Editorial

James V. Felicetta, MD

Editor-in-Chief

Weighing the Options for Antihypertensive Therapy: Are All Agents Created Equal?

These days, we are fortunate to have numerous options available for treating hypertension. But the downside of this abundance is the difficulty of discerning a clear message from the cacophony of competing claims—many of which bear the taint of commercial bias—regarding the efficacy of the various antihypertensive agents. Are some classes better than others or are they all essentially equal?

Let's see if we can make some sense out of the confusion. The first important point is that all antihypertensive medications are roughly equivalent in terms of their ability to lower blood pressure (BP). There can be some squabbling over what the comparable doses of different medications might be, but, in general, a drug from antihypertensive class A will reduce BP by just about the same amount as a drug from antihypertensive class B or even C. The trick is to make sure that different agents are compared in patients with the same degree of hypertension at baseline, so that the playing field is level to begin with. As a general rule, if you start with a patient whose systolic BP is between 140 and 160 mm Hg and whose diastolic BP is between 90 and 100 mm Hg, you can expect a single agent to produce a systolic reduction in the range of 10 to 15 mm Hg and a diastolic reduction in the range of 5 to 8 mm Hg.

There is some modest variation at the margins. It is well known, for example, that black patients typically achieve a slightly lower reduction in both systolic and diastolic BP, compared with white patients, in response to agents that work primarily by suppressing the renin-angiotensin-aldosterone system (RAAS), such as angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs). In addition, an older person with salt-sensitive hypertension typically will get slightly more BP lowering power from diuretics than a younger patient whose hypertension is less dependent on volume. But these are some of the minor exceptions that prove the rule: Overall, the degree of BP reduction produced by different classes of antihypertensive agents is remarkably similar.

Now that we have established this fact, we are faced with a potentially more interesting question: Does the overall reduction in the cardiovascular risks associated with hypertension vary depending upon the class of agent used? In other words, does lowering BP to a given level using antihypertensive class A afford a greater degree of risk reduction than lowering BP to that same level with antihypertensive class B? The general answer to that question trends in the direction of no, but there are some important subtleties.

One key study that illustrated the similarities of several antihypertensive classes in reducing cardiovascular events was the National Institutes of Health–sponsored Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT).[1] While this trial was not perfect, it basically showed that diuretics could hold their own against both ACE inhibitors and calcium channel blockers (CCBs), in spite of a small apparent increase in the development of new diabetes in the diuretic group.[2,3]

On the other hand, ALLHAT also showed us that alpha-blockers may be laggards in terms of risk reduction.[4] The alpha-blocker doxazosin, originally included as a fourth treatment arm of the study, was less effective than the comparator diuretic (chlorthalidone) in slowing progression to heart failure, one of the many adverse consequences of poorly controlled hypertension. As a result of this finding, the doxazosin arm was terminated early.

In a similar vein, a recent meta-analysis suggested that beta-blockers, especially atenolol, also are less effective in reducing cardiovascular risk than other classes of antihypertensive medications.[5] This could explain why the BP lowering arm of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) showed that the combination of atenolol and a hydrochlorothiazide was less effective at reducing cardiovascular events than the combination of amlodipine and perindopril.[6] The notion that the beta-blocker atenolol is less protective than the CCB amlodipine was supported by the Conduit Artery Function Evaluation (CAFE) substudy of ASCOT.[7] Using invasive monitoring to assess central aortic pressure, the CAFE investigators showed that amlodipine reduced this pressure far more than did atenolol—even when both drugs reduced peripheral BP to an equal extent.[7]

The other area in which there may be important differences among the various antihypertensive classes is proteinuria reduction. Since proteinuria clearly serves as a marker for increased risk of myocardial infarction and stroke, it seems logical that agents that reduce proteinuria might have special benefits. It turns out that medications that block the RAAS—such as ACE

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inhibitors, ARBs, and the newly available direct renin inhibitor aliskiren—are particularly effective at reducing proteinuria. The nondihydropyridine CCBs diltiazem and verapamil also have some efficacy in this respect, as do aldosterone receptor blockers such as spironolactone and eplerenone.

So we see that the answer to the question "Are all antihypertensive agents equivalent?" is both yes and no. While all of them have roughly the same capacity to reduce BP, a few appear to have a somewhat greater potential for reducing cardiovascular risk than others. Particularly when proteinuria is present, it seems prudent to favor those agents that can reduce proteinuria while simultaneously lowering BP. In other settings, the particular agents chosen may be considerably less important than the overall aggressiveness of the efforts to achieve the target BP level. Reducing BP provides powerful cardiovascular risk reduction, and it should be considered "job one" in the management of hypertension.

It's also important to remember that most patients need more than one class of antihypertensive medication to achieve their BP goal, so fussing about the distinctions between different classes may be of limited utility. When you get right down to it, all antihypertensive drugs have beneficial effects—the key is to use them aggressively in order to get the patient to goal. ●

Author disclosures

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