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It is common these days to have conversations at meetings related to outcome of endovascular procedures for acute stroke. Very often, interventionalists can be seen stating proudly how their good outcome rate (mRS <2) is >60%, or much higher than the other center in their city, or higher than the various trials in the literature. Of course, their basis of calculation for their good outcome rate uses the total number of stroke cases that underwent intra-arterial (IA) therapy at their center. Very often, the numerator and the denominator are limited to anterior circulation strokes. This process takes a further leap forward when devices or imaging paradigms (for acute stroke treatment) are being compared. Various recent studies such as IMS III,[1] SYNTHESIS,[2] MR-RESCUE,[3] TREVO 2,[4] SWIFT,[5] and STAR[6] have different good outcome rates. Speakers at meetings, discussions in hallways, and vendor sales pitches have a tendency to use these good outcome rates without necessarily paying enough attention to the denominator. What kind of patients received IA therapy? What were the precise selection criteria? Did every patient who fulfilled those criteria receive IA therapy, or was there a selection bias? I recently reviewed a paper for a pre-eminent journal. In the article, the authors claimed that perfusion imaging improves patient outcome. This is not the first time that I read this sentence. I have heard it said multiple times at meetings as well. Why is this wrong?

The "Denominator" Fallacy

Here is an illustrative example. Let us take two towns: City A and City B. Both towns have the same population and similar demographics. Both cities have 200 patients in the year 2012 with acute ischemic strokes caused by large-vessel occlusion, specifically the M1 segment of the middle cerebral artery. In City A, of these 200 patients, 120 patients receive IA therapy (on the basis of certain selection criteria), and, by use of device Extractor A, clots are removed. Sixty patients (50%) have a good outcome. In City B, of the 200 patients, 20 patients receive IA therapy (on the basis of slightly different selection criteria by use of complex, sophisticated imaging), and, by use of the device Decimator B, clots are removed. Eighteen patients (90%) have a good outcome. What can one conclude from the data? With the use of selective information, one could try and conclude that Decimator B is a superior device compared with Extractor A or that the interventionalists in City B are better than in City A or that complex imaging selection improves patient outcome. However, from a societal perspective, clearly, the treatment paradigm at City A (with a 30% good out-

come; 60 of 200) is better than that at City B (9% good outcome rate; 18 of 200). However, even that is not a totally correct statement. The correct way from a societal perspective would be, how many patients of the 200 had good outcome irrespective of whether they got endovascular treatment. On the basis of current literature and imaging-based patient selection paradigms, it seems likely that the "best" patients would get chosen for endovascular treatment (those with small core, large penumbra, good premorbid status, and those presenting early). Hence, it is quite likely that the patients who do not undergo endovascular treatment would have a very high likelihood of having a poor outcome. Of course, it is quite likely that some of the patients who underwent IA therapy could have had a good outcome without endovascular treatment, especially if they received intravenous thrombolytic agents[1] (potentially further reducing the effectiveness of City B's approach).

Cost and Resource Implications

Is City A spending much more money and resources compared with City B with many more futile recanalizations? This question is complex and must be considered in the overall perspective of the cost of stroke care. Recent data from Canada suggest that the first-year cost of disabling strokes (mRS 3–5) was approximately $108,000 as compared with approximately $48,000 for nondisabling strokes (mRS 0–2).[7] Given these figures, it would be easy to justify the costs associated with the "futile recanalizations." Although there is not much literature on the cost of endovascular stroke intervention, it is clearly going to be significantly less than the $60,000 difference from this study.

Natural History of the Untreated Patients and Complication Rate of Procedure

Unfortunately, we do not have very good data to answer the question: What is the natural history of a patient with M1 occlusion who may or may not be eligible for treatment with intravenous tPA and could be treated with endovascular devices within 8 hours of symptom onset (on the basis of the labeling on some of the recently approved stent retrievers)? The main factors that would determine patient outcome for the conservative arm probably would be: patient's premorbid status and comorbidities, quality of collaterals, brain eloquence, size of final infarct, and receiving intravenous thrombolytics. Of note, selective use of data from recent trials such as IMS III suffers from the same "denominator fallacy." The good outcome rate in IMS III of patients with M1 occlusion in the medical arm was 51%. The total number of patients in this category was 47, and we do not know the true denominator of the total number of patients with M1 occlusion who were treated at the centers participating in IMS III and those who were treated outside of the trial. Also, all patients in the medical arm of IMS III were treated within 3 hours of symptom onset with intravenous tPA. Thus, in my opinion, the natural history of these 200 patients at either City A or City B is essentially unknown. Recent multi-center studies with the use of newer devices such as

the STAR registry[6] demonstrate very low rates of symptomatic intracranial hemorrhage (1.5%), and, as such, intracranial hemorrhage is not likely to play a significant role in the overall picture. Overall, imaging-based patient selection cannot improve patient outcome. It can reduce the number of futile recanalizations. On the other hand, there is a definite possibility of reducing the likelihood of a good outcome by use of complex imaging-based patient selection, especially if centers spend large amounts of valuable time in complex imaging and decision-making.

Ceiling Effect

This brings up the question: Why bother with patient selection? Why not take all the patients to the interventional suite? Ultimately, it ends up being a balance between likelihood of benefit, potential complications, resource availability, existent data, and practice of evidence-based medicine. Also, it is very likely that there is going to be a ceiling effect wherein taking more and more patients to the interventional suite will not increase the number of patients with good clinical outcome. Where is the correct balance between, on the one hand, having very loose selection criteria and taking nearly all patients to the interventional suite versus, on the other hand, having very sophisticated, complex imaging-based criteria and taking very few patients to the interventional suite? When do we know that we have reached the "ceiling"? I suspect that the answer to the question of patient selection will be a somewhat middle ground and will need to be backed by good data. The ceiling probably is not fixed. It will be dependent on multiple factors, with the main modifiable one being efficiency, which can be improved with more societal education regarding recognizing stroke, and having patients reach the appropriate hospital faster and receive treatment faster. Over a period of time, anything that compromises efficiency of treatment is, in my opinion, probably not going to survive. Recent articles have talked about various parameters such as picture to puncture (P2P), and catheter to capture (C2C) and about focusing on efficiency.[8] We have previously reported our experience of ultrafast recanalization with "CT to recanalization" of <60 minutes.[9] However, ultimately, the only time that matters is "onset to recanalization" time. Of course, the other major factor would be the presence of collaterals that would keep the brain alive while vessel recanalization is achieved. At the current moment, however, we have no technology to increase collaterals before the stroke has taken place. The dream of neuroprotection also remains unfulfilled.

Conclusions

The only denominator that makes sense is the total magnitude of disease in the society—in this case, the total number of patients with acute ischemic stroke caused by proximal vessel occlusion. Stated this way, the results incorporate all the various aspects of stroke care including systems of transportation, patient selection, procedural efficacy, and complication. Also, when presented this way, one can determine the total impact on society across different locations and over different periods of time. It is quite understandable that in many situations at the current moment, this denominator is difficult to calculate. In any big city, there may be many different centers providing acute stroke care and hence it may not be possible to determine the total number of patients in the population with endovascular-amenable acute ischemic stroke. In the meantime, however, it may be prudent to refrain from making inaccurate comparisons across different trials with different centers, different imaging paradigms, and various devices unless these are tested in a head-to-head fashion, use the same denominator, and/or have the same selection criteria.

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