Guidelines Based on Politics - Not Science

PJR: Since others have confirmed your hypothesis and NHLBI has funded your research it is puzzling that renin is never referred to in their official reports. This reminds me of Schopenhauer’s observations about discoveries. “All truth passes through three stages: First, it is ridiculed; Second, it is violently opposed; and Third, it is accepted as self-evident.” New ideas are most often criticized not because they lack merit, but because they might turn out to be workable, which would threaten the reputations and possibly jobs of many people with conflicting opinions. The disastrous results of this are vividly illustrated by the recent ALLHAT study.

JHL: None of the numerous studies that confirm the renin hypothesis are ever quoted by ALLHAT or JNC reports, which is reprehensible. The word renin is rarely or never mentioned, which is like discussing diabetes without ever mentioning the word, insulin! With respect to ALLHAT, there were several flaws in the design and implementation of the study that raise serious doubts about the validity of its conclusions and especially their applicability to clinical practice. Over a third of patients were African Americans who are more apt to respond to diuretics because more of their hypertension tends to be volume (salt) related. The participants were all older than 55 (mean age 67) and 36% were diabetic, so it is also doubtful that any conclusions from such an elderly high-risk group would apply to low-risk hypertensives under the age of 55.

Nine out of ten were already receiving some type of antihypertensive drug therapy and there was no washout or medication-tapering period. On day 1 they were switched to one of four blinded randomized drug limbs: diuretic (hygroton), ARB (doxazosin), ACE inhibitor (lisinopril) or calcium channel blocker (amlodipine), so that “baseline” BP was meaningless as a control point for evaluating efficacy. The withdrawal of certain drugs may have caused subsequent adverse events such as heart failure rather than this being due to the new medication as the study authors concluded. The increased incidence of “heart failure” characterized by poorly defined edema in the doxazosin group that led to its discontinuation is particularly puzzling.

It is more likely that heart failure resulted from abrupt cessation of diuretic therapy in those patients who were placed on comparatively weak dosages of doxazosin since heart failure has not been a problem in other studies. The timing and pace at which patients were treated with medications were not consistent with good medical practice and potentially dangerous. As explained elsewhere, many of us would consider failure to achieve effective drug treatment for 6-18 months as overt malpractice. Drug dose titrations were programmed so that no changes at all were made in non-responders until after six months. Although the second drug was again often the wrong one, it still had to be titrated up for the next 9 to 12 months and it was only after 16 months that a step 3 drug was introduced. Consequently, some patients were put at increased risk for complications due to poor or no control of their pressure for a year and a half or more, during which they would likely also suffer from the side effects of increasing dosages of drugs not appropriate for their type of hypertension. I suspect this could lead to ALLHAT study malpractice litigation.

According to the trial protocol, if patients did not achieve the goal pressure on a properly titrated dose of the initial study drug, a second and if necessary a third medication could be added, provided it was not one of the study drugs (diuretic, ACE inhibitor or CCB). Physicians could choose from a beta blocker (atenolol) or centrally acting drugs (clonidine and reserpine). A beta blocker was the main drug usually added, which obviously would be most beneficial for non-responders on a diuretic. Conversely, patients who did not respond to an ACE inhibitor were prevented from receiving a diuretic or CCB and were condemned to receiving still another antirenin drug even though the first one failed. Thus, the design of the study was set up to favor a V drug (hygroton) and, either intentionally or inadvertently, to put an R drug (lisinopril) at a disadvantage. The tragedy is that the ALLHAT recommendations are the basis for the new JNC-VII guidelines.
