

A white paper on emerging issues in antihypertensive therapy

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Defining the role of renin/angiotensin-targeted antihypertensive therapy

IN DECREASING CARDIOVASCULAR RISK: EVIDENCE, GUIDELINE EVOLUTION, AND QUESTIONS TO BE RESOLVED

Key Points and Recommendations

- Management of hypertension is particularly important for primary care practitioners who must incorporate new options into therapeutic regimens and make treatment decisions based on the latest clinical evidence.
- The renin-angiotensin-aldosterone system (RAAS) carries out multiple functions that are essential for blood pressure (BP) regulation, water and salt balance, and tissue growth control under physiologic conditions, and it plays a pivotal role in the pathophysiology of cardiovascular and renal disease.
- RAAS blockade is effective for lowering BP in a wide range of patients and may have cardioprotective effects that are independent of BP reduction.
- Selection of antihypertensive therapy must consider multiple patient-related factors in addition to BP. These include age, race/ethnicity, and comorbid disease (eg, coronary, cerebrovascular, and peripheral artery disease, congestive heart failure, diabetes, renal disease, metabolic syndrome).
- Most patients with hypertension require multiple agents to achieve BP goals, and fixed-dose combinations of antihypertensive agents from different classes may simplify patient management.

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Many factors contribute to cardiovascular (CV) and cerebrovascular risk. Modifiable risk factors include smoking, diabetes, hypertension, abdominal obesity, psychological stress factors, inadequate intake of dietary fruits and vegetables, lack of exercise, and dyslipidemia (as reflected by the apolipoprotein B/apolipoprotein A-I ratio).¹ Attention to all modifiable risk factors is necessary for optimal CV risk reduction.²⁻⁴ One of the most common factors that raises the risk for cardiovascular disease (CVD) is hypertension, which has been estimated to affect 73 million people in the United States (33.6% of the population).⁵

Management of hypertension is particularly important for primary care practitioners who must incorporate new options into therapeutic regimens and make treatment decisions based on the best clinical evidence. This white paper considers the latest developments in the management of hypertension, focusing on therapies that modulate the actions of the renin-angiotensin-aldosterone system (RAAS).



The Burden of Hypertension is High and It Continues to Increase

Results from one recent study indicated that the age- and sex-adjusted mortality among patients with hypertension was 9.6 per 1000 people in 2005.⁶ A study of 9328 men and 10,062 women who were followed for 30 years indicated that uncontrolled systolic blood pressure ([SBP] ≥ 160 mm Hg) and/or diastolic blood pressure ([DBP] ≥ 95 mm Hg) resulted in a 47% increase in risk of death due to CVD in men and a 70% increase in women, compared with patients whose hypertension was treated and controlled.⁷ The percentage of coronary heart disease attributable to hypertension in a cohort of 600,000 adults ranged from 4% to 28% in men and from 8% to 39% in women; respective ranges for hemorrhagic stroke were 18% to 66% and 15% to 49% and for ischemic stroke were 8% to 44% and 12% to 45%.⁸ Hypertension increases the risk of hospitalization due to stroke by 52%.⁹ The total cost of CVD in the United States for 2008 is estimated to be \$448.5 billion; hypertension alone accounts for \$69.4 billion.⁵

Efficacy of Antihypertensive Therapy in Improving Clinical Outcomes

Results from many of the largest and most important studies of antihypertensive therapy have been subjected to meta-analyses by the Blood Pressure Lowering Treatment Trialists' Collaboration (BPLTTC). This group includes the principal investigators from large-scale studies of antihypertensive therapies who provide data sets from their trials for inclusion in meta-analyses. These evaluations have shown that any commonly used antihypertensive regimen decreases the risk for major CV events, and that BP reduction from baseline is closely correlated with risk reduction.¹⁰ Efficacies of different antihypertensive regimens in decreasing risk are comparable in patients with and without diabetes and in elderly (≥ 65 years of age) and younger (< 65 years of age) patients.^{11,12} Reports also support the efficacy of angioten-

sin-converting enzyme (ACE) inhibitors and calcium channel blockers (CCBs) and indicate similar BP-dependent benefits for ACE inhibitors and angiotensin receptor blockers (ARBs) in decreasing the risks for stroke, CHD, and heart failure.¹³ Results from the BPLTTC also suggested that ACE inhibitors may have BP-independent benefits in decreasing the effects of major coronary events.¹⁴

The Role of the RAAS in Hypertension and Its Consequences

Angiotensin II (ANG II) is currently believed to be the primary active hormone of the RAAS. It is a potent vasoconstrictor that has been shown to aggravate hypertension.^{15,16} It also has negative effects on both lipid and glucose metabolism and may contribute to the development of dyslipidemia and metabolic syndrome.^{15,16} ANG II also contributes to the development of atherosclerosis by promoting local uptake, synthesis, and oxidation of lipids; stimulating the migration and proliferation of inflammatory cells; destabilizing atherosclerotic plaques; promoting the expression of adhesion molecules involved in macrophage-vascular adhesion; and enhancing the activity of thrombocytes and coagulation.¹⁵⁻¹⁸ ANG II also promotes vasoconstriction of post-glomerular arterioles and increases glomerular hydraulic pressure and ultrafiltration of plasma proteins, which may contribute to progressive renal damage.¹⁹ Following myocardial infarction (MI), ANG II promotes myocardial remodeling and fibrosis. RAAS activity is increased in patients with heart failure, and its maladaptive mechanisms may lead to adverse effects, such as cardiac remodeling.^{18,20} The RAAS is therefore a key target for controlling BP, protecting the vasculature and target organs, and decreasing CV risk in patients with hypertension.

RAAS Blockade and Effect on Hypertension

The actions of the RAAS may be blunted by

inhibition of ACE, blockade of the ANG II type 1 receptor with an ARB, and direct renin inhibition. The clinical benefits of RAAS blockade in patients with hypertension and/or related cardiovascular conditions in key large-scale clinical trials are summarized in **TABLE 1**.²¹⁻²⁹ (Due to space limitations in the print version of this article, **TABLE 1** is available online for downloading and/or printing at: www.jfponline.com. Key features of this table include study objectives, patient numbers and characteristics, treatments, primary end points, and summary of main results.)

Although some of these trials included non-hypertensive subjects, the data contribute important evidence regarding the efficacy and safety of ACE inhibitors and ARBs that is applicable to the use of these agents to reduce CV risk in subjects with comorbid and/or compelling indications.

The Heart Outcomes Prevention Evaluation (HOPE) trial showed that treatment with ramipril was significantly superior to placebo in decreasing the risks for MI, CV death, and stroke in patients with vascular disease or diabetes who did not have clinical heart failure or low ejection fraction.²¹

The Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) trial revealed no significant differences in achieved SBP/DBP between losartan and atenolol in patients with essential hypertension and left ventricular hypertrophy (LVH). However, losartan-based therapy was significantly superior to atenolol-based therapy in decreasing the risk for CV death; fatal or nonfatal stroke or MI; and new-onset diabetes.²² This suggests a BP-independent benefit of losartan-based therapy in patients with hypertension and LVH.

The Candesartan in Heart Failure-Assessment of Reduction in Mortality and Morbidity (CHARM-Overall) trial assessed whether the ARB candesartan could decrease morbidity and mortality in patients with heart failure. Although not a hypertension trial, it demonstrated that the addition of candesartan to ongoing therapy for

heart failure, including an ACE inhibitor, was significantly more effective than was placebo in decreasing the risk for CV death and hospital admissions for chronic heart failure (CHF).²³

The Morbidity and Mortality After Stroke, Eprosartan Compared with Nitrendipine for Secondary Prevention (MOSES) trial demonstrated the significant superiority of the ARB eprosartan over the CCB nitrendipine in decreasing CV events in high-risk hypertensive patients with a recent cerebrovascular event. Despite no significant difference in the achieved SBP/DBP between study groups, eprosartan-based treatment was superior in decreasing the risk for combined CV and cerebrovascular events ($P=.014$) and for cerebrovascular events alone ($P=.03$).²⁴

The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint (ONTARGET) trial demonstrated similar efficacies of ramipril, telmisartan, and the combination of the 2 drugs for decreasing the risk for the composite end point of death from CV causes, MI, stroke, or hospitalization for heart failure in patients with vascular disease or high-risk diabetes. ONTARGET was very important in that it demonstrated that the ARB telmisartan conferred the same degree of protection against cardiac events as ramipril had achieved earlier in HOPE. However, the combination provided only a modest improvement in BP, did not provide greater CV protection than ramipril alone, and resulted in a significant increase in risk for hypokalemia, syncope, and renal dysfunction.²⁵

The Telmisartan Randomized Assessment Study in ACE iNtolerant Subjects with Cardiovascular Disease (TRANSCEND) trial focused on the potential benefit of the ARB telmisartan in patients with CVD or diabetes with end-organ damage who were intolerant of an ACE inhibitor. Although there is some controversy about the results, a significant, unadjusted 13% relative risk reduction was noted in the key secondary end point (CV death/MI/stroke), similar to the primary end

point in HOPE. This suggests a modest benefit of telmisartan in this high-risk population and indicated that telmisartan was well tolerated in patients unable to tolerate ACE inhibitors.³⁰

The Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial compared the efficacy of a benazepril/amlodipine combination to a benazepril/hydrochlorothiazide combination for decreasing CV morbidity and mortality in patients with hypertension who were at high risk for CV events. Although both combinations reduced BP to a similar degree, (no significant difference between groups), the benazepril/amlodipine regimen was significantly superior to the benazepril/hydrochlorothiazide regimen in decreasing the risk of the composite primary end point, fatal and nonfatal MI ($P=.04$), and coronary revascularization ($P=.04$).²⁶ Questions remain about the choice of drugs and doses used in this trial.³¹

The Study on Cognition and Prognosis in the Elderly (SCOPE) trial showed no significant difference in the SBP/DBP-lowering effects of antihypertensive therapy with or without candesartan. However, patients who received treatment with candesartan for isolated systolic hypertension had a significant decrease in the risk of stroke.²⁷

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack (ALLHAT) trial reported no significant difference between lisinopril- and chlorthalidone-based treatment for the primary composite end point of fatal CHD or nonfatal MI. The ALLHAT investigators also assessed treatment-related differences for a number of secondary end points.²⁸ Important effects were seen in a number of secondary outcomes, including heart failure. Discussion of these analyses is beyond the scope of this white paper and is considered in detail in a recently published review.³²

The Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial showed that a valsartan-based

regimen and an amlodipine-based regimen were similar in reducing the primary end point of CV morbidity and mortality in high-risk subjects despite a significant difference ($P<0.001$) in achieved SBP/DBP in the amlodipine-based regimen. However, amlodipine-based therapy was superior to valsartan-based therapy in decreasing the secondary end point of risk for MI ($P=0.02$).²⁹

In summary, results from the trials reviewed in this section support the benefit of RAAS blockade in patients with hypertension and related conditions. In addition, they underscore the central importance of BP control, regardless of the treatment regimen used.

Current Hypertension Treatment Guidelines

Current recommendations for the management of hypertension include a variety of drug classes, such as diuretics, CCBs, β -blockers, and aldosterone receptor antagonists, in addition to the ACE inhibitors and ARBs already discussed.³³ A challenge facing family practice physicians is integration of new data regarding these and other antihypertensive drug classes into existing clinical guidelines.

Diuretics. Thiazide diuretics are recommended as first-line therapy for most uncomplicated hypertensive patients and in conjunction with other agents when combination therapy is needed.³³ Diuretic side effects are mostly benign and mild but, in some instances, metabolic side effects include hypokalemia and impaired glucose tolerance, which require medical attention.³⁴

Calcium Channel Blockers. CCBs have generally demonstrated reductions in BP and decreases in CV morbidity and mortality similar to those achieved with other agents. However, the use of some agents in this class has been associated with an increased risk of heart failure.^{26,28,29,35}

TABLE 2
Compelling indications for treatment with specific classes of antihypertensive medications³³

High-Risk Conditions With Compelling Indication	Recommended Drugs					
	Diuretic	β -Blocker	ACE Inhibitor	ARB	CCB	Aldosterone Antagonist
Heart failure	✓	✓	✓	✓		✓
Postmyocardial infarction		✓	✓			✓
High coronary disease risk	✓	✓	✓		✓	
Diabetes	✓	✓	✓	✓	✓	
Chronic kidney disease			✓	✓		
Recurrent stroke prevention	✓		✓			

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CCB, calcium channel blocker.

β -Blockers. This class has well-established anti-hypertensive efficacy, but use of β -blockers may be limited by side effects such as sexual dysfunction, fatigue, depression, and metabolic abnormalities (eg, impaired glucose tolerance and lipid abnormalities).³⁶ Hypertensive patients with compelling indications (eg, post-MI, heart failure) may benefit from inclusion of β -blockers in their treatment regimens.³⁷

Aldosterone Receptor Antagonists. Agents in this class (eg, eplerenone) are not routinely used in the initial treatment of hypertension. Aldosterone receptor antagonists may decrease albuminuria in patients with renal dysfunction, but may also cause hyperkalemia, elevated serum creatinine concentrations, and reduced creatinine clearance.³⁸

Direct Renin Inhibitors. Although not included in current treatment guidelines, recent clinical trials have shown that direct renin inhibition with aliskiren is effective for the treatment of hypertension when used alone or in combination with

an ACE inhibitor or an ARB.³⁹⁻⁴² Direct renin inhibition may be particularly useful in patients with diabetic nephropathy or in African American hypertensive patients.⁴³

Compelling Indications. Specific agents are recommended for patients with compelling indications (TABLE 2).³³ CCBs are recommended for patients with diabetes or those at high risk for CHD. CCBs should, however, be avoided in patients with heart failure and, as mounting evidence suggests, those who are at risk for developing heart failure.³³ In patients with heart failure, diuretics, β -blockers, ACE inhibitors, ARBs, and aldosterone receptor antagonists are recommended. For patients at high risk for coronary artery disease, diuretics, β -blockers, ACE inhibitors, and CCBs are recommended. Patients with diabetes should receive a diuretic, β -blocker, ACE inhibitor, ARB, or CCB, and those with chronic kidney disease should receive an ACE inhibitor or an ARB. Both diuretics and ACE inhibitors are recommended for prevention of recurrent stroke.³³

Recent non-US guidelines have increased the

emphasis on use of ACE inhibitors and ARBs. For example, the Canadian Hypertension Education Program recommendations now include diuretics, β -blockers, ACE inhibitors, ARBs, and long-acting CCBs as suitable first-line therapy. ARBs are recommended for post-MI patients who are intolerant of ACE inhibitors.⁴⁴ The National Institute for Health and Clinical Excellence/British Hypertension Society currently recommends an ACE inhibitor or an ARB as first-line therapy for patients younger than 55 years of age.⁴⁵ The European Society of Hypertension/European Society of Cardiology guidelines favor ACE inhibitors or ARBs for patients with heart failure, post-MI patients, and those with diabetic nephropathy, LVH, atrial fibrillation, or metabolic syndrome.⁴⁶ They do indicate ARBs for use in hypertensive patients experiencing ACE-inhibitor-induced cough.

An update of the current Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) guidelines is under way and is expected in 2009. JNC 8 will then be integrated into a Cardiovascular Risk Reduction in Primary Care guideline developed by the National Heart, Lung, and Blood Institute, which will be published in 2010.

Optimizing Treatment for the Individual Patient

In selecting among hypertension therapies, the primary care physician must consider multiple patient-related factors in addition to BP. These include age, race/ethnicity, and comorbid disease (eg, diabetes, renal disease, metabolic syndrome).⁴⁷

Current Treatment Algorithm. The JNC 7 guidelines for patients whose BP is uncontrolled with diet and exercise alone recommend administration of a thiazide diuretic for those with stage 1 hypertension (SBP, 140-159 mm Hg, or DBP, 90-99 mm Hg). An ACE inhibitor, ARB, CCB, β -blocker, or combination may also be considered. For those

TABLE 3

Potential advantages of fixed-dose combinations for the treatment of hypertension⁴⁹

- Increased medication adherence, simplified titration, and convenience of use
- Potentiation of antihypertensive effects of single compounds
- Additive or synergistic effects
- Enhancing effect in specific populations
- Attenuation of adverse events
- Decreases in diuretic-induced metabolic changes with ACE inhibitors or ARBs
- Decrease in calcium channel blocker-related peripheral edema with ACE inhibitors or ARBs
- Improved overall results, greater blood pressure control, and lower cost

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

with stage 2 hypertension, the JNC 7 guidelines recommend use of a 2-drug combination (SBP \geq 160 mm Hg or DBP \geq 100 mm Hg).³³

Patient Monitoring and Enhancing Adherence

Patient monitoring is an important aspect of overall management. Most patients should be reevaluated monthly for titration of medications until BP goals are achieved. More frequent visits are indicated for patients with stage 2 hypertension or those with complicating comorbid conditions (eg, heart failure, diabetes, renal disease). Serum potassium and creatinine levels should be monitored at least 1 or 2 times per year. After BP is at goal and stable, follow-up visits can usually occur at 3- to 6-month intervals.³³

Patients must also be educated regarding the importance of adherence to therapy and should be monitored closely for adverse events.

Treatments should be adjusted as needed to maintain adherence and control BP.³³ Side effects, such as cough, dizziness, nausea, and headache, are frequently cited as reasons for poor adherence to hypertension therapy.⁴⁸ Physicians should consider nonadherence a cause of failure to reach BP goals. Physicians should encourage patients to bring all medications to each visit for review and to rule out iatrogenic causes of elevated BP. Physicians should also be willing to change unsuccessful regimens and search for those more likely to succeed.³³

Combination Therapy

Most patients will require administration of 2 or more drugs to achieve BP goals, and those with very high BP at initial presentation should receive combination treatment.³³ There are many fixed combinations that can be used for the treatment of hypertension, including ACE inhibitor/diuretic, ARB/diuretic, β -blocker/diuretic, ACE inhibitor/CCB, and ARB/CCB regimens.⁴⁹ An ACE inhibitor and an ARB can be used together in patients, but only with careful monitoring of renal function and serum potassium values. For overall CVD prevention, benefits have been shown to outweigh the risks.

However, for hypertension alone, the added benefit of this combination is minimal (eg, 4 mm Hg).²⁵ Patients who are intolerant of ACE inhibitors may be immediately switched to an ARB without gradually tapering the former or slowly titrating the latter agent.⁵⁰ Such a switch will continue to provide the cardioprotective effects of RAAS blockade. Advantages of fixed-dose combination therapy are summarized in

TABLE 3.⁴⁹

Conclusion

The major benefit of antihypertensive treatment results from BP lowering; selection of treatment should focus on achieving BP goals. However, blocking the RAAS may also have BP-independent benefits. ARBs and ACE inhibitors are effective for reducing BP and there is also evidence that they may provide CV protection. They are also useful in combination with antihypertensive medications from other classes or alone in patients with certain compelling indications. ARBs are safe in patients who cannot tolerate ACE inhibitors, and in patients for whom a decision is made to discontinue an ACE inhibitor, consideration may be given to the cardioprotective benefits that may be offered by ARBs. ■

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