Which patients with acute stroke due to proximal occlusion should not be treated with endovascular thrombectomy?

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EDITORIAL

Which patients with acute stroke due to proximal occlusion should *not* be treated with endovascular thrombectomy?

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Endovascular thrombectomy for acute anterior circulation large vessel proximal occlusion is the standard of care [1]. Evidence from recent trials and additional meta-analyses show that thrombectomy has broad efficacy in almost all subgroups. Overall, thrombectomy is effective irrespective of age, sex, or the stroke severity at presentation. DAWN [2], DEFUSE3 [3], and late window patients in ESCAPE [4] trials show the benefit of thrombectomy up to 24 h. Data from HERMES collaboration show benefit with thrombectomy even in patients with large ischemic core [(irrespective of whether evaluated on the Alberta Stroke Program Early CT Score (ASPECTS) or CT perfusion (CTP)] and moderate to good collaterals [5, 6]. While there remains no published data from randomized trials on more distal occlusions, evidence from quality registries on thrombectomy in sizable middle cerebral artery M2-segment occlusions suggests that thrombectomy is safe and effective [7–11]. The further incentive can be found in the dismal natural history of acute proximal occlusion and the low complication rate of thrombectomy, in trials and registries [1]. Based on data from randomized controlled trials, the procedure is cost-effective [12–14].

With this firm foundation of evidence, we have the luxury to delve not only into details regarding how to maximize the benefits of thrombectomy but also to examine whether other subgroups of acute stroke patients, who were not included in the trials, would benefit from thrombectomy. There is a tremendous amount of work being done in analyzing and improving the transfer of patients from the field to thrombectomy capable centers and, once the patient is in the hospital, decreasing door to groin puncture times. These are robust, easily documentable and indisputable improvements to the thrombectomy process. However, is it possible that we can push the envelope and attempt to predict procedural outcomes (hence, patient outcomes) in order to further guide our selection of patients? Data suggest that two events significantly influence patients' outcomes *after* the decision to proceed to thrombectomy is made: how *fast* and how *well* can the vessel be opened? [15] Importantly, we have shown that imaging parameters, especially on CTP, must be evaluated in conjunction with the likelihood of events occurring after decision-making, e.g., a relative cerebral blood flow of 25% can revert to normal if the vessel can be opened quickly and completely [16]. It is likely that the influence of other prognostic factors

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(e.g., age > 80 years or ASPECTS 3–5 or CTP ischemic core volume of 70–100 cc) alone or in combination varies with the speed and quality of reperfusion.

Given that the benefit of thrombectomy is broadly applicable and choosing patients by baseline factors cannot be reliable because the outcome and speed of the procedure are not known a priori, this raises the question: who should we not treat? We support the enrollment of patients into trials that challenge the boundaries of the current guidelines (e.g., low ASPECTS; low NIH Stroke Scale Score "NIHSS" with proximal occlusion). However, what should one do until the answers to these questions emerge? Are there patients who should not be treated?

We approach this question from five perspectives:

1. How do various prognostic elements work with each other? How do we think about treatment effect size and prognosis to make decisions?
2. Unique clinical situations: very low NIHSS with proximal occlusion; distal occlusion with disabling deficit.
3. How do the individual skill and work environment affect decision making?
4. What is a good outcome?
5. Should we concern ourselves with cost-effectiveness and health economics?

A framework for thinking about prognostic factors

Treatments may have an apparent effect size across multiple groups, yet treatment may not be the dominant predictor of outcome. For example, suppose that a treatment has a 5% absolute effect among all patients regardless of age. Young patients have a 35% chance of good outcome without treatment and 40% with treatment; older patients have a 2% chance of good outcome without treatment and 7% with treatment. In this example, the treatment effect size is consistent across age groups, but the clinical prognostic factor (i.e., age) is a more important determinant of the outcome compared to treatment effect, and the clinical impression will be that older patients do not respond or respond less well to treatment; in fact, the treatment effect is the same.

Prognostic factors function together and may be additive or synergistic. In stroke, key prognostic factors are age, stroke severity, comorbid illness, imaging-defined stroke severity (e.g., low ASPECTS or large predicted ischemic core volume on CTP), and the location of occlusion; all may act in concert to define prognosis. We recognize, without substantial evidence from RCTs, the concept of biological vs. chronological age [1] (conventional accelerators of biological aging are smoking, hypertension, diabetes, sedentary lifestyle, and comorbid conditions (heart disease, previous strokes, cognitive impairment, cancer, chronic renal disease, etc.). Often these factors are combined into the concept of frailty. Together, the prognosis may be so poor that treatment will be ineffectual, and this defines the futility of treatment. Such a patient is not possible to save with thrombectomy and should not be offered futile treatment.

While we can define key prognostic factors such as age, stroke severity, occlusion location, collaterals, pre-morbid status, and others [1, 17–22], we have an incomplete ability to quantitate prognosis truly. Our estimates are rough. Further, none of these factors modify the treatment effect, including imaging [23].

The only factor that modifies the treatment effect is the speed of treatment, in particular, the speed of in-hospital treatment processes. We can control and improve our treatment times. Because the treatment has broad efficacy and large effect size, it is currently difficult to decide who should not be treated. When selecting patients for treatment, by understanding prognosis, we recognize that it is intuitively and biologically evident that different infarcts progress at different rates (primarily driven by collaterals and likely influenced by other factors such as blood pressure and blood glucose): the so-called slow progressors and fast progressors [24]. Patients enrolled in DAWN and DEFUSE3 were, by definition, slow progressors (except patients with stroke-on-awakening who could have had a stroke anytime from last seen normal). Hypothetically, if we lived in a system that all patients presented to the hospital more than 6 h from onset, very few patients would be eligible for treatment based on imaging. Alternatively, if we were in a setup where all patients presented within 30 min of symptom onset, almost all patients would have "good" imaging [25]. Unfortunately, to date, we do not have good data on proximal occlusion patients who were not eligible for trials and were not treated [24] and therefore cannot judge a priori who is a "slow progressor" or a "fast progressor."

Because the overall complication rate of thrombectomy is low [1] our decision-making is not substantively impacted by adverse events. The current "art" of decision-making here means estimating prognosis. Quick questions about independence may not be sufficient as this may be answered affirmatively by family members when the patient requires help with most of the daily activity. Thrombectomy is broadly effective implying that it should be offered to most patients except where medical futility can be predicted based upon very poor prognostic factors. Once we have decided to treat, it is imperative that we modify the components of treatment that we can, and this means treating quickly (fast imaging to reperfusion times) and technically achieving the best possible reperfusion (TICI 3).

Unique clinical situations

Very low NIHSS with proximal occlusion

Current guidelines for thrombectomy suggest a lower cutoff of NIHSS of 6: chosen based on convention in most trials. However, this cutoff is used loosely in routine practice around the world. Based on the authors' personal discussions, many practitioners would treat a patient with NIHSS of 4 or 5 with an M1 occlusion especially if the deficit was disabling. However, what about a patient with an NIHSS of 1 with an M1 occlusion? Many neurologists may not even give intravenous alteplase for such a patient.

A patient must have excellent collateral circulation to have a low NIHSS score with proximal occlusion. The critical question here is: what the natural history of the disease is, and what is the complication rate of the procedure (including displacement of the embolus into distal circulation, thus worsening the clinical deficit). Some of these patients will deteriorate without thrombectomy but can we predict which ones will that be? This is an area that requires further work. Are we able to develop a challenge test to assess the robustness of the collaterals? Some have suggested sitting up the patient to see if the clinical deficit worsens. Another approach is to observe the patient closely and perform thrombectomy only in case of even a slight deterioration (not worrying about time from the onset as in theory there is little brain tissue at risk till the time of deterioration). To conduct an RCT to answer this question could be difficult as these patients are uncommon, and the required sample size may be too high. Practitioners may not have equipoise for patients with NIHSS 3–5 who have a disabling deficit and proximal occlusion. This will leave for enrollment proximal occlusion patients with NIHSS 0–2 or those with small ischemic core.

Distal occlusions (A2, A3, small M2, M3, P2, P3) especially in patients not eligible for IV tPA

There is evidence supporting the efficacy of thrombectomy for a sizeable M2 occlusion and a high NIHSS [7–9]. However, what are the limits of how small or distal one can go with thrombectomy. Additionally, there is no consensus in the field regarding the definition of MCA segments, including the M1 [26]. This disagreement may not be relevant from a practical stand when a patient with severe clinical deficit and an accessible intracranial occlusion will be a likely thrombectomy candidate in most centers worldwide (unpublished results of UNMASK-EVT survey, personal communication). The improvements in catheter and stent designs will soon make many M3/A3/P3 occlusions accessible and safe potential targets for thrombectomy. Individual skill and work environment may influence the decision-making in these circumstances.

Both of these unique conditions are derivatives of the situation where the patient has a reasonably good prognosis, defined by baseline factors (low NIHSS or branch vessel occlusion) and current "art" in deciding treatment depends upon picking the clinical patient who appears to have the poorer prognosis, and therefore higher risk of faring poorly.

Operator skill and workplace factors in decision-making

An important aspect in decision-making is the center organization and workflow: how fast is the emergency room to groin puncture time. The second is the degree of variance of these times. In many institutions, the variance could be high and is influenced by factors as time of day [22, 27]. There are very few data on factors affecting the time from groin puncture to reperfusion and the quality of reperfusion. There are data of how different techniques (standard balloon guide catheters with Stent retriever vs. direction aspiration vs. combined approaches) [28, 29] influence the quality of reperfusion and procedural time. However, the influence of individual skill and technique has not been well studied.

In addition to skills, there is also the issue of temperament. Many interventionists are primarily used to thinking and treating aneurysms and vascular malformations where there is no sense of emergency, with a focus on rational decision-making, preventing errors and complications and balancing risk vs. benefit at every stage of the procedure. It is possible that the field self-selected interventionists who had a natural inclination and temperament toward these qualities and they find the "chaotic" emergency setting of thrombectomy uncomfortable.

Simulation may allow us to understand some of these factors. Yes, the use of simulation technology has still not widely permeated the culture of surgical medicine [30]. There is a circular argument here: "I do not like to use simulation technologies to improve my skills because simulation technology is not helpful" and "simulation technology is not helpful as there is an insufficient investment into it due to lack of users." We collectively need to find a way to get past this obstacle and to be more open to auditing our skills and procedure times and use simulation technology to continue to monitor and improve skills throughout our careers as opposed to only using simulation during fellowship training.

Given the influence of speed and quality of reperfusion on final outcome, and the amount of variance at individual institutions, how should one use these data at the time of decision-making (since these factors will happen after decision-making)? This topic needs further study. We believe that the decision should be based on the answer to the question: what is the likelihood of a patient having a reasonable/good outcome if we were able to achieve successful reperfusion within a short period? The patient should be given the benefit of the doubt.

A good outcome?

The issue of good outcome has two embedded questions: what constitutes a good outcome from this patient/family perspective, and how confident are we at the point of decision-making of the likelihood to achieve that outcome. This is not easy. We can create mathematical modeling applications like the one created by MR CLEAN investigators (MR PREDICT) [31]. However, this proposal has several practical issues. Often, we have insufficient information (and time) regarding the patient/family values and views on the quality of life at the time of decision-making. Additionally, it is difficult to appreciate the many factors influencing stroke outcome as some of these factors happen after decision-making (speed and quality of reperfusion and other in-hospital complications like pneumonia) that influence the outcome. We are thus limited in accounting for these probabilities. For "bad" strokes (severe stroke, an older patient, moderate ASPECTS/collaterals), another approach is to proceed with thrombectomy and defer the decision regarding aggressiveness of care to the following 24–48 h. This gives a better sense of outcome (NIHSS at 24 h has been shown to be an excellent predictor of long-term outcome) [32] and provides the family with time to adapt and better understand the situation. Of course, at that time we have already invested resources, and it is possible that we have already committed the patient to an extended and undesirable state of disability. Further work needs to be done on predicting long-term outcome and on tools to help families understand that to facilitate an informed, ad-hoc, collective decision-making.

Health economics

The care for stroke patients is not cheap. US data suggests the annual cost of stroke was $28.3 billion in 2010 and is growing [33]. It is the most significant cause of non-traumatic disability. Thrombectomy has been shown to be cost-effective [13, 14, 34]. However, it is possible that widespread use of thrombectomy may increase the number of severely disabled patients who will require constant care and result in increased expense not only for the procedure but for subsequent follow-up. Similarly, there will be a dramatic health care savings when patients who would otherwise have been disabled are independent because of thrombectomy. What should frontlines physicians do with this information? Should this influence our decision-making? We suspect not. However, it is something we must be cognizant of and continue to pay attention to.

Conclusion

In summary, given the broad efficacy and safety of thrombectomy, one has to carefully think about which patients with proximal occlusion should not be offered treatment. Further work is required to better understand how various prognostic factors (age, time from onset, imaging parameters) act collectively to predict outcomes. However, these tools will be imperfect as many factors (speed and quality of reperfusion) after decision-making substantively affect patient outcome. Better tools are needed to help patients and their families understand stroke disability and individualize definition of good functional outcome. Decision-making at an individual institution should be put in context with the organizational skill set (speed and quality of reperfusion). Upcoming simulation technologies should be used to evaluate and improve skills continuously. In the meantime, given the poor natural history of disease in patients with proximal occlusion, proven efficacy and low complication rate of thrombectomy, it is probably better to err toward treatment rather than no treatment.

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 All procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent This article does not contain any studies with human participants or animals performed by any of the authors.

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