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TREVO Pilot: An Effective Flight with a Safe Landing? No!

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In this edition of *Cerebrovascular Diseases*, the results of the European TREVO thrombectomy trial in 60 acute stroke patients within 8 h are published (primary endpoint: recanalization TICI 2a-3) [1]. While this adds to the body of data on novel thrombectomy devices including the published results of TREVO 2, SWIFT, and presented data from STAR, among others, there are several aspects which merit discussion, especially with regard to the recently published negative trials (SYNTHESIS, IMS-3, and MR-RESCUE) [2]. While several aspects of these trials do deserve criticism, such as that there was a lack of comparability with the present technology, MCA occlusions did not fare worse with IV-rt-PA versus IA thrombectomy (IMS-3), or patients tended to be better with IVT (SYNTHESIS) [3].

There is no reasonable doubt that thrombectomy with new devices results in higher recanalization rates (approximately 80%), which should be measured by modified TICI 2b-3 rather than TICI 2a-3 as in TREVO. But higher than what? Higher than in historical series, or with older devices? In SWIFT the subjective recanalization success on site was substantially higher than the centrally adjudicated recanalization rate [4], illustrating the need for data adjudication and blinded independent outcome assessment. Recanalization rates of 80% do not equal good outcome rates, an observation coined futile recanalization. Other factors that reduce clinical efficacy are adverse events, particularly peri-interventional damage by the procedure and/or the ICU management the patients have to undergo, which they otherwise would not (such as intubation and sedation). Safety profiles vary among different stentriever [2], e.g. symptomatic hemorrhages (sICH), depending on the definition, range from 5 to 15% [5] and are uniformly more frequent than in patients treated with standard IV rt-PA only, especially if an equivalent definition of sICH is used. In fact, an appropriate and equivalent definition of sICH in thrombectomy trials is lacking as dissections and perforations with consecutive SAH in addition to generic sICH are typical procedure-related complications, not to speak of peri-interventional strokes in other territories. Furthermore, assessment of sICH mandates that the patient be awake; an intubated and sedated patient by definition will have 'symptoms' on the NIHSS and thus a high NIHSS score compared to baseline, which admittedly may be attributed to the necessary accompanying neurocritical care therapy – a complicating issue by itself.

The main problem is that all studies to date uniformly either alone or in combination are single-arm and single-blind or open studies, compare old experimental with new experimental devices or with historical groups, are underpowered for the chosen endpoints and do not have a clinical primary endpoint, have (too) late time windows, or, if early time windows are chosen, do not compare against standard intravenous rt-PA. Furthermore, in most trials, there was no adjudicated independent outcome assessment for clinical as well as angiography endpoints. The latter has become a standard with the SWIFT and TREVO 2 trials, finally and fortunately.

First of all, what is dearly needed is a randomized clinical trial with a blinded clinical primary endpoint and a secondary independently (core lab) assessed surrogate endpoint such as recanalization. After overuse and generous reimbursement of this experimental treatment in the past, rumor has it that reimbursement is being or may be halted by some insurance companies and in various countries [6]. So, second of all, to achieve rapid completion of an adequately powered trial, one effective approach might be to limit reimbursement to patients recruited into such a trial. Compassionate use should only be reimbursed if the patient does *not* fulfill the inclusion and exclusion criteria for randomization into such a trial. All of the latter patients should be obligatorily entered into an independently managed and monitored registry in order for reimbursement to occur. The author is aware that such an approach may not be possible in some countries due to regulations. However, a case in point often presented in discussions is the low recruitment rate of trials such as IMS-3 or the ongoing THERAPY trial. Only because some of us do not want to recruit, this does not mean it need not or cannot be done. Sometimes one wonders how many patients are presented in single center series rather than being recruited into respective trials [7]. After other device procedures such as breast or hip implants experienced public scrutiny, the call and drive for real trials was large; to my knowledge only a few remain after the dust has settled. Many companies have gone back to the drawing board or called their trials off; after all, 510K approval is enough to sell a product, isn't it?!

A conciliatory gesture: while the superiority of any interventional technique over IV rt-PA has *never* been demonstrated, this author is convinced that an adequately powered and adequately designed trial with new devices on top of IV rt-PA compared to IV rt-PA alone in an early time window will ultimately show a higher clinical efficacy with reasonable safety in favor of thrombectomy. This article should be considered an appeal to finally stop designing and performing small single or oligocentric studies. Is it really ethical to recruit patients into such trials instead of recruiting them into a high quality RCT of sufficient size and power? There is a clear and present danger that the baby will be thrown out with the bath water and there may only be one or two bullets left in the magazine before no further trials can be done and thrombectomy may be banned [8]. Therefore, it must be our joint goal to prevent this from happening.

Disclosure Statement

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