Mario Muto — Department of Neuroradiology, University of Naples, Naples, Italy (mutomar@tiscali.it)

Francis Turjman — Departement of Neuroradiology, Hôpital Neurologique, Centre de Neurosciences cognitives, Lyon, France (drturjman@gmail.com)

Salvatore Mangiafico — Interventional Neuroradiology Unit, University Hospital Careggi, Florence, Italy (mangiax@libero.it)

Jan Gralla — Departement of Neuroradiology, Inselspital Bern, Bern, Switzerland (Jan.Gralla@insel.ch)

Jens Fiehler — Department of Neuroradiology, University Medical Centre Hamburg-Eppendorf, Hamburg, Germany (fiehler@uke.uni-hamburg.de)

István Szikora — Department of Neuroradiology, National Institute of Neurosciences, Budapest, Hungary (h13424szi@ella.hu)

Christophe Cognard — Department of Neuroradiology, Hôpital Purpan, Toulouse, France (COGNARD.C@chu-toulouse.fr)

first 3 h after stroke with later extension of the therapeutic window to 4.5 h [10-19]. The EVT of AIS has rapidly evolved from intra-arterial (IA) chemical thrombolysis to mechanical thrombectomy [20-30].

Mechanical thrombectomy was initially performed with no specific tools (injection of saline within the clot, disruption of the clot with a microguidewire, “angioplasty” of the clot with remodeling balloons), then with first-generation devices, such as the Merci and Penumbra devices, developed to catch or aspirate the clot, and finally with second-generation devices (e.g. “stentrievers” such as Solitaire™) developed to promptly restore blood flow through retrieval of the clot. The clinical impact of the use of these novel devices has been impressively illustrated by the recent SWIFT and TREVO 2 trials comparing first-generation and second-generation devices and showing a higher efficacy of second-generation in terms of both recanalisation and crucially clinical outcome [31-32].

IMS III, Synthesis, and MR RESCUE are the first RCTs comparing EVT and IV thrombolysis of AIS. They illustrate the difficulties in designing studies for techniques that are in rapid evolution and have important weaknesses. The endovascular techniques used in these trials are varied with most of them now being well recognised to be obsolete. This is related to the relatively long period of inclusion in these trials with the appearance of more efficacious devices during the inclusion period. The length of the inclusion period is primarily due to the small number of patients included per centre per year (2 patients/centre/year in IMS III and 3.5 patients/centre/year in Synthesis) along with a related lack of expertise (this expertise can only be acquired from routine practice of EVT for stroke). The low number of patients/year/centre in the 3 trials probably indicates that all candidates for an IA treatment were not included in the trials and some of them may have been subjected to EVT outside the trial (compassionate use). Such an inclusion bias would severely affect the results of the trials, i.e., if patients likely to benefit from EVT had this treatment without being randomised. Another limitation in IMS III and Synthesis is that the detection of an occlusion of a major arterial trunk by CTA or MRA was not an inclusion criteria. In Synthesis, patients with very low NIHSS were included, but their evolution is most of the time favorable even without any treatment. Also no evaluation of the salvageable brain with perfusion CT or MR was made in IMS III and Synthesis and MR Rescue is inconclusive regarding the potential value of penumbra imaging.

IMS III, Synthesis, and MR RESCUE demonstrate that endovascular treatment is not appropriate for all patients with AIS. One very consistent and highly important finding from these trials is that endovascular treatment is as safe as IV rTPA, and there are no safety issues that should deter the evaluation of the thrombectomy approach in more refined trials. Future trials must focus on determining which treatments are the most efficacious and which patients will benefit from a particular treatment paradigm. A careful selection of patients will be necessary based on clinical status evaluated with NIHSS, initial extension of ischemic lesions evaluated with ASPECT score or other tools, arterial occlusion depicted by CTA or MRA or evaluation of the salvageable brain evaluated by methods that have still to be precisely evaluated. Patients with very low or very high NIHSS have to be excluded as well as patients without arterial occlusion detected with CTA or MRA. It would be probably more productive to design studies to evaluate a single endovascular approach rather than evaluating a wide spectrum of endovascular approaches in the same study. Also, comparison of the endovascular treatment alone to that of IV rTPA alone (as in Synthesis and MR RESCUE) demands a highly effective local organisation in order not to lose time before EVT can be initiated. The combined approach (EVT + IV rTPA) allows the physician to start treatment early and to synergise the efficacy of chemical and mechanical thrombolysis (this synergy has been suggested but has

still to be demonstrated). Participation of both patients and physicians in RCTs is essential to provide rapid answers to this very important clinical problem.

Difficulty in the recruitment of patients was encountered in most RCTs dealing with endovascular treatment. This may in part explain the long time periods needed to complete them. Mechanical thrombectomy is not yet a validated treatment and by not including all eligible patients in an RCT physicians take the risk of skewing the results. Therefore, ongoing or future thrombectomy trials must address the requirements for centres enrolling patients. Selection of the participating centres in the future RCTs in terms of physician competency and organisation of the centres is certainly important to reduce the delay in the performance of EVT. It is also crucial that all patients meeting the inclusion criteria are included in the trial (consecutive enrolment). If a pre-selection is applied by the centre before randomisation, the risk is that certain patients eligible for IA treatment are not randomised (for "compassionate" reasons). This would create a serious inclusion bias and affect the results of the trial. As endovascular treatment has yet not proven its superiority to IV rTPA in a RCT, physicians cannot argue for treating patients outside of the trial.

Conflict of interest

LP consults for Codman, Covidien/EV3, Microvention, Penumbra and Sequent. MS consults for Rapid Medical, Neuravi, Covidien/ev3 and has a research agreement with Philips Healthcare. JG consults for Covidien/EV3. CC consults for Codman, Covidien/EV3, Microvention, Sequent and Stryker. PW has research activity funded from Acandis, Codman, Covidien/EV3 and Microvention; he consults for Microvention and has speaker bureau activities for Codman and Covidien/EV3. JF consults for Codman and Stryker and has speaker bureau activities for Covidien/EV3.

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