OPTIMIZING
ANTIHYPERTENSIVE THERAPY

Number 40 August,1999

Should Recommendations Be Changed?

Since the publication of the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC IV)[1], several long-term morbidity and mortality trials and several comparative medication studies have been published. In addition, the World Health Organization International Society of Hypertension (WHO–ISH) guidelines[2] have also become available. In this *Heartbeat* we will review some of the guidelines and the results of these trials and make some recommendations based on this data. (The long-term comparative drug trials are still a few years away from being completed.)

Results from these new studies appear to reinforce, rather than suggest a major change in, JNC VI recommendations:

1) They confirm that the use of a diuretic or beta-blocker (BB) results in significant reductions of morbidity and mortality.[3] [4]
   - 52% decrease in occurrence of congestive heart failure (CHF)
   - 38% decrease in fatal and non-fatal strokes
   - 35% decrease in left ventricular hypertrophy (LVH)
   - 21% reduction in cardiovascular events
   - 16% drop in coronary heart disease (CHD)

To date, results of other agents have not been better. There is little evidence to support the popular contention that BB's or diuretics should not be used in patients with diabetes or hyperlipidemia.[5] They are, however, not tolerated as well.

2) The Hypertension Optimal Treatment (HOT) study[6] confirmed that blood pressure should be reduced <135/85. Even more beneficial benefits were seen in diabetics by lowering pressure to <130/80. Goal BP is 120/80. (The old plumbing analogy holds: "The lower the pressure in a 'closed' system, the less the wear and tear on the hoses and pump.") There appeared to be no evidence of a J-curve phenomenon (an increase in coronary events with diastolic blood pressure levels of <85 mm Hg) even in patients with preexisting CHD.

3) Results of the HOT study also confirm the necessity of using more than one drug to reduce BP to low enough levels to achieve low rates of cardiovascular events, especially in diabetics. Both JNC VI and WHO-ISH also recognize that combination products are important:

   - They will more likely get your patient the tight BP control necessary to decrease risk.
   - Using multiple medications in lower doses will frequently result in a better-tolerated program, since side effects are usually dose-related.

[If you had asked doctors 10-15 years ago about combination drugs, they probably would have said, they were out of date. When I started

practicing medicine, the most popular BP treatments were combinations of three drugs. It's taken 25 years to come full circle.]

4) The HOT study found that use of small doses of aspirin (75 mg/day) in patients whose BP had been controlled decreased their overall incidence of CHD by 15% and myocardial infarction by 36%.

5) The SYST-EUR trial[7] in the elderly supports the recommendation that a long-acting calcium-channel-blocker (CCB) could be used as an alternative in the treatment of isolated systolic hypertension, if a diuretic was ineffective or poorly tolerated. The Verapamil in Hypertension Atherosclerosis Study (VHAS)[8] results were consistent with the SYST-EUR trial, i.e. the use of longer-acting CCB's appears to be safe and effective, with no increase in adverse events. These studies, however, did not show a CCB-based program to be more effective than a diuretic-based program in reducing morbidity and mortality in patients with hypertension.

6) Two smaller studies [9] [10] suggest that angiotensin converting enzyme inhibitors (ACE- I's) are more effective than CCB's in controlling cardiovascular events in patients with Type II diabetes mellitus.

7) Two studies of hypertensive patients showed conflicting results and are now being evaluated in additional trials:

- The United Kingdom Prospective Diabetus Study (UKPDS) [11] compared an atenolol-based program, usually with a diuretic added to a captopril-based program, with a diuretic added if necessary to control BP, for Type II diabetic patients. Tighter control of BP resulted in a dramatic decrease in event rates between the two groups regardless of the medication used. These results are somewhat different than might be expected and may reduce concerns of some physicians about using BB's in diabetic patients.

- The Captopril Prevention Project Study (CAPPP)[12] also compared ACE-I/diuretic-based treatment to BB/diuretic treatment. While overall events were reduced equally, there were fewer new onset diabetics in the ACE-I/diuretic group, and the diabetics did better than those in the BB/diuretic group.

The Safety Committee of the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) is comparing different medications, including ACE-I's, diuretics, CCB's, BB's, and alpha-blockers in almost 1500 diabetic patients. After two years, authors of the study have not suggested a change in protocol, so it might be assumed that a specific medication has not emerged as more clearly beneficial than others.[13]

What should be the initial therapy?

The WHO-ISH report contrasts with JCN VI by not specifically recommending one or two medications for initial therapy. The first notes that, "while there is a large body of data demonstrating the benefits of the older agents, such a diuretics and beta-blockers, there are fewer data available on calcium antagonists and ACE inhibitors, and no reliable data available about alpha-blockers or the angiotension II receptor blockers (ARB's)." It further states that "based on recent trial evidence, there is yet no evidence that the main benefits of treating

---

13 Hypertens. 1996; 9:342-60(ALLHAT).
14 N Engl Med. J 1998; 339:489-97.
15 JAMA. 1998; 279:1903-7.
16 *Lancet. 1999; 353:2008-13.*

HBP are due to any particular drug property rather than to lowering of the BP per se, and that the randomized trials conducted to date have not provided any clear evidence of differential effects on outcome of different agents producing the same BP reduction."

Despite the lack of outcomes data with several classes of antihypertensive agents, the WHO-ISH reports that any of these classes (diuretics, BB's ACE-I's, CCB's, ARB's, and in some instances alpha-blockers) are acceptable choices for initial therapy. These recommendations appear consistent with the newer trial data. Obviously more information is needed with some of these agents, but it may just be the degree of BP lowering that makes the difference.

A point worth emphasizing is that the use of less expensive drugs may produce results as good as more expensive medication, and that physicians should not feel they are practicing "out of date" medicine if they do not use the latest drugs. Cost-effectiveness should be considered "state of the art."

What groups of patients should be treated differently?

JCN VI pointed out that high-risk patients need to be treated differently. These are people with diabetes, multiple risk factors with target organ damage, and conditions like dyslipidemia, cigarette smoking, lack of estrogen or being African American. These patients have associated endothelial dysfunction, and ACE-I's have been shown to be the most efficacious in treating it. Drugs that penetrate the tissues better, that bind more tightly to angiotensin-converting enzymes, like quinapril and other tissue specific ACE-I's, are likely to address altered vascular biology much better and should be used much more often.

What about the Angiotensin II Receptor Blockers?

Short-term studies suggest that those drugs are well tolerated and just as effective as other agents, especially if used with a diuretic. They reduce proteinuria in diabetic patients, cause regression of LVH, if present, and reduce sudden cardiac death in CHF patients. At present, despite the lack of outcomes data, the ARB's can probably be used in situations where an ACE-I is indicated.

CONCLUSIONS/ RECOMMENDATIONS

- Lowering of BP is probably a more important factor in reducing morbidity and mortality than the specific medication used. This is true even in diabetes. The lower the BP the better (to levels we've never tried to achieve before).

- Achieving these goal BP's frequently will require two to three drugs and sometimes four.

- Non-pharmacologic methods of treating HBP should be applied in ALL patients. This includes minimizing emotional stress, losing weight, engaging in a moderate exercise program, tobacco cessation, reducing salt intake and avoiding more than small amounts of alcohol.

- Medication should be added sooner rather than later, even in low-risk patients.

- Determine co-morbidities. Make drug selections and dose adjustments based on age, gender, race and the other diseases that are present. Start an agent and titrate it, realizing that the likelihood of controlling HBP with only one drug is small.

- In some patients certain choices of agents are still compelling as first and second choices, even though maybe only theoretically:

  CHD—BB's / ACE-I's /diuretics. BB's and ACE-1's are complementary and have been shown to preferentially benefit high risk MI patients.[14] It is probably worthwhile to initiate both agents early in low doses with up-titration as tolerated.

  Cardiomyopathy—ACE-1's and BB's /diuretics. ACE-1's and BB's are the obvious first choice because of proven mortality reduction.

  Diabetes—ACE-I's or perhaps later on an ARB /diuretics.

  Elderly—Diuretics / long-acting CCB's. Consider an alpha blocker in males with BPH symptomatology, watching carefully for orthostasis.

  African American—Diuretics /ACE-I's/ long- acting CCB's /alpha blocker's.

- Diuretics are more effective than BB's as first-line therapy for elderly patients with hypertension[15] and are a necessary component in whatever regimen is chosen to achieve goal BP in most hypertensive patients. Starting dose is 12.5 mg hydrodiuril to a maximum of 25 mg/day. Higher doses have not been shown to improve outcome and have been associated with more side effects.

- ACE-I's should be used in moderate to high doses because of their beneficial effect on endothelial dysfunction, realizing that adding other medication will probably be necessary to adequately control BP. Rises in serum creatinine should not be a limiting factor for use of ACE-I's. In the absence of a serum potassium of > 5.5 or in the absence of a >30 % rise in serum creatinine from baseline within the first two months of therapy, ACE-I therapy should not be terminated.

- It is a good idea to check electrolytes and renal function a few weeks after initiating diuretics or ACE-I's.

- The **ABCD** approach[16] is good for optimizing BP control. Under age 50, use **A**CE-I's and **BB's** initially as they are more effective in this age group, then go to **C**CB's and **D**iuretics if these are unsuccessful. The opposite strategy should be used in patients older than 60.

- Low-dose aspirin therapy is recommended in conjunction with intensive blood-pressure lowering, especially in diabetics.

Richard Kasama, M.D., F.A.C.P., Guest Editor
Mario L. Maiese, D.O., F.A.C.C.

1 *Arch Intern Med. 1997; 157:2413-46 (JCNVI).*
2 *J Hypertens. 1999; 17:151-83 (WHO-ISH).*
3 *Arch Intern Med. 1993; 153: 578-81.*
4 *J Am Coll Cardiol. 1996; 27:1214-18.*
5 *Arch Intern Med. 1999; 559: 1403-06.*
6 *Lancet. 1998; 351: 1755-62 (HOT).*
7 *Lancet. 1997; 350: 557-64 (SYST-EUR).*
8 *J Hypertens. 1997; 15: 1337-44 (VHAS).*
9 *Diabetes Care. 1998; 21:597-603.*
10 *N Engl J Med.1998; 338:645-52.*
11 *B M J. 1998; 317: 713-20 (UKPDS)*
12 *Lancet. 1999; 353:611-616 (CAPPP).*
13 *Hypertens.1996; 9:342-60 (ALLHAT).*
14 *N Engl J Med.1998; 339:489-97*
15 *JAMA..1998; 279:1903-7.*
16 *Lancet.1999; 353:2008-13.*

17 B M J. 1998; 317: 713-20 (UKPDS)

18 *Lancet. 1999; 353:611-616 (CAPPP).*

19 Hypertens.1996; 9:342-60 (ALLHAT).

20 N Engl J Med.1998; 339:489-97.

21 JAMA.1998; 279:1903-7.

22 *Lancet.1999; 353:2008-13.*