LETTERS TO THE EDITOR

From TROPHY With Pride

To the Editor:

We are responding to two editorials1,2 about the Trial of Preventing Hypertension (TROPHY) trial in the November 2006 issue of the American Journal of Hypertension. We wish to thank Drs. Meltzer, Persell, and Baker for their attention to TROPHY. Their editorials might motivate AJH readers to peruse the original TROPHY articles.3,4 TROPHY is a unique, innovative study and the thought that new readers will be informed gives us a great deal of pleasure.

Both editorials directly or obliquely express suspicion about our motivation in designing TROPHY. Here are the facts. Thirty five years ago5 we documented that borderline hypertension is associated with excessive mortality. Since then, new data erased any doubts; the negative impact of hypertension is associated with excessive mortality. Since facts. Thirty five years ago5 we documented that borderline hypertension, as well as with aberrations of metabolic and hematologic6 cardiovascular risk factors. We found evidence,5 we completed the epidemiologic Tecumseh study.7 Borderline hypertension was associated with target organ abnormalities, as well as with aberrations of metabolic and hematologic8 cardiovascular risk factors. We found evidence of vascular restructuring in early phases of hypertension,9 which suggested that early treatment might change the natural history of the disease. About 8 years ago, we designed a protocol that used a definition of hypertension acceptable to practicing physicians. Furthermore, we stipulated that there should be an active treatment period followed by a period of withdrawal of treatment, and that both periods should be equally long. We also requested that at the study end the raw data be transferred to TROPHY investigators for independent analysis. We spent several years contacting various sponsors. To our delight the then Astra Merck US, now AstraZeneca LTD, accepted the protocol and funded the study. Thus, TROPHY was designed by a group of experts and arose from an abiding interest in the topic rather than from a suspicious relationship with industry.

Dr. Meltzer expresses concern whether our change of terminology from “high normal blood pressure” to “prehypertension,” and to “feasibility” from “proof of principle” might be an adjustment to bring the terms in line with some hypertensives in TROPHY might have indeed had random BP variations. At present, such randomness determines whether an individual will be committed to lifelong treatment of hypertension and we cannot change that.

Drs. Persell and Baker are concerned about our way of presenting time-related BP trends in TROPHY. With patient safety in mind, we initiated pharmacologic treatment when a TROPHY participant reached the end point of hypertension. It was absolutely predictable that the continuous removal and treatment of hypertensives in both study groups would eventually erase between group BP differences. We, therefore, chose to apply the last observation carried forward method used in similar previous trials.4 The biological significance of this maneuver is not clear. Drs. Persell and Baker suggest an imputation based on patients’ mean BP. It is not self-evident why their form of imputation would be superior. We hope that various biological markers, collected but not yet analyzed in TROPHY, will clarify some of the issues.

We disagree with the notion that the first 2 years of the study should not be part of the overall analyses. Despite intensive efforts at lifestyle modification,13.6% of people developed hypertension in the candesartan group and the 40.4% in the placebo group, during that period. What would be the justification of suppressing these results in a global analysis? One of the solutions proposed by Drs. Persell and Baker was to temporarily withhold treatment from people meeting stage 1 criteria. We doubt this is feasible. In addition to ethical issues, there is the practical concern of patient cooperation. The best recruitment and retention tool in TROPHY was our promise to start antihypertensive treatment when a participant becomes hypertensive.

Drs. Persell and Baker suggested formation of a national consensus panel for design of future trials. Freedom of imagination is the major reason for the great success of American science. An official pronouncement about what is right or wrong, and what computer modeling should be used, is unlikely to help but surely would impede individual creativ-
ity. According to the proposal, the panel should have no ties to the pharmaceutical industry. Dr. Meltzer\textsuperscript{10} pointed out that trialists working for NIH should also not be trusted. Their ideal panel would therefore consist of people who had less or no practical experience with field work while precluding the advice and insight of many reputable scientists. To use the Persell–Baker adjective, the consensus idea has “fatal” flaws.

Debates without new data are not useful. Hopefully Dr. Meltzer, as well as Drs. Persell and Baker, will design improved studies, and in due course materially contribute to our knowledge. Generally our study has been very well received and new studies are planned. We are proud to have opened novel avenues for clinical research in hypertension.

STEVO JULIUS
ANTHONY SCHORK
University of Michigan
Ann Arbor, Michigan

BRENT M. EGAN
Medical University of South Carolina
Charleston, South Carolina
doi:10.1016/j.amjhyper.2007.01.002

Address correspondence and reprint requests to Dr. Stevo Julius, Division of Hypertension, University of Michigan Health Center, 24 Frank Lloyd Wright Drive, P.O. Box 322, Lobby M, Ann Arbor, MI 48106; e-mail: SJULIUS@UMICH.EDU

References


Reply to: From TROPHY With Pride

To the Editor:

We appreciate that Drs. Julius, Egan, and Schork responded to our editorial but disagree with their statement that debates without new data are not useful. We live in a country with a healthcare system that has not been able to meet the needs of the public, even for the most well-proven therapies and the costs of healthcare continue to increase.\textsuperscript{3} It is appropriate for us to critically appraise studies that could influence which treatments are offered to patients. Although they did not advocate using pharmacotherapy for patients with prehypertension at this point in time, some readers could interpret TROPHY in a way that would lead to an increase in prescribing for patients with blood pressure (BP) in the prehypertension range. Therefore, we believed that the methods deserved our scrutiny. Statements like, “The protocol was revised by . . . the sponsor,” did heighten our level of awareness, but it was the unusual study end point that really caught our attention.\textsuperscript{2} Most of all, we were curious about whether temporary treatment really has a lasting effect on BP. Because we were unable to determine from the results of TROPHY whether 2 years of treatment produced beneficial effects on BP that persisted after treatment was stopped, we felt compelled to enter this debate.

Contrary to what Dr. Julius and colleagues claim, we did not argue that patients did not have a true increase in their BP. We claimed that intervention and control groups may have had similar increases in BP, which appeared to differ due to the study’s end point, which included data from the first 2 years of treatment.\textsuperscript{3} We agree that random variation does factor into clinical decision making for hypertension but not in the same way that it may have influenced the outcome of this study. In practice it is certainly true that a patient with a mean BP below 140/90 mm Hg who happens to have two consecutive office visits with BPs above this threshold could be labeled as hypertensive and treated as such. This definition would be acceptable to practicing clinicians. In TROPHY, however, a patient who never had two consecutive visits with BPs $\geq 140/90$ mm Hg and who had a mean blood pressure $<140/90$ mm Hg would still be labeled as having hypertension if any 3 of 18 visits met the BP threshold (including the 9 visits when treatment differed between the groups). We imagine the differences in hypertension incidence between the study groups in the third and fourth years of TROPHY would disappear much more quickly if an alternative and more clinically appropriate definition of hypertension were used. For instance, if only the data from recent evaluations (such as the mean of the last two consecutive visits $\geq 140/90$ mm Hg) were used to define hypertension and no BP values from the first 2 years were used to define incident hypertension in the third and fourth years of the study, the results might not be the same. The investigators have the data needed to test this hypothesis.

We agree that comparing mean BPs during the course of the trial is methodologically challenging. All possible solutions to this problem have drawbacks. That said, the fact remains that if