

## A Tale of Two Large Trials (Heart Protection Study vs. the ALLHAT trial)

### One trial done quite well and the other suboptimally interpreted.

The following compares two very large randomized trials, one conducted very well, the Heart Protection Study<sup>1</sup>, and the other interpreted quite suboptimally, the ALLHAT hypertension trial<sup>2</sup>.

A very large randomized clinical trial effectively deals with the issue of ensuring adequate numbers for evaluating statistical significance.

However, a large trial does not guarantee that the treatment protocol being studied is good one or broadly applicable. Nor does a large trial guarantee that valid conclusions regarding the trial's outcome are made by the authors.

### Heart Protection Study (An Excellent Study)

The Heart Protection Study<sup>1</sup> was a trial of 20,536 patients. The patient population consisted of individuals at substantial risk for developing a future coronary artery disease event because of preexisting coronary disease or very high risk factors. The trial treated all patients with the same dose of cholesterol lowering medicine, simvastatin (Zocor 40 mg), regardless of whether the patient's pretreatment cholesterol was high, moderate, or low. This landmark trial reliably showed through the strength of its large numbers and clinically relevant treatment protocol, that the benefit of a statin (a cholesterol lowering medication) for this group of patients was the same regardless of the initial level serum cholesterol. The results of this trial will favorably change the treatment of patients at high risk for heart disease. The fundamental understanding of physicians of whether a baseline cholesterol level is pertinent in regards to initiation of therapy for this population has been effectively and appropriately changed.

However, even in this stellar trial, it would have been possible for the authors to extend their conclusions beyond what the trial results warranted.

The authors could have inappropriately concluded that their trial results applied only to the particular cholesterol drug tested, simvastatin. Their unfounded conclusion would then have been that only simvastatin should be used to treat patients with coronary heart disease who have a normal or low pretreatment cholesterol levels. In addition, the authors could have inappropriately concluded in their report's formal conclusions that their trial data proves that measuring cholesterol levels in this type of patients is not useful since all these patients should be treated with the cholesterol lowering medicine regardless.. Though individual authors of this study may have thought the trial raises the question of whether follow-up blood tests are really needed, they did not inappropriately extend their conclusions beyond what the trial directly tested.

Hence, even an excellent trial such as the Heart Protection Study could be substantially diminished if the authors of that trial had chosen to make inappropriate conclusions and if the editors of the journal that published the paper did not require those conclusions to be revised prior to publication.

Fortunately, the Heart Protection Study had excellent investigators, both in the formulation of their trial protocol and in the conclusions which they directly derived from the data.

### **The ALLHAT hypertension trial - A large trial, suboptimally interpreted**

The ALLHAT trial<sup>2</sup> on the other hand, is a poster child for conclusions extending beyond the data in a large randomized trial.

The ALLHAT hypertension trial<sup>2</sup> reported in JAMA 2002 studied 33,000 patients.

The ALLHAT trial failings result primarily from overextended and inappropriate conclusions. In addition, the trial treatment protocol specified specific blood pressure treatment regimens which had serious limitations in regards to substantially differing from the way hypertensive patients are routinely treated by physicians.

If the trial had been conservatively interpreted by the trial's authors, these limitations would have been noted and some conclusions deriving directly from the trial would have been formulated.

Instead, the authors in their 2002 report made a sweeping statement that their trial results indicated that a diuretic should be the first drug used for the treatment of hypertension.

There are a number of major limitations in regards to the ALLHAT trial results. Despite the fact that the primary end point was identical for the three treatment strategies, the ALLHAT authors inappropriately stated that their trial data proved that diuretic therapy is the preferred drug in initiating treatment for hypertension. In fact, what the ALLHAT trial reliably showed was the outcome for a particular combination of drugs used in this patient population. (See [ALLHAT detailed critique](#) for an extended critique of the ALLHAT trial.)

The advantage of this being a very large trial is that if this trial protocol was repeated for these particular suboptimal combinations of medication for this particular patient population, the same result would occur.

As an example, repeating the ALLHAT trial with a 100,000 patients rather than 33,000 patients would not make the specific blood pressure combinations studied more broadly applicable, though it would be expected to have the same patient outcome. A very large randomized trial only ensures reproducibility in that the same trial for the same patient population would have similar results if repeated in the same fashion.

Hence, very large randomized clinical trials effectively deal with the issue of having adequate numbers for statistical significance. A large trial, however, does not guarantee that the treatment protocols being studied are good ones, nor does it guarantee that appropriate conclusions regarding the trial's outcome are made by the authors.

1. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20536 high-risk individuals: a randomized placebo-controlled trial. *Lancet* 2002; 360: 7-22.

2. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs. diuretic: the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). *JAMA* 2002; 288: 2981-2997.