Commentary

Implications of recent hypertension trials for the generalist physician: whom do we treat, and how?

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Abstract

The publication of the results of the Swedish Trial in Old Patients with Hypertension-2 (STOP-2) and the termination of the doxazocin arm of the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack (ALLHAT) study again raise the question of whether all antihypertensives deliver equal cardiovascular outcome benefits. Data from research on congestive heart failure and from the Heart Outcomes Prevention Evaluation (HOPE) trial illuminate the roles and possible mechanisms of humoral mediators of vascular damage, suggesting, first, that some antihypertensives (thiazides, beta-blockers, and angiotensin-converting enzyme inhibitors) can deliver more improvement in outcomes than other agents and, second, that decisions on whom to treat are best made based on risk appraisal, not merely pressures.

Keywords: antihypertensive agents, comparative study, drug therapy, hypertension

These are exciting times for physicians interested in the treatment of hypertension, with new and important data emerging regularly. Translating the excitement into better outcomes for large numbers of patients, however, means placing the new information in the hands of generalist physicians (family physicians and general internists), and making the information clear enough to be usable rather than baffling. Hypertension practice guidelines should accomplish this information placement, but recent guidelines based on the most recent evidence reach conflicting conclusions in some ways [1–3]. The conflict centers around two key issues: does it matter how blood pressure is lowered?; and are there subsets of patients who benefit from antihypertensive drugs at lower pressures than we have conventionally believed, or who do not benefit unless pressures are higher than we have believed?

Two recent trials offer what appears to be confusing guidance on the first question. STOP-2 [4] compared newer and older antihypertensive agents, and concluded that there were no substantial differences in outcomes among them. This finding lends credence to the conventional view

ABCD = Appropriate Blood Pressure Control in Diabetes; ACE = angiotensin-converting enzyme; ALLHAT = Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack; CHF = congestive heart failure; HOPE = Heart Outcomes Prevention Evaluation; STOP-2 = Swedish Trial in Old Patients with Hypertension-2.

that blood pressure is the factor that matters, and lowering it by any means that has acceptably low side effect rates is the appropriate approach. Not long after the publication of STOP-2, however, the doxazocin arm of the ALLHAT trial was terminated because of an excessive rate of development of congestive heart failure compared with thiazides [5], suggesting that how blood pressure is lowered may indeed matter in terms of outcomes achieved. What is the primary care physician to make of these developments?

The 'pressure is what counts' view is attractive. It offers simplicity, and great flexibility in clinical choices: any treatment that reduces pressures and is acceptable to patients is a good treatment for hypertension. It is tempting to think that the ALLHAT findings may be an anomaly, or perhaps specific to doxazocin, and that the conclusion of STOP-2 is the correct one. Closer examination, however, suggests that this conclusion is not prudent.

STOP-2 did not really find that all the regimens were similar. It rather showed an excess of both myocardial infarction and congestive heart failure (CHF) in the calcium antagonist arm as compared with the angiotensin-converting enzyme (ACE) inhibitor arm, a finding attributed to chance due to the total of 48 such comparisons made. The similarity of that finding to the results of the earlier Appropriate Blood Pressure Control in Diabetes (ABCD) trial [6], however, lends support to the argument that it was not a chance occurrence. Furthermore, an excess of myocardial infarction almost reached significance among the conventional-therapy arm compared with that of ACE inhibitor. Conventional therapy in STOP-2 involved thiazides and beta-blockers, and there is evidence from other studies that beta-blockers are not as effective, in terms of outcomes in the elderly, as thiazides [7].

The marked change in our understanding of CHF over the past decade is worth considering in our thinking about hypertension. The results of recent antihypertensive trials are exciting, rather than being confusing and dismaying, when seen in light of the CHF research, and offer hope of getting closer to the real roots of the harm that hypertension does. A deeper understanding of the role of the renin–angiotensin–aldosterone system and the pathophysiological role of angiotensin II in vascular disease [8], in particular, adds more credence to the view that pressure *per se* may not be all that, or even mostly what, matters for the hypertensive patient's outcome. Antihypertensive drugs cause many effects other than lowering pressure, and those other effects are different for different classes. With the emergence of data demonstrating that ACE inhibition improves cardiovascular outcomes in high-risk diabetics even without hypertension [9,10] and the established efficacy of beta-blockers for CHF patients without hypertension [11], the role of humoral rather than merely mechanical factors in determining outcomes must be considered by the primary care physician when choosing medication therapies.

If humoral factors matter as much as or more than pressure *per se* in determining outcomes of hypertension, we must focus our research on interventions that affect those humoral factors. But changing our thinking about how we treat will not be enough. We must also think carefully about how we decide whom to treat. Beta-blockade improves outcome among patients with coronary artery disease, regardless of hypertension, and, as already noted, ACE inhibition also appears to do so for diabetics. Trials of what we regard as antihypertensive therapy could show improved outcomes among patients with high–normal or even normal pressures for reasons entirely unrelated to blood pressure, if the patients enrolled had significant baseline risks of cardiovascular disease. We might erroneously conclude that our threshhold for diagnosing hypertension should be lowered, and mistakenly extrapolate those findings to all patients above our lowered thresholds.

So what do the findings of these most recent trials imply for the generalist physician? First and foremost, we cannot assume that all antihypertensive drugs are created equal. We should preferentially prescribe for our patients those that have demonstrated the best outcomes. At the present time, considering these outcomes, low-dose thiazides, beta-blockers, and ACE inhibitors should be the mainstays of therapy. We also need additional research: direct comparisons of different classes of agents in randomized non-placebo (active control) trials. Those trials must compare real outcomes not blood pressures, and we must interpret those trials with care. At present, low-dose thiazides set the benchmark for outcome improvement among both elders with systolic hypertension and middle-aged patients with diastolic hypertension, and should be the active controls against which other agents are measured.

Finally, and most importantly, we are moving further from a single decision criterion for deciding whom to treat. Primary care is a tough challenge, in which most patients have a number of health problems and concerns. Hypertension is only one player on the stage and, to the patient, it may not even have the starring role. It was very helpful to have only one number, 140/90, to remember amidst those many competing agendas and time pressures of the primary care visit. It was … but is no more. We have just begun becoming comfortable with a different criterion for diabetics; we must now begin looking at treating patients who are not hypertensive by any criterion, if their cardiovascular risks are high enough. Conversely, it may well not be worth treating some stage I hypertensive patients who are at such low risk that their potential absolute risk reduction from treatment is miniscule. Primary care physicians must shift their thinking to treating cardiovascular risks, rather than blood

pressure numbers, and begin to develop the decision support models that allow this treatment in the busy, distracting, time-constrained context of primary care.

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