A Glance Back: One Year Into the Millennium

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This first issue of the American Journal of Hypertension for 2001 gives us the opportunity to canvass the road behind us, like highway driving with a glance through the rear view mirror, as we move forward on a road destined to surprise. The year 2000 provided valuable studies of hypertension; several were unexpected yet powerful enough to change widespread views about how hypertension and those at risk for cardiovascular diseases should be treated.

The Heart Outcomes Prevention Evaluation (HOPE) study entered those patients over 55 years of age without heart failure, but with a high risk of fatal and nonfatal cardiovascular events, irrespective of whether or not hypertension was present. Groups were randomized to ramipril, a long-acting angiotensin converting enzyme (ACE) inhibitor, or placebo and treated according to usual practice. Among the various outcomes we might look at, one says it all: cardiovascular mortality was 26% lower for the group receiving ramipril, an absolute reduction of 2%. And for the diabetic group described in MICRO-HOPE, cardiovascular mortality was 37% lower when the ACE inhibitor was given, an absolute decrease of 3.5%. HOPE’s outcome was extraordinary in relation to the very small difference between group average blood pressures over the course of the trial (2 to 3 mm Hg). Nonetheless there are those that attribute HOPE’s results to changes in blood pressure rather than any unique action of ACE inhibitors.

Because the action of ACE inhibitors includes, but is not restricted to, blockade of the renin-angiotensin system, HOPE provides some confirmation for the hypothesis that increased renin activity contributes to cardiovascular disease as an independent cause. Some will point out that kinin potentiation and its complex relation to prostaglandin and nitric oxide generation may account for benefits of ACE inhibitors. But the occurrence of these downstream changes is always highly associated with antecedent reduction in plasma angiotensin II or blockade of its receptor. Both sides emphasize that the HOPE trial clearly implies that the benefit is provided by physiologic vascular mechanisms that, in a given patient, may or may not lower blood pressure. I predict that from now on, cardiovascular risk, rather than hypertension per se, will assume center stage as the target for therapy except for those who have very high arterial pressures. Guideline writers may have to go back to their drawing boards quite soon to deal with this issue.

Another large trial published in 2000 concluded that α1 receptor blockers might be less beneficial, even if they did lower pressure. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) is a hefty study with promise to settle many questions for clinicians who treat hypertension. Three antihypertensive drugs, amiodipine, doxazosin, and lisinopril, were to be compared to chlorthalidone as initial treatment. In January 2000 the trial monitoring group chose to stop the doxazosin limb because, on serial monitoring, there was a “...significant 25% higher incidence of major cardiovascular disease (CVD) events in participants assigned to the doxazosin group compared to the chlorthalidone group.” Most of this difference was related to hospital admissions for congestive heart failure, but there were trends to suggest higher rates of stroke and several coronary disease events, as well in the group given doxazosin, compared to that given the diuretic chlorthalidone. This outcome was an unanticipated result. Nonetheless, the size and quality of ALLHAT confer clinical significance to its outcome. Perhaps doxazosin should depart the ranks of those drugs considered for initial or single treatment of hypertension and confine itself to fewer well-defined indications, symptoms of prostatic obstruction and refractory hypertension, when alternate treatments are ineffective or unacceptable.

Calcium blockers also got some show time in 2000. The NORDIL (diltiazem) and INSIGHT (nifedipine GITS) studies were published. In brief, the outcomes were a tie for both studies: the calcium blockers were no more effective than the diuretics given in comparison groups. However, in the INSIGHT study, dropouts due to adverse effects were 8% higher for those assigned to the calcium blocker. Because ALLHAT continues with amlodipine in...
one of its three limbs, we will await its final act with great anticipation.

A new monogenic form of hypertension was elegantly described in 2000 by Lifton’s group: salt-sensitive hypertension occurring in pregnancy. The cause is a mutation in the mineralocorticoid receptor gene that then recognizes progesterone as an agonist. The implications for this “gain of function” mutation will, no doubt, be actively explored in the next year and beyond.

Will 2001 resolve important issues, such as whether ACE inhibitors and angiotensin receptor blockers are equivalent for treatment of those at high risk, but without heart failure? Will guidelines be revised to reflect the progress of 2000? Stay tuned—an exciting development or two may be just around the bend.

References


