

# Letters to the Editor

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## Ordinal Reanalysis of the SHEP Trial

To the Editor:

The article by Patel and colleagues relating to long-term follow-up of patients in the SHEP study<sup>1</sup> highlights a common problem in vascular prevention trials, namely that the sample size needed to detect an effect on 'all' stroke (or the composite of stroke, myocardial infarction, and vascular death) is insufficient to assess effects on fatal events alone. In the case of SHEP, chlorthalidone-based antihypertensive therapy significantly reduced all stroke (269 events) but not fatal stroke (only 24 events, relative risk=0.91,  $P=0.51$ ).<sup>2</sup> Conventional solutions to this problem of low statistical power include extending follow-up (as Patel and colleagues do<sup>1</sup>) or looking for effects on fatal events across related trials, eg, using meta-analysis as done with aspirin.<sup>3</sup> Demonstrating reductions in both stroke and fatal stroke supports the claim that the intervention reduces both stroke and its severity. We have proposed an alternative solution which achieves this aim in one analysis, namely that binary vascular outcomes such as stroke/no stroke can be converted into a 3-level ordered categorical outcome, eg, fatal stroke/nonfatal stroke/no stroke.<sup>4</sup> Adding transient ischemic attack (TIA) generates a 4-level outcome: fatal stroke/nonfatal stroke/transient ischemic attack/no stroke. These data may be analyzed using nonparametric approaches including Mann-Whitney  $U$  test and ordinal logistic regression.<sup>5</sup>

The following analyses may be performed using data from Table 1 of Patel's article (outcome for active then control patients with analysis using ordinal logistic regression):

Stroke (2-level/binary)—106 (stroke)/2259 (no event) versus 163/2208, odds ratio 0.64 (95% CI 0.49 to 0.82),  $z=-3.53$ .

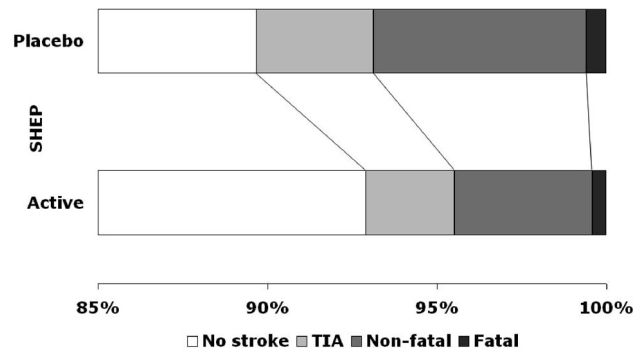
Stroke (3-level)—10 (fatal stroke)/96 (nonfatal stroke)/2259 (no event) versus 14/149/2208, odds ratio 0.64 (95% CI 0.49 to 0.82),  $z=-3.53$ .

Stroke/TIA (4-level)—10 (fatal stroke)/96 (nonfatal stroke)/62 (TIA)/2197 (no event) versus 14/149/82/2126, odds ratio 0.66 (95% CI 0.54 to 0.81),  $z=-3.94$ .

These data show that chlorthalidone-based antihypertensive therapy reduces both stroke and its severity, ie, the interventions 'shift' patients from fatal stroke to nonfatal stroke, nonfatal stroke to TIA, and TIA to no event (Figure). The use of ordinal statistical approaches has the added benefit that trials may be smaller for a given power, and mimics the approach increasingly being taken in acute stroke.<sup>6,7</sup>

## Disclosures

None.



**Figure.** Four-level ordinal outcome showing fatal stroke, non-fatal stroke, TIA and no stroke. Note, most patients with no stroke are not shown to highlight those patients with events.

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