Studying Interventions to Prevent the Progression from Prehypertension to Hypertension: Does TROPHY Win the Prize?

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Systolic blood pressure increases steadily with age, and most individuals with systolic blood pressures in the range of 130–139 mm Hg will develop hypertension. Given the burden of cardiovascular disease and stroke attributable to hypertension, delaying its progression using an intervention in the prehypertension stage would be attractive.

Testing whether a temporary treatment alters the progression from prehypertension to hypertension, however, raises specific methodological challenges. The research question is not, “Do antihypertensive medications lower blood pressure?” but rather, “Does temporary treatment alter the subsequent course of an individual’s blood pressure?” Because the focus is on durable effects after treatment has ended, outcomes must be assessed using only data from the post-treatment period for the intervention and control groups. Using data obtained during the initial active-treatment period to assess outcomes will inevitably give the spurious impression of a sustained difference in blood pressure when this may not exist.

The recent Trial of Preventing Hypertension (TROPHY) examined whether treating patients with candesartan for two years resulted in a sustained reduction in blood pressure after candesartan was discontinued. TROPHY reported that treatment with candesartan significantly reduced the risk of incident hypertension over the four-year study interval. However, given the way the study’s primary endpoint was defined, these results are likely invalid. Here we describe how the methods of TROPHY biased the findings in the third and fourth years of the study (when both groups were treated with placebo).

Random Variation in Blood Pressure and the TROPHY Endpoint

Incident hypertension, the primary endpoint of TROPHY, was defined as any of the following: 1) blood pressure at a clinic visit (the average of multiple readings) equal to or greater than 140/90 mm Hg for any three visits (not necessarily consecutive), 2) one clinic visit with a mean blood pressure equal to or greater than 160/100 mm Hg, 3) the presence of target-organ damage, 4) other reasons to initiate pharmacotherapy, or 5) blood pressure equal to or greater than 140/90 mm Hg at the visit at month 48. Sixty-nine percent of participants reaching the primary endpoint did so by meeting the first criteria. This endpoint is problematic. For individuals with a mean blood pressure modestly below 140/90 mm Hg, there is a chance on any given day that the blood pressure will be above 140/90. However, if they take a medication that reduces their blood pressure, the chance that the blood pressure will be above 140/90 on any given day is reduced while on the medication. Thus, the TROPHY endpoint criterion of elevated blood pressure at any three visits was much more likely to be met by a person who did not have his/her blood pressure lowered in the first two years than for someone treated with an antihypertensive drug in the first two years, even if candesartan had no lasting effect on blood pressures.

Since the endpoint allowed data from years one and two (when active treatment was administered) to be used as part of the endpoint assessed in year three or four when both groups received placebo, a difference in the rates of achievement of the primary study outcome at four years may have appeared to be present even if blood pressures were identical. This problem is not a reason to interpret the data with caution, as has been suggested. It is a fatal flaw.

Hypothetical Patients in TROPHY

Imagine a participant in the placebo arm of the TROPHY trial with an average systolic blood pressure of 134 mm Hg. Despite the lack of a decrease in blood pressure, the participant meets the criteria for incident hypertension at the four-year endpoint. This spurious result occurs because of the evaluation of baseline blood pressure at the four-year visit rather than the average of clinic visits in the first two years. The study is not designed to compare intervention effect, only to assess the incidence of hypertension. For this reason, the results of TROPHY may be misleading. We recommend that future studies use a more appropriate and meaningful endpoint.
during the first year, rising to 137 mm Hg in the fourth year. The measured visit blood pressures vary normally around the mean, and at each visit there is a modest probability that the \( \geq 140 \text{ mm Hg} \) threshold would be reached for that visit. With 9 visits in the first two years, many people like this one would have one or two visits with systolic blood pressure \( \geq 140 \text{ mm Hg} \) during the first two years. Therefore, in years three and four, it would take only one or two additional visit blood pressures this high to meet the study endpoint. If however, the systolic blood pressure were lowered by a mere 5 mm Hg during the first two years, the mean blood pressure becomes 129 mm Hg and it becomes much less likely that any given visit will reach the 140 mm Hg threshold. Therefore, this same person (assigned to drug treatment) is less likely to enter year three with any prior visit blood pressures meeting the 140 mm Hg threshold.

The figure illustrates what systolic blood pressure measurements varying around these means might look like. The black boxes show data for a placebo treated patient and the circles show the same data with systolic blood pressures 5 mm Hg lower for the first two years and equal for the third and fourth years. Even though measurements are identical in years three and four, the placebo treated patient reaches the study outcome at visit (A) because this is the third visit at which the blood pressure reached the threshold of 140 mm Hg or higher. The patient in the active treatment group in years one and two, however, never reaches the endpoint because his blood pressure at the clinic visits during the first two years never was 140 mm Hg or higher.

### Impact of Carrying the Last Observation Forward on Blood Pressure Differences

TROPHY reported persistent differences between the study groups’ mean blood pressures during years three and four.

To address the difficulty in comparing blood pressures once drug treatment was initiated in patients diagnosed with hypertension, the authors chose to carry forward the blood pressure from the last visit prior to the initiation of drug therapy. This method of data imputation, however, could have introduced bias if the measurements carried forward exceeded participants’ mean blood pressures and the rates of carrying forward were unequal in the two groups.

Imagine again the two patients from the Figure with identical blood pressures during years three and four. At the time of visit A, the patient in the placebo arm (black squares) has a third blood pressure exceeding 140/90 mm Hg (i.e., 142 mm Hg systolic). She has met the trial endpoint, and antihypertensive therapy is begun. Therefore, the blood pressure from visit A will be carried forward, even though it does not represent her average blood pressure. In contrast, for the patient who received candesartan during the first two years (white circles), the blood pressure at visit A is only the second above 140/90 mm Hg. Therefore, she does not meet endpoint criteria, and therapy is not initiated. At the next two visits, her blood pressure has regressed back towards her mean and remains below 140/90 mm Hg. The blood pressure from the month 48 visit, 139 mm Hg systolic, is used in the final statistical analysis. Thus, by choosing this method of carrying the last pretreatment blood pressure forward, it is made to appear that the blood pressure at the study’s end was lower for the patient initially receiving candesartan despite the fact that the readings for these two patients were actually identical during the third and fourth years of the study.

### Recommendations for Future Trials

Future trials seeking to determine if a short-term intervention has long-term effects on blood pressure once the intervention has ceased must not use an endpoint that includes measurements observed during the active intervention period. Using the mean of the most recently observed 2 or 3 office visit blood pressures to assess the outcome of incident hypertension rather than using an “ever observed” criteria would allow a more direct group comparison on long-term follow up and prevent many individuals with mean office blood pressures below 140/90 mm Hg from being incorrectly classified as having hypertension.

For studies of prehypertension in low-risk populations, temporarily withholding pharmacotherapy from persons meeting the criteria for Stage 1 hypertension would allow for a direct comparison of blood pressures off all antihypertensive medications and would probably be of acceptably low risk. However, for patients for whom a short time period without treatment is deemed unsafe, a final blood pressure could be imputed based on their mean blood pressure and the intensity of their medical regimen. Although this has its own limitations, it should introduce far less bias than the methods employed in TROPHY.
Conclusions

Current estimates suggest 70 million Americans have pre-hypertension.\(^7\) Thus, the consequences of drawing erroneous conclusions from studies of treatments to prevent progression from pre-hypertension to hypertension are enormous. An expert panel of statisticians and trial methodologists without ties to pharmaceutical companies should be convened to provide consensus recommendations for how future studies addressing the prevention of hypertension should be conducted and reported. Computer models should also be used to confirm that the study methodology would not make it appear that a treatment for prehypertension had sustained benefits when, in fact, none existed.

References