Trial of Preventing Hypertension (TROPHY)
Design and 2-Year Progress Report
Norman M. Kaplan

The article “Trial of Preventing Hypertension (TROPHY): Design and 2-Year Progress Report” by Stevo Julius et al in this issue of Hypertension provides assurance that this ground-breaking trial will likely be successful in providing the first evidence in humans of the ability to delay, if not stop, the development of hypertension by the use of an antihypertensive drug.

To their credit, the investigators obtained financial support from the pharmaceutical marketer of an angiotensin II–receptor blocker, an appropriate choice in view of the cited animal data on the particular ability of angiotensin–converting enzyme (ACE) inhibitors to prevent hypertension in susceptible rats. They carefully selected 809 middle-aged subjects at 71 study centers. The subjects had “high-normal” BP (ie, 130 to 139 systolic or 85 to 89 diastolic) and were, as expected, moderately overweight (body mass index = 29.9 ± 5.3).

The protocol randomly allocated the subjects to take either active therapy with candesartan 16 mg/day or placebo for 2 years, followed by another 2 years of only placebo for both groups. The end point is the development of clinical hypertension (ie, BP above 140/90 mm Hg anytime during the entire 4 years). As they explain, this prolonged placebo-follow-up should obviate problems of interpretation of changes during or immediately after active therapy. The study was able to enroll fewer patients than projected for adequate statistical power, but the likelihood for a successful conclusion is buttressed by a lower rate of dropout and a higher rate of clinical hypertension in those who were enrolled.

The authors shrewdly propose a number of possible outcomes and have prepared to analyze the data “to ensure a priori objectivity at the conclusion of the study.”

In reviewing the entry and 2-year data (which do not identify which group the hypertensives are in), one rather small surprise is noted: the home-recorded blood pressures were almost identical to the clinic-recorded pressures (ie, there was virtually no “white-coat effect”). Perhaps the 1-week period of home recordings was not long enough to overcome the tendency for home readings to be higher at first and to then become lower.

Potential Value of the Trial
As the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) clearly notes, blood pressures >120/80 but still <140/90 are associated with enough risk to call them “prehypertensive.” JNC-7 recommends only the use of appropriate lifestyle changes in those patients to prevent further progression.

This conversion from the term “high-normal” to “prehypertensive” has caused consternation among some experts who are concerned that the label may engender additional expenses and anxiety, well known to be a cause of symptoms in newly diagnosed hypertensives. Moreover, the 2003 European and the 2004 British guidelines continue to classify patients with blood pressures of 130 to 139/85 to 89 mm Hg as high-normal.

Recalling the bell-shaped curve of blood pressure in the population, the largest group of people will be those with blood pressures in the prehypertensive range. Whereas all agree that lifestyle changes are most appropriate for them, to call them “prehypertensive.” JNC-7 recommends only the use of appropriate lifestyle changes in those patients to prevent further progression.

Therefore, the audacity of Julius et al in crossing the border into active drug therapy is to be applauded. As they conclude: “The TROPHY study seeks only the proof of principle that early pharmacological treatment of prehypertension might delay or prevent development of clinical (stage 1) hypertension.” If TROPHY shows such delay or prevention, further studies, larger and longer, will obviously be needed.

Some may argue that, in view of the woeful inadequacy of current therapy to adequately control those with overt and high-risk hypertension, it is foolish to go after many millions more. But, an ounce of prevention, even if it costs a fair amount, is well worth a pound or more of inadequate treatment. The final conclusions from TROPHY, hopefully to be available in 2 years, are eagerly awaited. They may lead to a major rethinking of our current attitude about prevention of hypertension.

References
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