Who Should Be Treated With Combination Therapy as Initial Treatment for Hypertension?

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There is currently consensus regarding the need to initiate antihypertensive therapy with a combination of two agents from different antihypertensive classes in selected patients. This consensus extends to the need to bring blood pressure to the appropriate level but has not been defined regarding optimal strategies for selection of combinations that may be most effective at reducing the morbidity and mortality associated with hypertension. Because of the heterogeneous nature of hypertension, there may be unique population-specific strategies for selecting antihypertensive regimens. Appropriate combinations of antihypertensive agents are particularly relevant for patients with diabetes, renal disease, and isolated systolic hypertension as well as for African Americans with high-risk hypertension. The antihypertensive regimen for high-risk patients should be based on those agents for which the patient has compelling indications, with the addition of agents deemed most likely to bring the patient to the appropriate blood pressure goal as quickly as possible. (J Clin Hypertens. 2003;5 (4 suppl 3):21–28) ©2003 Le Jacq Communications, Inc.

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Recent trends in hypertension research and treatment guidelines have emphasized stratification of the hypertensive population by risk level to provide greater specification in therapeutic strategies. This increased focus on special populations reflects the growing recognition of the heterogeneous nature of hypertension, the strong correlations of high blood pressure with increased risks for cardiovascular disease (CVD) and renal morbidity and mortality, and the need for hypertension treatment designed to help reduce these associated disease risks by providing target-organ protection beyond blood pressure reduction alone. There is some consensus at this time regarding the need to initiate antihypertensive therapy with two agents in selected patients[1]; however, the consensus extends primarily to the issue of bringing blood pressure to goal as quickly as possible. Combining antihypertensive agents

Table. Cardiovascular Disease Risk Factors[1]

Major Risk Factors	Signs of Target-Organ Damage	
Hypertension Cigarette smoking Obesity (BMI ≥30 kg/m^2) Physical inactivity Dyslipidemia Diabetes Microalbuminuria (or estimated GFR <60 mL/min) Age (>55 years for men, >65 years for women) Family history of premature CVD (men <55 years or women <65 years)	Heart	LVH Angina History of MI History of cardiac revascularization Heart failure
	Brain	Stroke Transient ischemic attacks
	Other	Chronic kidney disease Peripheral arterial disease Retinopathy

BMI=body mass index; GFR=glomerular filtration rate; CVD=cardiovascular disease; LVH=left ventricular hypertrophy; MI=myocardial infarction

to provide optimal target-organ protection to high-risk patients has received less attention. This article addresses the question of how to determine the level of risk that suggests the need to initiate antihypertensive therapy with more than a single agent, and which combinations are optimal for high-risk patient populations.

COMBINATION THERAPY BASED ON RISK FACTORS

There are essentially three tasks in selecting the optimal antihypertensive regimen for a patient: 1) performing a CVD risk assessment; 2) setting a blood pressure goal that reflects the risk status of the patient; and 3) creating an antihypertensive drug regimen that will get the patient to goal and provide needed target- organ protection. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) addresses all three of these areas.[1] CVD risk factors that are recognized in JNC 7 are listed in the Table.

Blood pressure goals for the uncomplicated hypertensive population remain at <140/90 mm Hg, whereas for high-risk patients with diabetes or renal disease the blood pressure goal is <130/80 mm Hg. However, this goal is very difficult to attain in high-risk patients whose blood pressure is difficult to control due to advanced disease and associated conditions. In one large study of hypertensive patients enrolled in eight health care plans throughout the United States, only 18.5% of patients with diabetes had blood pressure levels <130/85 mm Hg.[2]

The JNC 7 report suggests initiating pharmacologic therapy with two drugs (either as separate prescriptions or in fixed-dose combinations) for those patients whose blood pressure is >20/10 mm Hg above their appropriate blood pressure goal; clearly this will apply to most patients with the lower blood pressure goal. Finally, based on the strength of clinical trial evidence, JNC 7 lists compelling indications that require certain antihypertensive drug classes for high-risk conditions, such as heart failure, post-myocardial infarction (MI), diabetes, and chronic kidney disease.[1] In particular, there is overwhelming evidence suggesting that an agent that blocks the renin-angiotensin system (RAS) should be included in the antihypertensive regimen for a wide range of high-risk patients. Angiotensin-converting enzyme (ACE) inhibitors are recommended for all of the indications included (i.e., heart failure, post-MI, high risk of coronary heart disease, diabetes, chronic kidney disease, and recurrent stroke prevention)[1]; thus, they are a good building block for the antihypertensive regimen for all high-risk patients.

Diabetes

CVD is the major cause of morbidity and mortality among patients with type 2 diabetes; it is estimated that up to 80% of these patients will develop CVD or die of vascular diseases.[3] Data from the US population show that patients with diabetes have a prevalence of coronary heart disease that is double the rate of persons without diabetes.[4] Hypertension, in particular, increases the risk of major CVD events in this group.[5] Along with the presence

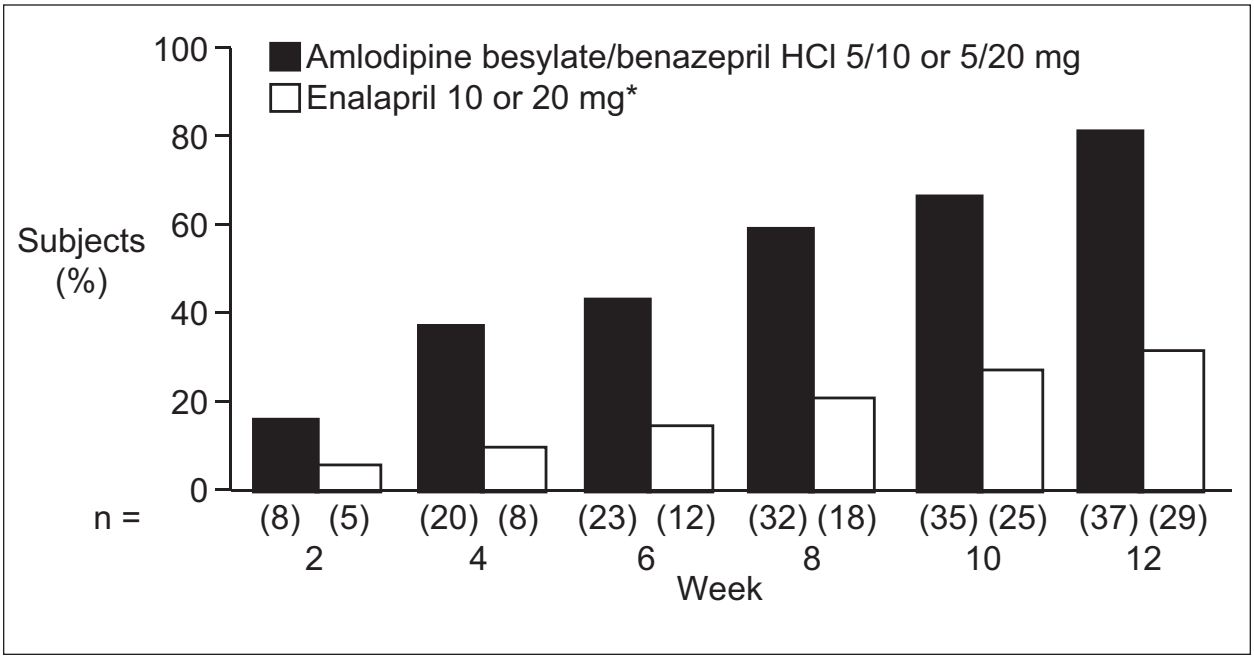

*Figure 1. Cumulative percentage of subjects with firsttreatment success, defined as the first incidence of blood pressure <130/80 mm Hg, in patients with diabetes and hypertension in the Study of Hypertension and the Efficacy of Lotrel in Diabetes (SHIELD) study. n=cumulative number of subjects with first-treatment success; *12.5 mg hydrochlorothiazide was added at Week 8 if target blood pressure was not reached; amlodipine besylate/benazepril HCl subjects given hydrochlorothiazide were excluded from data analysis*[12]

of CVD and associated target-organ damage, diabetes is a major predictor of uncontrolled systolic hypertension.[6] Importantly, there is extensive evidence that tight blood pressure control substantially reduces the risk for CVD events and death in patients with diabetes.[3,7,8]

The American Diabetes Association (ADA)—in agreement with JNC 7—strongly recommends lowering blood pressure to <130/80 mm Hg in patients with diabetes.[9] Further, the ADA notes that accomplishing this goal is likely to require three antihypertensive agents. Although investigators for the recently published Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)[10] recommend thiazide diuretics as first-line therapy for patients with diabetes, a meta-analysis of four trials comparing ACE inhibitors with other agents in patients with type 2 diabetes suggests that ACE inhibitors are the preferred agents for this population.[11] The ADA sanctions ACE inhibitors, angiotensin II receptor blockers (ARBs), β blockers, and thiazide diuretics as initial therapy in patients with diabetes, although its recommendations clearly favor ACE inhibitors for diabetic patients over age 55 years, even in the absence of blood pressure elevations, to reduce the risk of CVD events.[9] The ADA also favors ACE inhibitors and ARBs for the prevention of, or for slowing the progression of, diabetic nephropathy, and suggests that dihydropyridine calcium channel blockers (CCBs) should be used for those patients requiring additional agents to achieve target blood pressure.[9]

Thus, an acceptable regimen for a patient with type 2 diabetes and hypertension should be designed to lower the patient's blood pressure to <130/80 mm Hg and should include an ACE inhibitor (or an ARB in a patient who is intolerant of ACE inhibitors). A patient with diabetes is a good candidate for initiating therapy with a second agent, either a thiazide diuretic, dihydropyridine CCB, or β blocker (particularly if the patient is post-MI). Ultimately, this patient's regimen is likely to include drugs from three classes.

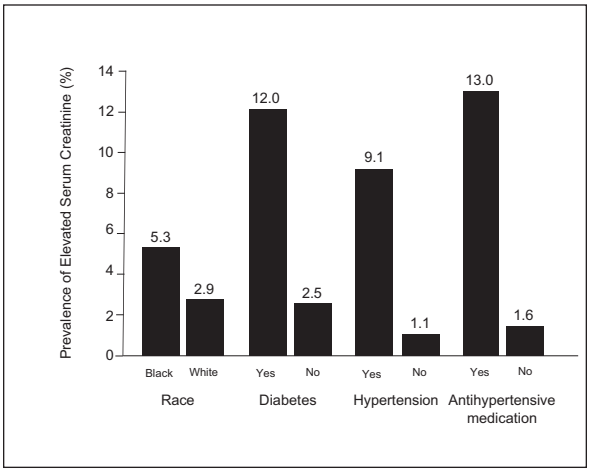

Figure 2. Differences in the prevalence of elevated serum creatinine level (defined here as ≥1.6 mg/dL for men and ≥1.4 mg/dL for women) among selected groups, depicting those who are at higher risk: patients who are African American, patients with diabetes or hypertension, and patients taking antihypertensive medications.[14]

Given the very poor blood pressure control rate among diabetic patients, the use of fixed-dose combination therapy is an important therapeutic consideration, as it facilitates quicker and easier attainment of goal blood pressure and should lead to a greater proportion of people with diabetes achieving blood pressure goal. In the Study of Hypertension and the Efficacy of Lotrel in Diabetes (SHIELD),[12] 214 patients with hypertension and diabetes were randomized to receive the fixed-dose product amlodipine besylate/benazepril HCl at 5/10 mg/d or enalapril (an ACE inhibitor) 10 mg/d and were followed for 12 weeks. If after four weeks patients did not achieve the target blood pressure of <130/85 mm Hg, the dose of study drugs was titrated to amlodipine besylate/benazepril HCl at 5/20 mg/d or enalapril 20 mg/d. If after four more weeks of therapy target blood pressure was not achieved, hydrochlorothiazide 12.5 mg/d was added to the treatment regimen. The cumulative percentage of subjects who attained first-treatment success, defined as the first incidence of blood pressure <130/80 mm Hg, was significantly greater among participants who received fixed-dose combination therapy with amlodipine besylate/benazepril HCl compared with those who received enalapril at every study time point. The statistically greater control rates with amlodipine besylate/benazepril HCl were maintained even when amlodipine besylate/benazepril HCl subjects who received adjunctive hydrochlorothiazide were removed from the analysis (Figure 1). This practical study demonstrates that initiating patients on combination antihypertensive therapy yields improved control rates compared with patients who are titrated on monotherapy, and thus lends support to JNC 7 recommendations for initiating combination therapy in a wider segment of hypertensive patients.

Renal Disease

High blood pressure is recognized as a strong independent predictor of the development and progression of chronic renal disease.[13] Further, tight blood pressure control is an established cornerstone for slowing the progression of chronic renal disease and the prevention of renal failure. Yet chronic renal disease, like hypertension, is often asymptomatic; it therefore may frequently go undiagnosed. Significantly elevated serum creatinine levels, an indicator of chronic renal disease, are far more common than typically appreciated and strongly related to the inadequate treatment of high blood pressure.[14] An analysis of data from the third National Health and Nutrition Examination Survey (NHANES III) showed that the prevalence of elevated serum creatinine was higher among men than women and among older than younger persons.[15] Further, elevated serum creatinine level was more common in non-Hispanic African Americans than non-Hispanic whites, diabetic patients than nondiabetic patients, hypertensive than nonhypertensive patients, and people already using antihypertensive medications compared with those not using medications[14] (Figure 2). In fact, 75% of the hypertensive population with elevated serum creatinine levels was being treated with antihypertensive medications, although with suboptimal regimens. These data suggest an important relationship between inadequately controlled hypertension, diabetes, and chronic renal disease, with a more pronounced effect in men, African Americans, and older persons.

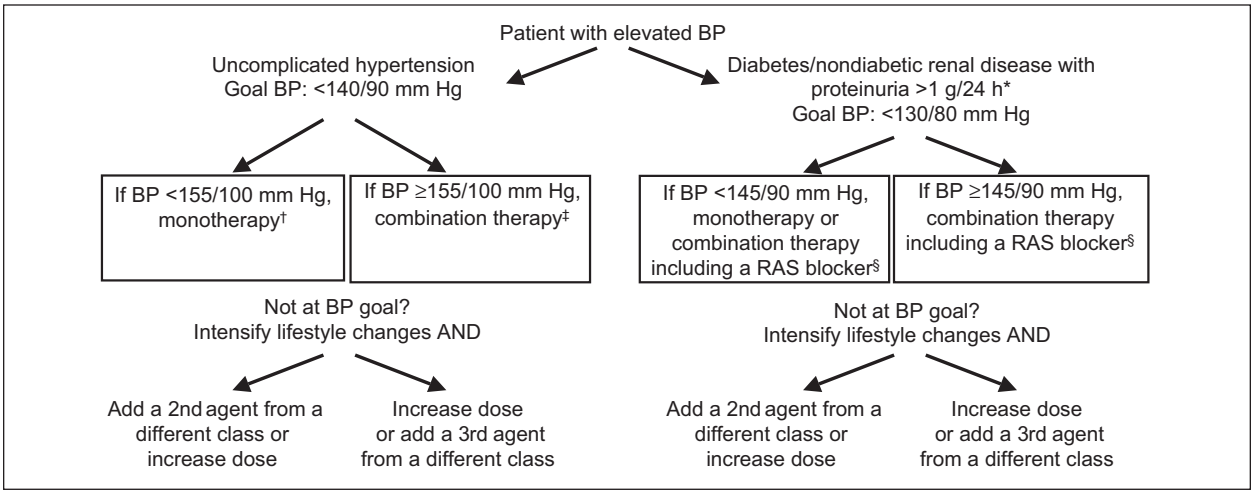

*Figure 3. Algorithm for management of high blood pressure in African Americans.[23] *Preferable blood pressure (BP) goal for patients with renal disease with proteinuria >1 g/24 h is <125/75 mm Hg. †Initiate monotherapy at the recommended starting dose with an agent from any of the following classes: diuretics, β blockers, calcium channel blockers (CCBs), angiotensin-converting enzyme (ACE) inhibitors, or angiotensin II receptor blockers (ARBs). ‡To achieve BP goals more expeditiously, initiate low-dose combination therapy with any of the following combinations: β blocker/diuretic, ACE inhibitor/diuretic, ACE inhibitor/CCB, or ARB/diuretic. §Consider specific clinical indications when selecting agents. RAS=renin-angiotensin system*

There is clear evidence of the benefits of RAS blockade in patients with renal disease. In a meta-analysis of randomized, placebo-controlled trials, treatment with ACE inhibitors was found to delay the progression of renal disease, compared with placebo, in both diabetic and nondiabetic chronic renal disease.[16] This benefit with ACE inhibitors—beyond their ability to lower blood pressure—was also demonstrated in African-American patients in the African American Study of Kidney Disease and Hypertension (AASK) to a similar degree as other agents.[17] Recently, ARBs also have proven very beneficial in slowing the progression of renal disease in patients with diabetic nephropathy.[18,19] In most of these trials, multiple medications, which usually included a diuretic, were necessary to achieve goal blood pressures.

Some data suggest that ACE inhibitor/CCB combination therapy may provide even greater renal protection than ACE inhibitor monotherapy. In a small study,[20] patients (n=45) with hypertension, type 2 diabetes, and microalbuminuria were treated with a combination of amlodipine besylate and benazepril HCl, or with benazepril HCl monotherapy. After 6 months of treatment, combination therapy increased creatinine clearance and produced a greater reduction in urinary albumin excretion than did monotherapy (19.7% vs. 12.6%, respectively). Another larger study[21] evaluated amlodipine besylate or fosinopril as monotherapy or in combination for 48 months in 309 patients with hypertension and diabetes. The combination therapy was more effective in reducing blood pressure than either drug alone and provided a greater decrease in urinary albumin excretion and a lower rate of CVD events compared to monotherapy with either agent. These results strengthen the rationale for use of an ACE inhibitor/CCB combination in the treatment of hypertensive patients with type 2 diabetes, and particularly in those with microalbuminuria or renal insufficiency.

African Americans

African Americans have disturbingly higher rates of CVD mortality, stroke, hypertension-related heart disease, congestive heart failure, type 2 diabetes, hypertensive nephropathy, and end-stage renal disease.[22] Inadequately treated hypertension is an important factor that is implicated in this enormous burden of disease for African Americans. The Hyper-

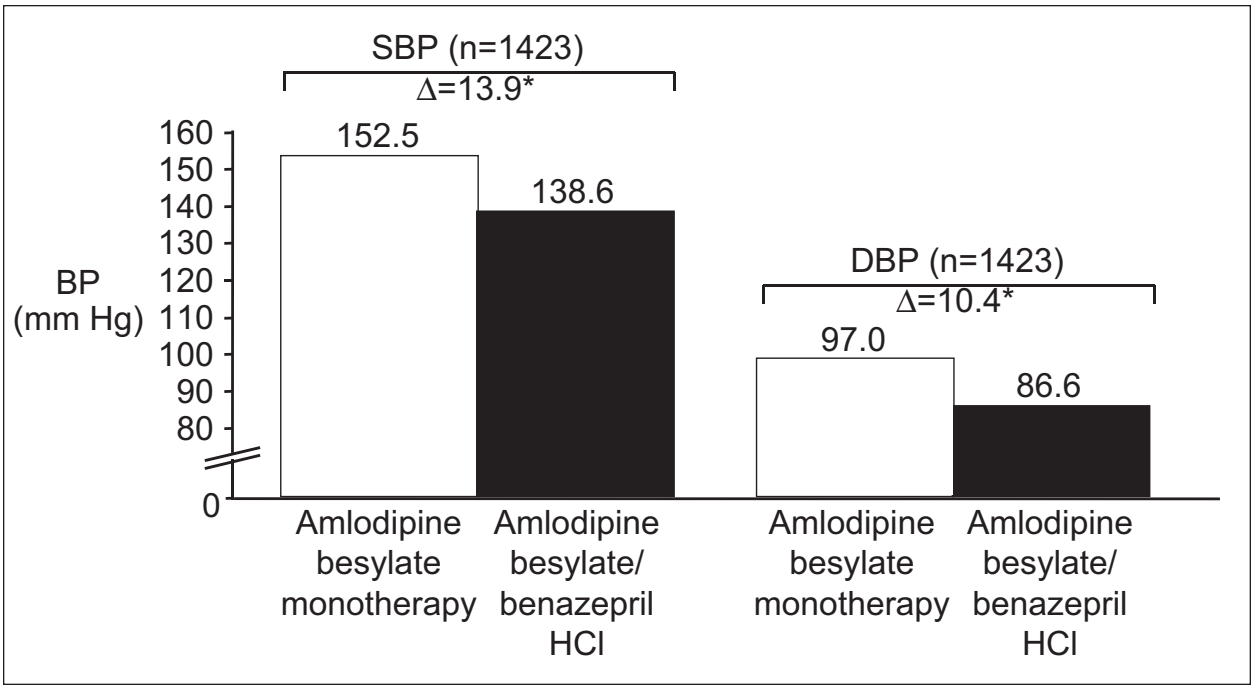

Figure 4. Change in blood pressure with amlodipine besylate/benazepril HCl combination therapy among African-American subjects with inadequate control on amlodipine besylate monotherapy. *p<*0.001 for incremental reductions with amlodipine besylate/benazepril HCl over those attained with amlodipine besylate monotherapy.*[24] *SBP=systolic blood pressure; DBP= diastolic blood pressure*

tension in African Americans Working Group recently recommended the use of combination therapy as initial therapy for selected patients. This group published a set of guidelines[23] for achieving target blood pressure values and lowering the risks associated with target-organ damage in African Americans with high blood pressure. These guidelines include initiating combination therapy in patients who are 15/10 mm Hg above an appropriate blood pressure goal (Figure 3). This group found that among African-American patients with hypertension, at least two drugs are frequently required to achieve blood pressure goals. Further, they reiterated that β blocker and ACE inhibitor monotherapy may have less blood pressure-lowering efficacy than in white patients, whereas thiazide diuretics and CCBs may have greater blood pressure–lowering efficacy. Nonetheless, although compelling indications have been identified for prescribing β blockers or RAS-blocking agents (either ACE inhibitors or ARBs), these compelling indications should be applied equally to African-American patients.

The combination of an ACE inhibitor with either a CCB or diuretic would also help bring the benefits of target-organ protection provided by ACE inhibitors to African Americans, who are at disproportionately high risk for CVD and renal morbidity and mortality. Data from AASK[17] have clearly indicated that ACE inhibitors are associated with better renal outcomes, compared with conventional drugs, in African Americans with hypertension and mild renal insufficiency.

The Lotrel: Gauging Improved Control (LOGIC) trial[24] was a large, open-label, practice-based study of patients (N=6410) whose blood pressure was uncontrolled with amlodipine besylate monotherapy. All patients were switched to amlodipine besylate/benazepril HCl (5/10 mg/d) combination therapy, and, after four weeks, combination therapy produced an additional mean reduction in blood pressure of 15.6/11.5 mm Hg (p<0.001 vs. amlodipine besylate monotherapy). An analysis of the African-American cohort of this study (n=1423) found results similar to those in the overall group: The switch from

amlodipine besylate monotherapy to combination therapy produced an additional mean reduction in blood pressure of 13.9/10.4 mm Hg ($p<0.001$ vs. amlodipine besylate monotherapy) (Figure 4).

Isolated Systolic Hypertension

There are some additional factors to consider before deciding that a patient without diabetes or chronic kidney disease should be classified as "uncomplicated." Isolated systolic hypertension (ISH) is a case in point. In general, almost three fourths of treated patients with hypertension achieve diastolic control, whereas only one third achieve systolic control.[6] A recent study[25] found that among treated patients with hypertension within the Central Arkansas Veterans Healthcare System, 58% of patients had controlled blood pressure. However, of the uncontrolled patients, 77% had ISH. In this population, patients with ISH were on average taking more antihypertensive medications than patients with controlled blood pressure, suggesting the difficulty of controlling systolic blood pressure (SBP). Randomized clinical trials show similar poor control of SBP. In ALLHAT, for example, only 63% of patients achieved the SBP goal of <140 mm Hg.[10]

Most of the uncontrolled hypertension observed in the Framingham Study was found in those with ISH, and this phenomenon is also very common in African Americans, among the elderly, and in patients with diabetes.[26] Combination therapy is frequently required to bring SBP to goal. This is an important point because lowering diastolic blood pressure (DBP) adequately without similarly lowering SBP to goal increases pulse pressure (the difference between SBP and DBP). Increased pulse pressure generally reflects stiffening of large arteries and is independently associated with several CVD risk factors.[26,27] It would certainly be reasonable to consider initiating therapy with two agents in patients with ISH, after taking into account the individual patient's risk for postural hypotension if blood pressure is lowered to goal too rapidly.

SUMMARY

It is clear that initiating antihypertensive therapy with two agents is indicated in a wide range of patients, including many of those with diabetes, renal disease, and ISH. Combination therapy brings patients to blood pressure goal more rapidly, with fewer medications, additions, or changes needed than with initial monotherapy. The recommendation to initiate combination therapy may be based on the level of hypertension (>20/10 mm Hg or >15/10 mm Hg above goal), the blood pressure goal (particularly for those patients who should achieve blood pressure values <130/80 mm Hg), or global CVD risk assessment. The chosen regimen for high-risk hypertensive patients should be based on those agents for whom the patient has compelling indications (e.g., ACE inhibitors for patients with diabetes, RAS-blocking agents for patients with renal disease, β blockers for patients post-MI). A second agent should be chosen that will offer the greatest likelihood of bringing the patient to goal blood pressure without the addition of a third agent. These agents may include low-dose thiazide diuretics or dihydropyridine CCBs. Nonetheless, many patients will require a three-drug regimen to achieve blood pressure control. Initiating combination therapy with a fixed-dose combination product (like amlodipine besylate/benazepril HCl) has been shown to be a good clinical strategy for many patients.

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