Recent Update in The Management of Hypertension

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ABSTRACT

Hypertension is still the leading cause of death worldwide. Hypertension increases not only the risk for progression of chronic kidney disease (CKD) but also for cardiovascular (CV) morbidity and mortality. For most patients it is the systolic blood pressure rather than the diastolic blood pressure that most strongly predicts adverse events. The optimal target for BP control for most hypertensive patients is < 140/90 mmHg, or < 130/80 mmHg for patients with diabetes and CKD. Certain lifestyle measures such as weight reduction, smoking cessation, restriction of dietary sodium intake, moderation of alcohol intake and an increase in physical activity can lower BP. Except for progression of proteinuric kidney disease and congestive heart failure (CHF), it is the achieved BP and not the class of agent that is most important in reducing morbid outcomes. If BP is more than 20/10 mmHg above the goal, therapy should be initiated with 2 drugs, one of which should be a thiazide-type diuretic. A strong consideration should be given to initiate anti-hypertensive therapy in patients with kidney disease with renin-angiotensin-aldosterone system (RAAS) blockers, usually in concert with diuretics. Patients with proteinuria > 1 g/day despite optimal BP control with angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) monotherapy may benefit from a combination therapy.

Key words: hypertension, systolic blood pressure, proteinuria, microalbuminuria.

INTRODUCTION

What is the leading cause of death worldwide? The great infectious disease such as tuberculosis or malaria? Maybe it is AIDS? Perhaps it is smoking? How about malnutrition or its opposite, obesity? Surprisingly, it is none of these. Ezzati et al analyzed the worldwide attributable mortality due to 26 health risk factors for the World Health Organization and concluded that high BP was the single factor responsible for 12.8% of all deaths worldwide, or more than 7 million deaths per year.1 This is 46% more than can be attributed to tobacco use, high BP’s closest competitor (Figure 1). It is well known that hypertension increases not only the risk for progression of CKD but also for CV morbidity and mortality.2

Despite increasing awareness of hypertension among the public and the doctors, national surveys in the United States continue to show substantial underdiagnosis, undertreatment, and poor rates of BP control.3 The failure to achieve better BP control is related to poorly organized health care systems, the expense of anti-hypertensive medicines, compliance problems related to need for multiple medicines, the unpleasant side effects of the drugs and the fact that high BP is relatively silent until its complications strike.

DEFINITION OF HYPERTENSION

The Seventh Joint National Committee Report (JNC 7) now defines three levels of elevated BP:2 (Table 1) Stage 1 hypertension is defined as systolic blood pressure (SBP) between 140 to 159 mmHg and/or diastolic blood pressure (DBP) between 90 to 99 mmHg. Stage 2 hypertension refers to all levels of SBP > 160 and/or DBP > 100 mmHg. JNC 7 introduced the classification of BP between 120 to 139 mmHg SBP or 80 to 89 mmHg DBP as “prehypertension” based on the risk of progression and associated CV risk. Patients with BP in the 130/80 to 139/89 mm Hg range
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HYPERTENSION AND PROGRESSION OF KIDNEY DISEASE

Epidemiologic studies indicate that hypertension is closely associated with progression of kidney disease. Several trials involving proteinuric renal diseases consistently demonstrate a relationship between reduction in proteinuria during antihypertensive therapy and the probability of slowing disease progression. A recent post hoc analysis of non-diabetic patients in the African-American Study of Kidney Disease (AASK) indicates that the greater the magnitude of reduction in proteinuria following the initial six months of BP treatment, the greater the slowing of glomerular filtration rate (GFR) decline, a relationship that was independent of BP level. This relationship with proteinuria reduction is also seen in the outcomes of the COOPERATE trial, i.e., those with an additional 25% to 30% reduction in proteinuria, had less progression to endstage renal disease (ESRD) and doubling of creatinine compared to the comparator groups at similar levels of BP. Both JNC 7 and Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines recommend lower BP targets (<130/80 mmHg) for patients with diabetes and CKD.

HYPERTENSION AND CARDIOVASCULAR DISEASE (CVD)

There was a fear in the past that reducing BP too far might increase the risk of CV mortality. This is related to the concept of the “J” curve, where lowering BP below a certain level that maintains coronary perfusion increases CV risk in those with coronary heart disease. However, results from randomized controlled trials have confirmed that a further reduction in BP among normotensive individuals (baseline BP < 140/90 mmHg) indeed lowers the risk of CV events. In a meta-analysis involving almost one million participants, there was a linear association between both SBP and DBP and risk of CV mortality down to 115 mmHg SBP and 75 mmHg DBP. For every 10 mmHg lower usual SBP or 5 mmHg lower usual DBP during long-term follow-up, there is a 40% reduction in risk of death from stroke and a 30% reduction in risk of death from ischemic heart disease. Thus, the current evidence confirms that the risk of CV events follows a linear relationship with BP and achieving further BP reductions within the so-called ‘normal’ range indeed reduces the risk of CV events.

<table>
<thead>
<tr>
<th>Table 1. The Seventh Joint National Committee on Hypertension (JNC -7) Definitions, Risk Stratification, and Treatment Approach a</th>
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</thead>
<tbody>
<tr>
<td>SBP b (mmHg)</td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td>Normal</td>
</tr>
<tr>
<td>Prehypertension</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Stage 1</td>
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<tr>
<td>Stage 2</td>
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</table>


a SBP, systolic blood pressure; DBP, diastolic blood pressure; ACEI, angiotensin -converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, β-blocker; CCB, calcium channel blocker.

b Treatment determined by highest BP category.

c Treat patients with chronic kidney disease or diabetes to BP < 130/80 mmHg.

d Consider 2 drugs or low-dose fixed dose therapy (caution in elderly).
TREATMENT OF HYPERTENSION

The long-term follow-up studies of the Multiple Risk Factor Intervention Trial have revealed that for most patients it is the SBP rather than the DBP that most strongly predicts adverse events. Most patients with hypertension will reach the DBP goal once SBP is at goal. Therefore, the primary focus should be on achieving the SBP goal. The JNC 7 guideline recommend the optimal target for BP control for most hypertensive patients is < 140/90 mmHg, or < 130/80 mmHg for patients with diabetes and CKD.

LIFESTYLE MODIFICATION

Recent trial has shown that certain lifestyle measures can lower BP. Recommendations for all patients with hypertension include weight reduction in those individuals who are overweight or obese, smoking cessation, restriction of dietary Na+ intake to <100 mmol/d (2.4 g of sodium or 6 g of salt), moderation of alcohol intake and an increase in physical activity. Lifestyle modifications can reduce BP, enhance antihypertensive drug efficacy and decrease risk of CVD.

WHEN TO START PHARMACOLOGIC TREATMENT?

The Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial and the Anglo Scandinavian Cardiac Outcomes Trial (ASCOT) make clear the consequences of failing to intervene early in the course of hypertension in those with multiple CV risk factors. Subjects who achieved the BP goal within the first six months had a lower CV event rate than those who achieved the goal after six months. Those who are 20/10 mmHg above goal BP should be started on combination therapy. Therefore, the initial BP-lowering agents need to be from drug classes with a compelling indications and low side effect profile, shown to reduce CV events and are well tolerated.

DOES THE SPECIFIC DRUG USED MATTER?

A series of recent trials, especially the anti-hypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), has provided strong evidence that except for progression of proteinuric kidney disease and CHF, it is the achieved BP and not the class of agent that is most important in reducing morbidity outcomes. Thiazide-type diuretics should be used for most patients with hypertension either alone or in combination because many trials have confirmed that they can prevent the CV complications of hypertension.

Whereas reductions in proteinuria (> 300 mg/d) are strongly associated with decreased progression of kidney disease, reductions in microalbuminuria (> 30 and < 300 mg/d) correlate with decreased CV mortality. Absence or very low levels of albuminuria is associated with low CV risk, whereas the CV risk increases markedly with increasing amount of albumin in the urine (even within the now considered normal range). However, for albuminuria to be a target for therapy, one needs to prove that lowering of albuminuria per se is cardioprotective. The Prevention of Renal and Vascular Endstage Disease Intervention Trial (PREVEND-IT) is the only randomized trial to study the effect of albuminuria lowering in microalbuminuric “healthy” individuals. Asselbergs et al indeed showed that the lowering of albuminuria with the ACE inhibitor fosinopril tended to be cardioprotective. A recent post hoc analysis of the LIFE trial found similar results in hypertensive patients: The more the angiotensin II antagonist losartan lowered albuminuria, the more the patient was cardioprotected, irrespective of the effect on other CV risk factors. Although microalbuminuria has been discovered as a strong and independent indicator of increased CV risk among hypertensive individuals, it has not penetrated all guidelines.

ANTIHYPERTENSIVE THERAPY IN CHRONIC KIDNEY DISEASE

In patients with CKD, the goal of antihypertensive therapy is to slow the deterioration of renal function and prevent CVD. The ACE inhibitor and ARB have demonstrated favorable effects on the progression of diabetic and nondiabetic renal disease. The greater the magnitude of reduction in proteinuria, the greater the slowing of GFR decline that is independent of BP level. ACE inhibitor and ARB should also be used in advanced CKD since in all trials, the patients who garner the greatest benefit from such agents are those with the most advanced form of kidney disease. A rise in serum creatinine by as much as 35% above baseline during ACE inhibitor or ARB therapy is acceptable and not a reason to withhold treatment unless hyperkalemia develops. In addition, a number of recent clinical trials have noted that the incidence of new-onset diabetes was reduced with ACE inhibitor and ARB.

COMBINATION THERAPY WITH ACE INHIBITOR AND ARB IN CKD

A number of investigations have reported that dual blockade of the RAAS with ACE inhibitor and ARB in combination is superior to single blockade with either
## Table 2. Compelling and Possible Indications, Contraindications, and Cautions for The Major Classes of Antihypertensive Drugs

<table>
<thead>
<tr>
<th>Class of drug</th>
<th>Compelling indications</th>
<th>Possible indications</th>
<th>Caution</th>
<th>Compelling contraindications</th>
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<tbody>
<tr>
<td>α blockers</td>
<td>Benign prostatic hypertrophy</td>
<td>-</td>
<td>Postural hypotension, heart failure*</td>
<td>Urinary incontinence</td>
</tr>
<tr>
<td>Angiotensin converting enzyme inhibitors</td>
<td>Heart failure Left ventricular dysfunction post-myocardial infarction or established coronary heart disease Type 1 diabetic nephropathy Secondary stroke prevention¶</td>
<td>Chronic renal disease† Type 2 diabetic nephropathy Proteinuric renal disease</td>
<td>Renal impairment † Peripheral vascular disease‡</td>
<td>Pregnancy Renovascular disease§</td>
</tr>
<tr>
<td>Angiotensin II receptor blockers</td>
<td>Angiotensin converting enzyme inhibitor intolerance Type 2 diabetic nephropathy Hypertension with left ventricular hypertrophy Heart failure in angiotensin converting enzyme intolerant patients, after myocardial infarction</td>
<td>Left ventricular dysfunction after myocardial infarction Intolerance of other antihypertensive drugs Proteinuric renal disease, chronic renal disease† Heart failure</td>
<td>Renal impairment † Peripheral vascular disease‡</td>
<td>Pregnancy Renovascular disease§</td>
</tr>
<tr>
<td>β blockers</td>
<td>Myocardial infarction, angina</td>
<td>Heart failure**</td>
<td>Heart failure** Peripheral vascular disease Diabetes (except with coronary heart disease)</td>
<td>Asthma or chronic obstructive pulmonary disease Heart block</td>
</tr>
<tr>
<td>Calcium channel blockers (dihydropyridine)</td>
<td>Elderly patient, isolated systolic hypertension</td>
<td>Angina</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Calcium channel blockers (rate limiting)</td>
<td>Angina</td>
<td>Elderly patient</td>
<td>Combination with β blockade</td>
<td>Heart block, heart failure</td>
</tr>
<tr>
<td>Thiazides or thiazide-like diuretics</td>
<td>Elderly patient, isolated systolic hypertension, heart failure, secondary stroke prevention</td>
<td>-</td>
<td>-</td>
<td>Gout ††</td>
</tr>
</tbody>
</table>

* In heart failure when used as monotherapy
† ‡ used with caution, close supervision, and specialist advice when there is established and significant renal impairment.
‡ Caution with angiotensin converting enzyme inhibitors and angiotensin II receptor blockers in peripheral vascular disease because of association with renovascular disease.
§ Angiotensin converting enzyme inhibitors and angiotensin II receptor blockers are sometimes used in patients with renovascular disease under specialist supervision.
¶ In combination with a thiazide or thiazide-like diuretic
** β blockers are used increasingly to treat stable heart failure but may worsen heart failure
†† Thiazides or thiazide-like diuretics may sometimes be necessary to control blood pressure in people with a history of gout, ideally in combination with allopurinol.
ACE inhibitor or ARB in both diabetic and nondiabetic nephropathy. The notion that the combination of an ACE inhibitor and an ARB should be used only for proteinuric renal disease and not for BP reduction is supported further by a meta-analysis of studies that used the combination. In my opinion, patients with proteinuria > 1 g/day despite optimal BP control with ACE-inhibitor or ARB monotherapy may benefit from a combination therapy.

IS COMBINATION THERAPY RISKY?

Bakris et al reported that ARB did not cause an increase in serum potassium to the same degree as ACE inhibitor in the presence of renal insufficiency. These differential effects on serum potassium were related to a relatively smaller reduction in plasma aldosterone as a result of the ARB and were not related to changes in GFR. Therefore, hyperkalemia with combination therapy is determined mainly by the ACE inhibitor. The incidence of hyperkalemia in the COOPERATE trial was 7.9% in the combination therapy group, 9.3% in thetrandolapril group, and 4.4% in the losartan group. Patients should be regularly monitored for hyperkalemia. Co-administration of drugs that interfere with renal potassium excretion such as nonsteroidal anti-inflammatory drugs or spironolactone should be avoided. In addition, patients should follow a low-potassium diet with specific counseling against the use of salt substitutes that contain potassium.

CONCLUSION

High BP is still the leading cause of death worldwide. For most patients it is the systolic rather than the diastolic BP that most strongly predicts adverse events. Except for progression of proteinuric kidney disease and CHF, it is the achieved BP and not the class of agent that is most important in reducing morbid outcomes. Physicians should focus on achieving a BP goal of < 140/90 mmHg for most hypertensive patients, or < 130/80 mmHg for patients with diabetes and CKD. A strong consideration should be given to initiate antihypertensive therapy in patients with kidney disease with RAAS blockers, usually in concert with diuretics. Patients with proteinuria > 1 g/day despite optimal BP control with ACE inhibitor or ARB monotherapy may benefit from a combination therapy.

REFERENCES


