Reply to Visit-to-Visit Blood Pressure Variation: Time to Reanalyze All The Data From the TROPHY Study

To the Editor:

We are glad to see that 6 years after publication of the Trial of Preventing Hypertension (TROPHY),[1] the results are still being debated. Only truly new and important findings can elicit such an interest.

TROPHY reported more robust results in the first 2 than in the second 2 years of the study.[1] Two years of treatment with candesartan produced a 66.3% relative risk reduction (RRR) of hypertension, and the treatment was well tolerated. At the end of year 4, the RRR in the group that had been switched from candesartan to placebo at year 2 was highly significant but clinically modest (15.6%). We stated that "we do not advocate treatment of 25 million people with prehypertension and that further studies are needed." This call for action was a smashing success. The Short Treatment with the Angiotensin Receptor Blocker Candesartan Surveyed by Telemedicine (STAR CAST) study in Japan will analyze the reversal from stage 1 to prehypertension and is nearly completed.[2] The CHINON study in China[3] recruited 10,000 patients and will compare cardiovascular outcomes in active treatment and placebo groups. In Brazil the Hypertension Prevention in Pre-Hypertensive Individuals (PREVER) study[4] evaluates the effect of diuretic treatment in patients with prehypertension who failed to respond to lifestyle modification.

In the meantime, we responded to an early critique of TROPHY by reanalyzing data according to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) definition of hypertension.[5–7] In the reanalysis, all original findings were confirmed[5] and the median time to hypertension as defined by JNC 7 was 4.0 years in the group previously randomized to candesartan. Thus, according to current standards for initiation of treatment, 50% of patients did not need to resume medication up to 2 years after cessation of a 2-year course of candesartan. We are disappointed that this body of work had escaped Dr Schalkwyk's and Turner's attention.

We have recently published a paper in this Journal on the measurement of visit-to-visit variability of blood pressure (BP) using data from the placebo arm of the TROPHY trial.[8] This work was intended to investigate different approaches to the estimation of visit-to-visit variability, an active area of BP research. The authors of the letter note that the BP visit-to-visit variability is higher in treated compared with the untreated patients, referring to the results in Figure 1 of the article. Their observation is what one would expect when BP is treated; that is, the visit-to-visit variability for patients initiating treatment for hypertension will be higher than those not initiating treatment because of the effect of treatment. For example, if a patient has systolic BP readings of 143, 139, 145, and 146 mmHg at visits 1 through 4 without antihypertensive medication use (pretreatment: standard deviation=3.1 mm Hg) and 134, 128, 135, and 132 mm Hg at visits 5 through 8 following antihypertensive medication initiation (post-treatment: standard deviation=3.1 mm Hg), the overall standard deviation will be 6.5 mm Hg, which more than doubles from the actual value due to treatment effect. When the effect of treatment is excluded, that is, the post-treatment BP measures were censored, the variability in patients who initiated treatment vs patients always untreated was similar (Figure 1).

TROPHY produced a rich set of data that we will continue to analyze according to our sense of priorities. We anticipate that ongoing trials will clarify many questions that TROPHY could not resolve. However, there is a need for additional studies. None of the ongoing trials of prehypertension will discontinue active treatment and thereafter evaluate incident hypertension. We invite Drs Schalkwyk and Turner to join the international community and design an Australian-New Zealand study that could provide new insights and verify or disprove their assumptions.

Disclosures: The authors declare no conflict of interest.

Stevo Julius, MD, ScD;[1] Niko Kaciroti, PhD;[1]
Suzanne Oparil, MD[2]
[1]*University of Michigan, Ann Arbor, MI;*
[2]*University of Alabama, Birmingham, AL*

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