Published in final edited form as:

Ann Emerg Med. 2010 February ; 55(2): 226–229. doi:10.1016/j.annemergmed.2009.09.024.

Response to: “A Graphic Reanalysis of the NINDS Trial”

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When performed correctly, graphical display of clinical trial data can provide useful additional insights regarding treatments that statistically demonstrate benefit, like fibrinolytic therapy for acute ischemic stroke. Unfortunately, in their article graphically analyzing the two NINDS TPA Trials, Drs. Hoffman and Schriger depart from best practices appropriate for the visual display of quantitative information.¹

All 13 of the charts in their main paper fail to graphically take into account the ordinal, non-interval nature of the NIH Stroke Scale's, functional significance and the skewed population distribution. For example, improving from an NIHSS score of 31 to 21 barely affects patient disability, while going from an NIHSS score of 11 to 1 results in a dramatic improvement in daily functioning, although both are a 10 point lowering. Giving lower range score changes equal visual weighting to upper range score changes is misleading.

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Disclosures: Dr. Saver is an employee of the University of California, which holds a patent on retriever devices for stroke; is a scientific consultant regarding trial design and conduct to CoAxia, Concentric Medical, Talecris, Ferrer, AGA Medical, BrainsGate, PhotoThera, and Cygnis (all modest); has received lecture honoraria from Ferrer and Boehringer Ingelheim (modest); received devices for use in an NIH multicenter clinical trial from Concentric Medical (modest); has declined consulting/honoraria monies from Genentech since 2002; has declined serving as a medicolegal expert in TPA litigation since 2002; is a site investigator in multicenter trials sponsored by AGA Medical, Vernalis, Paion, Lundbeck, and Neurobiological Technologies for which the UC Regents received payments based on the clinical trial contracts for the number of subjects enrolled; is a site investigator in the NIH IRIS, CLEAR, IMS 3, SWISS, and SAMPRIS multicenter clinical trials for which the UC Regents receive payments based on the clinical trial contracts for the number of subjects enrolled; administers stroke thrombolytic therapy in his practice (<5% of effort); and is funded by NIH-NINDS Awards P50 NS044378 and U01 NS 44364.

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Moreover, NIHSS score values of 32 to 41 are virtually impossible for any patient to obtain at entry and 90 days and were almost completely absent in the data. So showing a scale range from 0 to 42 or -42 to 42 compresses the true clinical response range and treatment effect as the range is 35% too large ($42/31=1.35$).

Compounding these graphical issues, the NIHSS change scales in figures 1b, 2b, 3b, 4b, and 5b, are between two to twenty times the range achievable by individual patients, severely compressing the apparent treatment effect and giving the appearance of an effect too small to be of clinical importance.

Several methods exist that are appropriate to the graphical depiction of scales with ordinal functional values and skewed population distributions, including charting normalized gain and loss and charting clinically relevant ordinal categories. Graphical analysis of the NIHSS and delta NIHSS scores in the two NINDS-TPA trials, when conducted in this proper manner, delineate large magnitude treatment benefits of under 3 hour fibrinolytic therapy in acute stroke.²

Try as they might, for more than a decade, the anti-treatment contrarians have not been able to find a legitimate fault, statistically or now graphically, with the original two NINDS TPA trials. Multiple analyses of the data have shown benefit, including individual excellent outcome binary endpoints, combination of excellent outcomes by global statistic (the prespecified primary analysis), entry-severity adjusted endpoint analysis,³ and now appropriate graphical depictions of change in NIHSS score. Moreover, the results of these two trials are confirmed by under 3 hour and 3–4.5 hour data from multiple other trials of TPA that enrolled patients in these time windows.⁴ Emergency physicians and neurologists, working together as partners for patient benefit in acute stroke centers and regional stroke systems of care worldwide,⁵ can be reassured that that they are delivering substantial benefits to patients when providing under three hour fibrinolytic therapy, figuratively, as well as literally.

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