Putting the Patient First: Comments on Scientific Rationale for the Inclusion and Exclusion Criteria for Intravenous Alteplase in Acute Ischemic Stroke

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Article Text

The American Stroke Association (AHA/ASA) has released a Scientific Statement entitled “Scientific Rationale for the Inclusion and Exclusion Criteria for Intravenous Alteplase in Acute Ischemic Stroke”, which was affirmed by the American Academy of Neurology as an ‘educational tool’ and endorsed by the American Association of Neurological Surgeons and the Congress of Neurological Surgeons. This scientific statement, written by Demaerschalk et al, is published almost 20 years to the day from our publication of the National Institutes of Neurological Disorders and Stroke (NINDS) trial of recombinant tissue plasminogen activator (rt-PA) for acute ischemic stroke in the New England Journal of Medicine. The day prior to the New England Journal publication, trial leadership held a press conference at the NINDS in Bethesda, MD, to announce these landmark results. My most vivid memory of that press conference is focusing really hard on not tripping over the television camera cables as we authors walked into the packed room. By prior arrangement, the elders did the talking: Tom Brott, Jim Grotta, John Marler. During the preparation beforehand, I recall being instructed to avoid any over-statements should I be asked any questions; in the event, alas, one sports analogy did manage to find its way into some major media outlets: ‘we expected to hit a single or double and we ended up with a grand slam’. Oops.

Given that the trial showed such a phenomenal and impressive result, why wasn’t it a ‘grand slam’? Why has it taken 20 years—and to be honest the publication of successful neurothrombectomy trials—to really unleash intravenous thrombolytic therapy? The effect size (both relative and absolute) swamp anything previously seen in Neurology—uptake of this therapy should have been swift and sure. Did initial professional envy and a “not invented here” syndrome block wider/faster adoption? Was uptake inhibited by the self-appointed demagogues who were hawking their newsletters and bashing science they did not understand? Or did the published selection criteria pose too steep a barrier for most neurologists to embrace IV rt-PA, as suggested by Demaerschalk et al?

The scientific rationale for the inclusion and exclusion criteria discussed by the AHA/ASA writing group is based on exhaustive summarization of the literature, most of which did not exist during the writing of the original trial protocol. The inclusion and exclusion criteria used in the original trial derived from...
are being treated; more neurologists graduate from training with competence in thrombolysis; more medical students are interested in joining our ranks. This

overcome uncritical opposition, fear, and conflicts of interest. Additionally, we as a specialty have progressed from diagnosis to intervention: more patients

The statement provides a superb summary of this complex issue and if one were to read only one section, this would be it.

A significant contribution to this problem is that the NIHSS fails to detect cognitive dysfunction. Also, deficits need to

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Some of us testified at an FDA advisory panel against using the clinical trial criteria as the indications for clinical use, for two reasons. First, as mentioned, our clinical trial criteria were based on consensus, not data, and were overly conservative. Second, we felt—as asserted by Demaerschalk et al—that the selection criteria might prove an impediment to swift adoption of the treatment.

The drug was approved, marketed, and over the intervening years the use of IV rt-PA for acute ischemic stroke has slowly but inexorably increased. Today no rational physician doubts the benefits, or that the risks are far outweighed. So is there really a need for an exhaustive review of the ‘Scientific Rationale’ for the selection criteria as published here? The writing committee felt that their work is timely and necessary and could serve to assuage the fears of practicing physicians faced with the patient in potential need of IV rt-PA. More importantly, the document explores “…some popular myths regarding treatment”, and contra-dogma myth busting is always welcome. I note in passing, however, that these myths have been busted before5, 6; perhaps this time the readership is ready to reassess dogma, and accept data where before only emotion proved persuasive.

Fourth, the writing committee exhaustively summarizes ALL available data, discussing together data from clinical trials as well as observational data collected in registries and case series. When it comes to evaluating a putative therapy, data from uncontrolled case series and registries is close to useless. Large registries help us answer questions such as “what happens to older patients after stroke”. Without randomized controls, such registries contribute nothing to answering questions such as “do older patients respond to rt-PA as younger patients do”. That is, if you compare rt-PA treatment response in old vs. young patients without controls, you will find a lower proportion of responders among the aged group. The uncritical observer might therefore conclude rt-PA is less effective in the aged. As Demaerschalk et al eloquently illustrate, despite a lower overall absolute benefit the effect of rt-PA treatment compared against placebo is at least as strong as among younger patients.9 Clinicians are inundated with review articles, subgroup analyses, and pseudo meta-analyses that get this point dead wrong, it is understandable that confusion arises at the bedside. The data presented by Demaerschalk et al clearly debunk the dogma here. As another example, consider stroke severity, as scored with the National Institutes of Health Stroke Scale (NIHSS). Popular meta-analyses that get this point dead wrong, so it is understandable that confusion arises at the bedside. The data presented by Demaerschalk et al clearly debunk the dogma here. As another example, consider stroke severity, as scored with the National Institutes of Health Stroke Scale (NIHSS). Popular meta-analyses that get this point dead wrong, so it is understandable that confusion arises at the bedside. 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One final thought: the debate over IV rt-PA illustrates to me a larger question of the role of science in society. Recently, a young Emergency Physician told me he did not “believe” in thrombolysis, and quoted some of the popular myths and dogma discussed here and elsewhere. I thought his choice of the word “believe” to be quite telling, as if one could chose to believe in the data one liked best. Can we choose to believe in gravity? I suppose so, but at some risk. In popular culture, we hear about choosing whether to “believe” in such science as climate change or childhood vaccination, so maybe it is unsurprising that younger physicians might adopt a similar posture towards data. It seems to me that little else threatens us more than the pernicious idea that individuals (and legislatures) have the freedom to choose whether they will ‘believe’ in some scientific findings and not others. Demagoguery and thoughtless opposition to IV rt-PA cost thousands of patients a chance at living disability free, and cost the US hundreds of thousands of dollars. What will be cost to all of us if unscientific ‘belief’ continues to dominate political and social discourse?

References


-- The opinions expressed in this commentary are not necessarily those of the editors or of the American Heart Association. --
AHA/ASA indicates American Heart Association/American Stroke Association. Kingdom and found to vary across groups, but the suitability of the scale to predict outcomes has not been fully established. Alternative prediction models have been developed using other cohorts and different sets of stroke risk factors. Recent guideline statements from the AHA/American Stroke Association have emphasized the importance of including both stroke and coronary heart disease events as outcomes in risk prediction instruments intended for primary prevention. The AHA/American College of Cardiology (ACC) CV Risk Calculator is available online for use in estimating risk at http://my.americanheart.org/cvriskcalculator.
Epidemiology and Prevention. The increase in heart failure (HF) rates throughout the developed and developing regions of the world poses enormous challenges for caregivers, researchers, and policymakers. Therefore, prevention of this global scourge deserves high priority. Identifying and preventing the well-recognized illnesses that lead to HF, including hypertension and coronary heart disease, should be paramount among the approaches to prevent HF. Aggressive implementation of evidence-based management of risk factors for coronary heart disease should be at the core of HF prevention strategies. Questions currently in nee