Selecting Antihypertensive Therapy

By Dean Haxby, Pharm.D. and Robert Drewett, Pharm.D. Candidate

Hypertension (HTN) is one of the most common chronic conditions encountered in clinical practice and is a major risk factor for cardiovascular (CV) disease. Numerous clinical trials demonstrate the ability of a variety of antihypertensive medications to reduce hypertensive complications. (1-4) Several factors should be considered when selecting antihypertensive pharmacotherapy. This article will review the advantages and disadvantages of the major classes of antihypertensive drugs and provide recommendations for selecting therapy.

Prior to initiating pharmacotherapy, the diagnosis should be made with blood pressure (BP) readings using proper technique (Table 1). Several visits are required, with at least two measurements taken per visit. The work-up should identify: 1) secondary forms of HTN, 2) other CV risk factors and CV risk, 3) target organ damage and 4) any co-morbidities that influence choice of therapy. Readers are referred to three recent clinical practice guidelines for detailed information regarding the diagnosis and work-up of hypertensive patients. (1-3) Lifestyle modification is recommended for all patients with HTN. (1,3) Lifestyle modification is the primary therapy for prehypertensive patients and may delay the onset of disease. Changes can also be the initial therapy in patients with stage 1 HTN and at low risk of CV disease.

Pharmacotherapy

Pharmacotherapy is indicated for patients with stage 2 HTN and high-risk stage 1 HTN; and for low risk stage 1 HTN not controlled by lifestyle modification.(3,4) The BP goal is <140/90. For patients with diabetes or renal disease, treatment is recommended when pressures are above 130/80. (1)

While choice of agents is debated in the literature, there are data to support the efficacy of each drug class reviewed below in reducing the complications of HTN. In general, the strongest predictor of reduced complications is control of BP, which most often requires the use of more than one agent. (3,5) There are some important differences as discussed below, and summarized in Table 2.

Thiazides: The thiazide-like diuretics are the “gold standard”. (1) Overall they have the strongest body of evidence to support use as a first-line agent. (1,4) In the ALLHAT study, low dose chlorthalidone was comparable to amlopidine and lisinopril for ability to prevent CV events, and performed better for some endpoints. (6) In African American patients, chlorthalidone was more effective than lisinopril in preventing strokes, CV events and congestive heart failure (CHF), and more effective than amlopidine in preventing CHF. (7) They also have additive effects when combined with other antihypertensives.

The thiazide-like diuretics are well tolerated. (8,9) However, high doses of thiazides, or thiazides combined with beta-blockers are associated with increases in new diabetes cases. (3) Metabolic effects are reduced with low doses (25mg or less) of hydrochlorothiazide or chlorthalidone. In ALLHAT, chlorthalidone was as effective as lisinopril or amlopidine at preventing CV complications in diabetics (6). Hypokalemia, hypotension, hypomagnesemia and elevations of calcium and uric acid may also occur. Switching to a combination of a thiazide with a potassium sparing diuretic such as triamterene, is a convenient method to correct the hypokalemia. Potassium supplements are another option, but may be less convenient and more expensive.

Beta-blockers (BBs): As a class, BBs reduce the risk of HTN complications. However, recent meta-analyses suggest BBs may be less effective than other antihypertensives when used as initial therapy for primary prevention of hypertensive complications. (10,11) Similarly, atenolol regimens were found to be less effective than losartan (12) or amlodipine therapies. (13) BBs are associated with an increased incidence of new diabetes cases (3,13). This raises concern about using BBs as first line agents for uncomplicated HTN, and whether they are suitable to use as a control treatment in clinical trials. This concern does not apply to secondary prevention, where there is compelling data to recommend BBs as first line therapy post myocardial infarction, heart failure (defined as left ventricular systolic dysfunction, ejection fraction ≤ 40%) and in the management of angina. (1,4)

Angiotensin Converting Enzyme Inhibitors (ACEIs): The overall efficacy of ACEIs appears comparable to thiazides. The exception is in African American patients, where ACEIs are less effective than thiazides. (7) Compelling data shows benefit of ACEIs in patients with heart failure (defined as left ventricular systolic dysfunction, ejection fraction ≤ 40%), post myocardial infarction, diabetic nephropathy and chronic renal disease, and patients at high CV risk. (1,4) ACEIs are associated with lower rates of new diabetes cases compared with BBs or thiazides. (3)

The most common side effect is the development of a dry non-productive cough. While many cases resolve spontaneously, persistent cases may require a class change. Angioedema occurs in up to 1% of patients overall (usually mild), but more common in African Americans. (6) Patients at risk of hypotension when therapy is initiated include those with volume depletion (dehydration, diuretic therapy), CHF, hyponatremia or renovascular HTN. For these patients start with low doses and carefully monitor.

Angiotensin Receptor Blockers (ARBs): Data on the ability of ARBs to prevent complications of HTN is more limited compared to other drug classes. For primary prevention, candesartan was not better than placebo for the primary endpoint of first major CV event, but did reduce the risk of non-fatal stroke. (14) In high-risk patients, losartan was more effective than atenolol (12), but atenolol may not have been the optimal control therapy due to concerns mentioned above. Studies have shown benefit of ARBs in the management of heart failure (defined as left ventricular systolic dysfunction, ejection fraction ≤ 35%), and in slowing decline in renal function in patients with diabetic or nondiabetic nephropathy. (14) However, ACEIs have a much stronger evidence base in these populations, so it is recommended to reserve ARBs for patients that cannot tolerate an ACEI due to cough or angioedema. (15) Angioedema has been reported with ARBs, although less frequently than with ACEIs.

Calcium Channel Antagonists (CCBs): CCBs appear to have similar overall efficacy as thiazide diuretics for most clinical endpoints with the exception that thiazides are better at preventing CHF. Data supports the use of long-acting CCBs in patients with isolated systolic HTN, and in African Americans, where they are a good alternative when thiazides should not be used. (1,7) Rapid acting CCBs are not recommended for HTN management. Several agents are effective in treating patients with angina and they can be used as an alternative to BBs. CCBs should be avoided in patients with systolic dysfunction (defined as left ventricular, ejection fraction ≤ 40%) due to the potential to worsen systolic function. Should a CCB required in these patients, amlopidine or felodipine are least likely to cause problems. Verapamil and diltiazem should be avoided in patients with grade 2 or higher AV block or those taking BBs.

Combination Therapy: A majority of hypertensive patients will not be controlled with a single drug. (1) The JNC guidelines recommend initiating therapy with a two-drug combination for patients with Stage 2 HTN. (1) The British HTN Society (BHS) Guidelines recommend an algorithm for combining agents. (3) The BHS recommendations are based on additive BP effects and have not yet been validated in a clinical trial. (3) For two drug combinations, they recommend combining either a diuretic or CCB with either an ACEI or Beta-blocker or ARB.

Table 1: Classification of Blood Pressure for Adults According to JNC-7 (1)

<table>
<thead>
<tr>
<th>Category</th>
<th>SBP (mm Hg)</th>
<th>DBP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;120</td>
<td>&lt;80</td>
</tr>
<tr>
<td>Prehypertension</td>
<td>120-139</td>
<td>80-89</td>
</tr>
<tr>
<td>Hypertension Stage 1</td>
<td>140-159</td>
<td>90-99</td>
</tr>
<tr>
<td>Hypertension Stage 2</td>
<td>&gt;160</td>
<td>&gt;100</td>
</tr>
</tbody>
</table>
For three drug regimens (step 3), they recommend a diuretic plus a CCB plus either an ACEI or beta-blocker or ARB. A recent Cochrane Review found using a regimented stepped care approach is the best way to improve BP control, which lends some support to the BHS recommendations. (16)

Summary

There are a wide range of proven drug therapy options available to provide effective and affordable regimens for most hypertensive patients. There are substantial differences in cost among various antihypertensive agents. Table 2 provides suggestions for selecting therapy for a variety of patients based on published treatment guidelines and considering cost.

Reviewed by: Temi Bianco, Pharm.D., OSU College of Pharmacy; Kristen Benkstein, Pharm.D., CareOregon; Kathy Crispell, M.D., Chief of Cardiology, Northwest Kaiser Permanente

Table 2: Summary Information Regarding the Major Antihypertensive Drug Classes

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Recommended Populations</th>
<th>Potential Advantages</th>
<th>Cautions/Concerns</th>
<th>Average Annual OHP Cost*</th>
</tr>
</thead>
</table>
| Diuretics (low dose thiazide or chlorthalidone) | HTN w/o compelling indication | Metabolic changes; high doses or combinations with BBs associated with increased DM compared to ACE/ARB. Hypokalemia, hyporeninemia, hypomagnesemia and elevations of calcium and uric acid. | Hydrochlorothiazide - $24
Chlorthalidone = $24
Bimatoprost/Timolol - $36 |
| Beta Blockers (BB) | Prior MI with ACEI | May benefit patients with tachyarrhythmias, hyperthyroidism or frequent migraines. Inexpensive generics | May be less effective without compelling indication. Avoid in asthma/COPD, AV Block (grade 2 or 3), glucose intolerance, athletes or physically active patients. Should not be abruptly stopped, especially in high CVD risk patients Not recommended initially for elderly/isolated systolic HTN | Atenolol - $36
Metoprolol - $36
Labetalol - $30
Coreg - $1,215 |
| ACE Inhibitors (ACEI) | CHF + diuretic +/- BB +/- spironolactone | Fairly well tolerated Inexpensive generics | Not recommended as initial therapy for African Americans Pregnancy; Hyperkalemia; Bilateral renal artery stenosis; Cough 1% incidence of angioedema | Captopril - $36
Enalapril - $36
lisinopril - $108 |
| ARBs | Elderly/isolated systolic HTN CHF Nephropathy (+/- DM) | May benefit patients with tachyarrhythmias, peripheral vascular disease or migraine prophylaxis (verapamil) | Avoid with AV Block (grade 2 or 3), CHF, and BBs. Constipation with verapamil Rapid acting CCBs are not recommended for hypertension management | Verapamil 12 hr tab - $180
Verapamil 24 hr cap - $280
Diltiazem 24 hr cap - $280 |
| CCB (non-DHP) | HTN w/o compelling indication | Not as protective for CHF, some agents may aggravate CHF Rapid acting CCBs are not recommended for hypertension management | | Nifedipine XL - $540
Felodipine ER - $600
Norvasc - $600 |
| CCB (DHP) | HTN w/o compelling indication | | | |

* Based on average retail cost per day to OHP in 1/05; excludes rebate