The stated purpose of the Trophy trial was “to examine whether early pharmacologic treatment of patients with ‘high normal’ blood pressure would prevent or delay the development of clinical hypertension.”1 To this end 809 study subjects from 71 different study centers were randomized to receive either 16 mgms. of candesartan or a placebo for two years. After that, all patients were observed on placebo for an additional two years. The only primary end-point was the diagnosis of clinical hypertension. The authors concluded (changing their wording) that “treatment of prehypertension appears to be feasible.”2

The results of this trial deserve careful scrutiny because they may be used to greatly expand the number of people labeled and targeted for long term drug treatment. There are three key issues compromising the trial’s validity:

1. The way the primary endpoint was determined, including the omission of vital data they claim to have collected.
2. The misuse of the terms “prehypertension” and “feasibility.”
3. The author’s failure to even mention their own predetermined analysis of possible outcomes which, if adhered to, could only have led to their own predefined conclusion, “treatment (with candesartan) not feasible.”

Criticisms Concerning the Primary Endpoint and Its Applicability to Clinical Practice

For the determination of the primary endpoint, clinical hypertension, four criteria were used, the first of which was highly unusual and never used in clinical practice. 1. Average clinic blood pressure either greater than 140 systolic or greater than 90 diastolic at 3 different visits during the 4-year study period, not necessarily consecutive. 2. BP over 160/100 at any single visit. 3. Patients requiring anti-hypertensive drug treatment. 4. Average clinic BP over 140/90 on the last visit. The number of patients diagnosed by each of these 4 modalities was: #1-70%, #2-7%, #3-21%, #4-2%. Although additional blood pressures were taken at home, twice daily for one week at baseline and again at the end of each year of the study, those data were not published.

An accompanying editorial3 criticized end-point criteria #1, because treated patients had only half the time (2 years instead of 4) to go over the 140 or 90 thresholds. (Clinical Specialists in Hypertension (and most trialists) usually require at least 2 or 3 weekly or biweekly measurements exceeding 140/90 consecutively.) The shorter time period also translated into fewer clinic BP measurements, 9 vs. 18. Considering its volatility, the chance of getting three non-consecutive BP readings above 140 increases with the number of readings taken, favoring the placebo arm. This criticism is bolstered by the additional observation that end-point #1 was the only one that achieved statistical significance.

In a letter to the editor,4 Conen and Martina describe a hypothetical patient who on screening for entry had consecutive blood pressures of 140/88, 142/85, and 132/91, the mean of those three readings qualifies that patient for inclusion as a prehypertensive. Were that patient placed in the placebo arm, and had the very same blood pressures non-consecutively during follow up, he would be classified as developing clinical hypertension, not from the mean, but because the threshold for systolic was reached twice and diastolic once within the four study years, satisfying TROPHY’s unusual diagnostic criteria for the primary endpoint. This criticism was not answered responsibly by the authors,4 thereby conceding the clinical inapplicability of their odd primary endpoint.

Analysis of the cohort reveals that the average age was 48, the average BMI 30, weight 89.9 kgm. and all had abnormal lipids. This cohort is unusual and not comparable to Framingham5 or TOHP,6 verified by the fact that 63% of the control arm and 56% of the candesartan treated arm converted to their odd definition of clinical hypertension at the end of 4 years. In Framingham,5 the high normal group conversion rate was 37% in 4 years, albeit including a wider BP range and was similar in the TOHP study,6 10% per year. In addition to differences cause by the unusual “any three endpoint” definition, some of this difference could relate to the fact that TROPHY came somewhat later in time and Americans are getting heavier every year. TROPHY’s cohort does comport with the more recent NHANES III. Clinicians need to assess care-
fully whether a specific patient fits the study cohort, before acting on the study conclusions. But if you don’t believe the study has proved its point, it won’t matter too much.

**Criticisms Concerning Post Hoc Changes of Terminology**

Further straining the question of applicability is the confusion between what the authors said they would do and what they actually did. They renamed TROPHY a “feasibility” study, without specifically defining the term. It usually means a pilot study, but TROPHY was not designed as a pilot, but, to use the author’s own words, TROPHY “seeks only the proof of principle that early pharmacologic treatment of prehypertension might delay or prevent development of clinical hypertension.” Instead of calling the cohort “high normal” they switched to the term “prehypertension.” But they failed to distinguish the new arbitrary epidemiological definition of prehypertension from the previous work of the lead author, in which the term was defined clinically in a much younger group and was associated with increased sympathetic tone. Clinicians rightly suspect bias when the trial language is changed post hoc to allow more accommodation to the data.

**Criticisms Concerning Study Conclusions**

The major conclusion of this study is that at 4-years there was a 9.8% decrease in the primary endpoint reached for those treated compared to controls, proving to the authors that candesartan treatment prevented the development of hypertension. But the control group at 4 years had an average systolic BP only 1.5% lower, and average diastolic BP only 0.8% lower, than those treated. The fact that such a small decrement in average BP, translated into a 9.8% difference in endpoints, says something about the appropriateness of using any arbitrary endpoints as a measure of success when we know that cardiovascular risk is directly related seamlessly to the height of the BP. But even these BP data must be taken with a grain of salt. It is presently recognized that clinic blood pressures, even automated, as they were in TROPHY, are not as accurate as ambulatory 24 hour blood pressure monitorings or home blood pressures, and therefore a weak choice for testing any new idea. According to protocol, home blood pressures were measured at baseline and annually, but weren’t reported. These considerations also work to diminish the robustness of study conclusions.

The most telling criticism of TROPHY was actually suggested by the trial authors themselves. In their publication submitted halfway through the trial, under the subheading “Proposed Data Analysis”: Concepts and Methods, 5 possible scenarios are predicted. These scenarios were, in the authors’ own words, meant “to guide analysis” “to ensure a priori objectivity at the conclusion of the study.” The hypothetical scenarios are each represented in 5 Kaplan-Meyer graphs. The two extreme possibilities were labeled “Masking HT” and “Eliminating HT.” Masking was indicated by a rapid return of the treated cohort to control levels by the third year. Eliminating HT showed a plot continuing the low rate during the treatment phase for the final two years. Neither of these scenarios represent what actually happened. Two forms of “Delaying HT” were also illustrated, one where the new incidence curve parallels the control rate soon after the second year with the same slope, and the other, “Profoundly Delaying HT,” in which the curve resumes promptly but rises with a slower slope. Neither of those two scenarios fit.

Only the fifth scenario, “Slow Unmasking of HT” fits with the study data. Both the data from the trial and the hypothetical data show a prompt rise in the development of clinical hypertension in the treated group after going on placebo with a steeper slope than the control group. The incidence of clinical hypertension is still rising and almost reaches the control line by year 4. TROPHY’s own a priori (and therefore unbiased) interpretation of these results is that it reveals “Slow Unmasking” of hypertension. Their conclusion for this scenario was: “Prevention of hypertension not feasible.”

Logical Bayesian trial analysis suggests that each of the 5 hypotheses had a pre-test probability that could have been statistically analyzed using the trial data to yield a post-test probability as proposed by Diamond and Kaul. Not only did the authors fail to subject their own hypotheses to any statistical analysis, they never even mentioned their own prior analysis or explained that omission.

What conclusions might actually be appropriate? TROPHY proved that 2-years of candesartan treatment of patients with “high normal” or “prehypertension” did not prevent or delay the development of hypertension, but instead caused a “slow unmasking.” Reasonable acceptance of the author’s own predetermined guidelines would have necessitated publishing a negative study, which paradoxically could have been a great benefit to the hypertension literature. Instead, TROPHY was presented in a way that enables those who want to believe in the original idea despite the evidence against it, still can and still do. Even as the author’s trumpet candesartan’s success in the paper’s conclusions, and in public presentations, the conclusion section of TROPHY paradoxically states that they do not advocate treating the 25 million people with prehypertension, but don’t explain why.

Most clinicians and other medical scholars should reject this paper as a noble effort gone sour. Its idiosyncratic primary endpoint seriously impairs external applicability. Its conclusions are fundamentally weakened by the bias inherent in a post-hoc rearrangement of design and a failure to follow its own predefined guidelines for interpretation of the data. The study did not prove what it was designed to prove but was published in a way that allowed the authors and others to claim success through disingen-
uous use of the vague term “feasibility.” This usage led to emphasis on claims that candesartan caused no side effects (as though that was a good reason for using it) and was cost effective, strange claims for authors who said they did not advise treatment. Such unwarranted speculation has the unfortunate effect of encouraging those willing and anxious to treat based on the unjustified conclusions of a flawed study that, in addition, had no hard endpoints! Unfortunately, this exposes 25 million Americans to the prospect and nuisance of patienthood, including the fears doctors often engender to facilitate compliance in the asymptomatic, and the medical risks of unproven long term drug treatments. Perhaps we should humbly pause before taking on pharmacotherapy of a huge group that is even healthier than those with stage 1 hypertension where control is presently still far from ideal.

References


9. Julius S. Background and Rationale for TROPHY and Main Study Findings. The TROPHY Study Sessions; Friday May 19, 2006 12:30 PM East Ballroom.