

## LETTER TO THE EDITOR

### Letter by van der Ende et al Regarding Article, “Redefined Measure of Early Neurological Improvement Shows Treatment Benefit of Alteplase Over Placebo”

Nadinda A.M. van der Ende<sup>1</sup>, MD; Vicky Chalos, MD; Diederik W.J. Dippel, MD, PhD

#### To the Editor:

With great interest we read the article by Agarwal et al,<sup>1</sup> who proposed a redefined measure of early neurological improvement (ENI). This ENI, defined as percentage change in National Institutes of Health Stroke Scale (NIHSS) from baseline to 24 hours, showed treatment benefit of alteplase in the NINDS trial. This is an important finding. However, we have some comments.

The authors propose that ENI is a reliable and sensitive measure of treatment effect in trials of acute reperfusion therapy for ischemic stroke. There are several limitations to the approach of the authors that preclude such a conclusion. First, the authors used descriptive statistics to assess treatment benefit of alteplase, which—in contrast to regression models—do not allow for adjustment of prognostic covariates. In general, including baseline linear variables as covariate in a regression analysis is more efficient than using percentage change.<sup>2</sup> Regression models have the additional advantage that they accommodate covariate adjustment to increase statistical power considerably.<sup>3</sup> Second, it is unclear what NIHSS score was assigned to patients who died within the 24-hour period after inclusion in the trial. This may affect the size and interpretation of the effect parameter “percent change.” Third, a strong predictive ability for 3-month outcome, and one statistically significant effect by itself does not ensure that ENI is a valid surrogate marker of treatment effect. A surrogate outcome should be able to replace the true outcome as a measure of treatment effect, and should lie in the causal pathway between the intervention and true outcome.<sup>4</sup> Statistical validation of these criteria require assessment with a causal mediation model, even when intuition may suggest that these criteria will be satisfied anyway.

We argue that a more extensive study, which takes all these issues into account, is needed. We are very happy to point out to the authors that such a study has already been done, and has recently been published in *Stroke*.<sup>5</sup> Using data of two trials of endovascular treatment, that

study showed that the NIHSS at 24 hours satisfies the requirements for a surrogate outcome. Patients who had died before posttreatment NIHSS assessment received the maximum score of 42, which led to a non-normal distribution, requiring log10-transformation.

As mentioned by the authors, the definition of ENI varies across studies. The most statistically efficient definition and method of analyzing ENI is currently unknown and a comparison of these definitions and methods is necessary.

In conclusion, we thank the authors for drawing our attention to the use of NIHSS as a sensitive early measure of treatment effect in trials of acute reperfusion therapy for ischemic stroke. It is important to decide which types of studies benefit most of this early outcome measure and how it should be analyzed. We already knew that linear regression with covariate adjustment increases statistical power, but the most efficient definition and method of analyzing ENI is not yet known and needs to be studied further.

#### ARTICLE INFORMATION

##### Affiliation

Department of Neurology, Erasmus MC University Medical Center, Rotterdam, the Netherlands.

##### Disclosures

Dr Dippel reports funding from the Dutch Heart Foundation, Brain Foundation Netherlands, The Netherlands Organisation for Health Research and Development, Health Holland Top Sector Life Sciences & Health, and unrestricted grants from Penumbra, Inc, Stryker, Stryker European Operations BV, Medtronic, Thrombolytic Science, LLC and Cerenovus for research, outside the submitted work, all paid to institution. The other authors report no conflicts.

#### REFERENCES

1. Agarwal S, Scher E, Lord A, Frontera J, Ishida K, Torres J, Rostanski S, Mistry E, Mac Grory B, Cutting S, et al. Redefined measure of early neurological improvement shows treatment benefit of alteplase over placebo. *Stroke*. 2020;51(4):1226–1230. doi: 10.1161/STROKEAHA.119.027476

For Disclosures, see page e134.

© 2020 American Heart Association, Inc.

*Stroke* is available at [www.ahajournals.org/journal/str](http://www.ahajournals.org/journal/str)

2. Vickers AJ. The use of percentage change from baseline as an outcome in a controlled trial is statistically inefficient: a simulation study. *BMC Med Res Methodol.* 2001;1:6. doi: 10.1186/1471-2288-1-6
3. Hernández AV, Steyerberg EW, Butcher I, Mushkudiani N, Taylor GS, Murray GD, Marmarou A, Choi SC, Lu J, Habbema JDF, et al. Adjustment for strong predictors of outcome in traumatic brain injury trials: 25% reduction in sample size requirements in the IMPACT study. *J Neurotrauma.* 2006;23:1295–1303. doi: 10.1089/neu.2006.23.1295
4. Fleming TR. Surrogate endpoints and FDA's accelerated approval process. *Health Aff (Millwood).* 2005;24:67–78. doi: 10.1377/hlthaff.24.1.67
5. Chalos V, van der Ende NAM, Lingsma HF, Mulder MJHL, Venema E, Dijkland SA, Berkhemer OA, Yoo AJ, Broderick JP, Palesch YY, et al; MR CLEAN Investigators. National Institutes of Health Stroke Scale: An Alternative Primary Outcome Measure for Trials of Acute Treatment for Ischemic Stroke. *Stroke.* 2020;51:282–290. doi: 10.1161/STROKEAHA.119.026791



# Stroke