Future trials on endovascular stroke treatment: the not-so-easy-to-pluck fruits

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Received: 11 December 2017 / Accepted: 15 December 2017 / Published online: 23 December 2017
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The EXTEND-IA trial showed a positive result in 71 patients (31% absolute effect size for mRS 0–2) [1].

Data from the HERMES collaboration showed an NNT of 2.5 for a one point improvement in mRS in patients undergoing endovascular thrombectomy [2]. The DAWN trial showed an absolute difference of 35% for mRS 0–2 between the thrombectomy and control arms [3].

These massive effect sizes are very uncommon in any medical field. How did these treatment effects occur? It is likely a combination of factors. First, we did not really expect IMS3 [4] that studied evolving endovascular stroke treatment techniques to show a negative result. It was a neutral study due to a combination of factors. Cherry picking (taking younger, earlier, healthier patients outside of the trial direct to endovascular thrombectomy) may have been a factor. Other factors commonly associated with IMS-3 that contributed to the negative results are as follows: absence of vascular imaging to definitively document the presence of LVO; lack of additional imaging markers such as collaterals or perfusion imaging to exclude patients with poor collaterals or a very large ischemic core; not using modern thrombectomy devices such as stent retrievers, an equal reperfusion rate in both treatment arms; and finally, insufficient focus on efficiency and workflow of the thrombectomy procedure. The results of IMS3 as

well as SYNTHESIS Expansion [5] and MR RESCUE [6] galvanized the stroke community into action, and many trials were then designed and successfully executed. These trials were for the most part designed to overcome the limitations of IMS3 as described above and furthermore, knowingly or unknowingly, selected inclusion/exclusion criteria so as to conclusively demonstrate a large benefit of endovascular treatment. After the first group of trials, a second group of trials led by DAWN and DEFUSE-3 were conducted to show benefit in a highly focused group of patients (selected by imaging) beyond 6 h from stroke onset. Once again, the effect size of treatment was staggering.

With the success of all these trials (MR CLEAN, ESCAPE, EXTEND IA, SWIFT PRIME, REVASCAT, THRACE, DAWN [1, 7–11]), there is the obvious question: are there other sub-populations of patients who would benefit from endovascular thrombectomy that were not sufficiently included in the prior trials? If so, should we use the success and momentum from the successful trials to show definitive proof for these sub-populations as well?

What is the total relevant population? Patients of any age (including pediatric) up to 24 h from onset (this question is already settled to some extent with DAWN) using a much wider definition of LVO (ICA, M1, M2, large M3, A2, P2, Basilar) with any size of core: practically, this would mean ASPECTS 0–5 (ASPECTS 6–10 has already been shown to be beneficial) and with any severity of clinical deficit (NIHSS score > 0).

Of course, it is obvious that certain combinations of the above would not work with each other, e.g., the likelihood of having NIHSS < 6 but ASPECTS < 6 is extremely low. Similarly, patients with an A2 occlusion by definition would have an ASPECTS of 10.

Thus, it would make sense to group the above broad categories into clinically relevant categories and ask the following questions:

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1. In the pediatric population, do patients presenting with acute ischemic stroke due to LVO do better with endovascular thrombectomy? It is likely that there would be some key sub-groups within the pediatric population where it would make intuitive sense, e.g., older children would behave like adults. The issues of a trial in the very young is complicated where there are many unknowns including (a) what is the natural history of disease; (b) what are the common causes of ischemic stroke due to LVO? It is likely that these are quite different with dissection forming a large group; (c) are our current devices suitable for treating small children? Are there additional risks, e.g., of vessel rupture or dissection?; (d) are there diseases inherent to the vessel wall, e.g., vasculitis that would need to be treated with alternative techniques?; and (e) what is the total magnitude of disease? Given all these questions, we feel that the question of pediatric population especially the younger pediatric population needs further study with well organized and conducted registries.
2. Do patients presenting with a clinically disabling deficit within 6 h of onset of symptoms and having a relevant A2, P2, or a small M2/big M3 occlusion benefit from endovascular thrombectomy or is thrombolysis sufficient?
3. Do patients with a low NIHSS (<6) and a relevant M1 occlusion benefit from endovascular thrombectomy?
4. Do patients with a clinically severe LVO stroke and ASPECTS < 5 benefit from endovascular treatment?
5. Is there a late time window population beyond the imaging selection criteria of DAWN that would still benefit from endovascular treatment?

Minimal clinically important difference (MCID) Imagine a patient with LVO who has an ASPECTS of 4, has the likelihood of a good outcome (mRS 0–2) of 20% with non-endovascular treatment (the current standard of care) and has a likelihood of good outcome increased to 30% after endovascular treatment (NNT of 10). Most of us would say that the treatment is worthwhile. On the other hand, if endovascular treatment changes the outcome only to 22%, many of us would still feel that the treatment is not worth it. So, in this example, what is the lowest difference in good outcome between the two treatment options that would lead you to think that endovascular treatment is worthwhile? In talking to many of our colleagues, it seems that the number is somewhere around 5–7%. Of course, cost-effectiveness must be considered as well. Data from SWIFT PRIME showed clear evidence of cost-effectiveness from a US perspective [12]. These calculations will vary from jurisdiction to jurisdiction based on whether good outcome is defined by a shift analysis of the total modified Rankin scores or by mRS of 0–2. Thus, it is possible and

likely that cost-effectiveness data for individual situations in individual jurisdictions influence the MCID number as described above.

A similar example with different numbers can be used to illustrate the same principle using the situation of a low NIHSS with LVO. A patient presents with an NIHSS of 2 and has an M1 occlusion. Imagine this patient has a likelihood of excellent outcome (mRS 0–1) of 55% and a likelihood of good outcome (mRS 0–2) of 85%. Imagine that these good outcome rates get elevated to 65% for excellent and 95% for good outcome with endovascular treatment. Once again, most of us would feel that the treatment is worthwhile but may not feel it worthwhile if the excellent and good outcome rates elevated to 57 and 87%, respectively.

Therefore, it seems reasonable to assume that an absolute increase of 5–7% in the excellent or good outcome rates is worthwhile pursuing.

Cherry picking The issue of cherry picking has been previously written about [13–15]. The relevant question as we embark into the next generation of acute endovascular trials is: are we more likely or less likely to face cherry picking? There are arguments on both sides. On the one hand, we have collectively learned from all the successful trials that we have to some extent increased the culture of evidence-based medicine. We know what it takes to run a good trial and the potential harm of “cherry-picking.” On the other hand, we are getting better and better at what we do both in terms of efficiency of treatment and in terms of the quality of reperfusion. These factors have been shown to correlate with patient outcomes. Thus, it seems likely that we will individually in clinical practice start to push the limits of currently accepted treatment indications whether it is an ASPECTS 4–5 in a younger patient or a patient with an NIHSS of 4 (with aphasia) with an M1 occlusion. Many centers are already treating such patients. Will we be able to effectively randomize such patients in new trials because the question is neither considered standard-of-care nor part of the guidelines? If not, this would also result in further picking of the low-lying fruit and likely to reduce the effect size seen in a clinical trial.

With each low-lying fruit that we pluck, by inference, the rest of the fruit is not-so-low lying We have already solved most of the easy problems. These are now the standard of care and, as such, those patients are and should be treated with endovascular treatment. This is the low-lying fruit, and we were able to demonstrate massive treatment effect sizes in the recent clinical trials. It is quite likely that the effect sizes may be smaller in the not-so-low lying fruit. The fact that the low-lying fruit is gone further exacerbates the problem. Imagine the following thought experiment. Patients beyond 6 h are presenting with an ICA/M1 occlusion. We design a trial with very simple imaging: exclude all patients with

ASPECTS 0–2. Now imagine that the true effect size for this population is 11%. But as soon as we start running the trial, we realize that DAWN eligible patients are no longer eligible for this trial because they are appropriately undergoing endovascular thrombectomy based on the available evidence. Thus, those patients are excluded and what we may be left with is a “true” effect size of 5–7%. Imagine that we had chosen our sample size based on an expectation of 10% effect size: our trial would be underpowered to detect this magnitude of a treatment effect and be negative.

The rest of the questions are clearly worthwhile to answer. In the practice of medicine and in specific stroke, an NNT of 12–15 seems reasonable.

However, the low-lying fruit is gone.

The effect sizes in future trials are likely to be much more modest than the previous trials. This may be further compounded by “cherry-picking.” That does not mean that the questions or the relevant patients are in any way less important. All it means is that we need bigger sample sizes, longer trial duration, more centers, continued tenacity, teamwork, and commitment. Generally speaking, this would translate to larger budgets. This likely will translate to the need for greater cooperation and partnerships between traditional funding agencies and industry partners, as well as an expanded clinical trial network to perform these much larger trials.

Compliance with ethical standards

Funding No funding was received for this study.

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval Not applicable.

Informed consent Not applicable.

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