

Are your **MRI contrast agents** cost-effective?

Learn more about generic **Gadolinium-Based Contrast Agents**.



**FRESENIUS  
KABI**

caring for life

**AJNR**

## Acute Stroke Intervention Results: The "Denominator" Fallacy

M. Goyal

*AJNR Am J Neuroradiol* 2014, 35 (4) 616-618

doi: <https://doi.org/10.3174/ajnr.A3770>

<http://www.ajnr.org/content/35/4/616>

This information is current as of April 14, 2024.

tests such as the American SAT (Scholastic Aptitude Test) and the ACT (American College Testing) concentrate in measuring 2 subjects: mathematics and linguistics (the pillars of linear thinking, as stated previously). Mr. Hacker proposes that perhaps just basic algebra and what he astutely calls “citizen statistics” may be enough for most us, whereas more advanced courses such as calculus should be reserved for fewer, gifted individuals who seek careers that depend on the understanding of higher mathematics. As Sir Ken Robinson states, “We are educating people out of their creative capacities.”

Does studying liberal arts and the humanities make us better physicians? I believe it does. I have been unable to notice any differences with respect to knowledge of biologic sciences in our daily work between residents who come from a “hard” science background and those with a liberal arts education, and I find that personally I like the latter better. Medical schools are aware of this, and some such as Boston University and Brown University encourage this type of liberal arts curriculum and reserve a number of places in their medical schools for these individuals. More than 40% of medical students at the University of Pennsylvania come from non-premed backgrounds.<sup>7</sup> The liberal arts may also be useful to medical students, and the Mount Sinai School of Medicine in New York has a specific humanities and medicine program. The separation of liberal arts from sciences is, in my opinion, damaging and ends up suppressing the human qualities of many excellent and caring young individuals. Because liberal arts are characterized by lateral thinking, bringing these individuals into our world of linear thinking will prove to be beneficial for all.

I am not aware of imaging methods having been used to study these different types of thinking. There are, however, several principles that control all human thought processes.<sup>8</sup> A basic principle of thinking is that it is the product of concurrent brain activity in multiple regions that together form a large-scale cortical network. This is a type of functional connectivity that has been documented in thousands of fMRI reports. Also, each cortical region can perform multiple functions, and these same functions can also be performed by different regions, an observation that may explain thought (and function) plasticity. Rather than a strict linear or vertical organization, the brain prefers a lateral or horizontal organization that serves as its own backup and redundant system. Unfortunately, each cortical region can only do so much and thus has a limited capacity. Conversely, these constraints force other parts of the brain to collaborate, and this helps it adapt to many situations. The topologies of large-scale networks are in constant flux, adapting themselves to the demands of tasks. The brain is not dumb: it uses the minimum amount of resources needed for each activity, but, if one network becomes insufficient, additional ones are immediately recruited. The brain’s topology has 2 components: membership and connectivity, and both are in constant flux. Just as the Internet does, the brain also has a limited bandwidth, resulting in a finite amount of resources that it can use. This bandwidth, up to a certain extent, varies from individual to individual and thus some are more successful in multitasking than others. Increased brain bandwidth seems to be connected to lateral thinking.

Lateral thinking is important and is not used sufficiently in the sciences, but this is beginning to change. Of course, we radiolo-

gists can take it to a silly extreme, as seen in a recent advertisement that intended to recruit a lateral-thinking technologist for a vertical MR imaging (upright) scanner!<sup>9</sup> Radiologists actually think dimensionally, and 2D and 3D processes play an important role in the interpretation of images in which it all begins as the former and ends as the latter. I like to think of this as a process that also begins vertically and then branches horizontally. Some of our trainees have more trouble making this transition and thus take longer to learn the specialty. It is possible that some may survive and graduate not being able to think 3-dimensionally, but they will never survive if they think circularly.

## REFERENCES

1. **Circular reasoning.** [http://en.wikipedia.org/wiki/Circular\\_reasoning](http://en.wikipedia.org/wiki/Circular_reasoning). Accessed on May 2, 2013
2. **Is linear thinking bad?** <http://www.andyeklund.com/creativestreak/2012/06/is-linear-thinking-bad.html>. Accessed on May 2, 2013
3. <http://www.howardgardner.com>. Accessed on May 2, 2013
4. Heller N. **List and Learn.** *The New Yorker*, July 9, 2012
5. [http://www.ted.com/talks/ken\\_robinson\\_says\\_schools\\_kill\\_creativity.html](http://www.ted.com/talks/ken_robinson_says_schools_kill_creativity.html). Accessed on May 2, 2013
6. Hacker A. **Is algebra necessary?** *The New York Times*, July 28, 2012. <http://www.nytimes.com/2012/07/29/opinion/sunday/is-algebra-necessary.html>. Accessed on May 2, 2013
7. Kliff S. **Why medical schools like to accept STS majors.** *Newsweek*, September 10, 2007
8. Just MA, Varma S. **The organization of thinking: what functional brain imaging reveals about the neuroarchitecture of complex cognition.** *Cogn Affect Behav Neurosci* 2007;7:153–91
9. <http://www.radmagazine.co.uk/JobPDFs/441115.pdf>. Accessed on May 2, 2013

## EDITORIAL

### Acute Stroke Intervention Results: The “Denominator” Fallacy

M. Goyal

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,<sup>1</sup> SYNTHESIS,<sup>2</sup> MR-RESCUE,<sup>3</sup> TREVO 2,<sup>4</sup> SWIFT,<sup>5</sup> and STAR<sup>6</sup> 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

<http://dx.doi.org/10.3174/ajnr.A3770>

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 outcome; 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<sup>1</sup> (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).<sup>7</sup> 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<sup>6</sup> 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.<sup>8</sup> We have previously reported our experience of ultrafast recanalization with “CT to recanalization” of <60 minutes.<sup>9</sup> 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 de-

vices unless these are tested in a head-to-head fashion, use the same denominator, and/or have the same selection criteria.

### REFERENCES

1. Broderick JP, Palesh YY, Demchuk AM, et al. **Endovascular therapy after intravenous tPA versus tPA alone for stroke.** *N Engl J Med* 2013;368:893–903
2. Ciccone A, Valvassori L, Nichelatti M, et al. **Endovascular treatment for acute ischemic stroke.** *N Engl J Med* 2013;368:904–13
3. Kidwell CS, Jahan R, Gornbein J, et al. **A trial of imaging selection and endovascular treatment for ischemic stroke.** *N Engl J Med* 2013;368:914–23
4. Nogueira RG, Lutsep HL, Gupta R, et al, for the TREVO 2 Investigators. **Trevo vs MERCI retrievers for thrombectomy revascularisation of large vessel occlusions in acute ischemic stroke: a randomized trial.** *Lancet* 2012;380:1231–40
5. Saver JL, Jahan R, Levy EI, et al, for the SWIFT Trialists. **Solitaire flow restoration device versus the Merci retriever in patients with acute ischaemic stroke (SWIFT): a randomized, parallel-group, non-inferiority trial.** *Lancet* 2012;380:1241–49
6. Gralla J, Pereira VM, Davalos A, et al. **Prospective, multi-center, single-arm study of mechanical thrombectomy using Solitaire FR in acute ischemic stroke: STAR.** *Stroke* 2013;44:2802–07
7. Mittmann N, Seung SJ, Hill MD, et al. **Impact of disability status on ischemic stroke costs in Canada in the first year.** *Can J Neurol Sci* 2012;39:793–800
8. Zaidat OO, Lazzaro MA, Gupta R, et al. **‘Time’ for success.** *J Neurointerv Surg* 2013 [Epub ahead of print]
9. Almekhlafi MA, Eesa M, Menon BK, et al. **Ultrashort imaging to reperfusion time interval arrests core expansion in endovascular therapy for acute ischemic stroke.** *J Neurointerv Surg* 2013;5(Suppl 1):i58–56