Case Studies in Primary Hypertension

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I. INTRODUCTION

Several randomized clinical trials of blood pressure (BP)–lowering drugs have been published during the past 2 decades. The earlier trials established the benefits of multiple risk factor intervention as well as diuretic-based and β-blocker–based therapies. More recent trials have shown that angiotensin-converting enzyme (ACE) inhibitors or calcium channel blockers are equally effective. Select randomized clinical trials are described in this article, including the Multiple Risk Factor Intervention Trial (MRFIT), the Systolic Hypertension in the Elderly Program (SHEP) trial, the Hypertension Optimal Treatment (HOT) trial, the Losartan Intervention For Endpoint (LIFE) reduction in hypertension study, and the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT).

The initial choice of drug therapy should be individualized based on concomitant conditions and risk factors as previously discussed in the first half of this article (see "Diagnosis and Treatment of Primary Hypertension," in the Hospital Physician Cardiology Board Review Manual, Volume 8, Part 1). The case studies are designed to discuss various presentations of primary hypertension and to incorporate the knowledge gained from randomized clinical trials for hypertension management. Data from continuing trials of BP-lowering drugs may indicate differences in treatment regimens comparing either drug classes or differing intensities, which can be used to select the best regimen for individual patients.

II. CLINICAL TRIALS

Randomized clinical trials are the backbone of evidence-based medicine. Large epidemiologic studies (Framingham, National Health and Nutrition Examination Survey [NHANES]) and many clinical trials have provided the basis for diagnosis, treatment, and determination of risk and prognosis for patients with hypertension.

MRFIT

Investigators in MRFIT assessed whether a multi-risk factor modification program would decrease mortality from and prevent coronary heart disease (CHD). In the study, 12,866 high-risk men aged 35 to 57 years were randomly assigned to their usual form of primary care or to a special intervention program, consisting of stepped-care treatment of hypertension using thiazide diuretics, tobacco cessation counseling, and counseling on lowering cholesterol intake. After 7 years, no statistically significant differences were seen in either study group for cardiovascular morbidity or incidence of cardiovascular events. The intervention-group patients did show statistically significant improvements in risk-factor control. Subsequently, 16 years after randomization, an 11.4% decrease in cardiovascular mortality and a 20.4% reduction in the rate of myocardial infarction (MI) were observed in intervention patients compared with patients receiving “usual care.”

HOT TRIAL

Conflicting evidence exists regarding the possibility of increased cardiovascular events with aggressive reductions in diastolic BP (DBP). A J-shaped curve has been demonstrated in trials showing a decline in cardiovascular events as the DBP is lowered from 100 to 85 mm Hg, with a subsequent increase in adverse events as the DBP is lowered further below 80 to 85 mm Hg. It is thought that occult coronary disease may be unmasked, as coronary filling occurs during diastole, thus accounting for the increased adverse events observed with more aggressive therapy.

The HOT trial randomly assigned 18,790 patients with diastolic hypertension between 100 and 115 mm Hg to 3 groups with target DBP goals (≤ 90 mm Hg, ≤ 85 mm Hg, and ≤ 80 mm Hg) to address the controversial existence of the J-curve. The antihypertensive treatment consisted of felodipine 5 mg per day. If the BP was not controlled, additional therapy was given. Unfortunately, the attained DBPs in the 3 target groups were 85.2 mm Hg, 83.2 mm Hg, and 81.1 mm Hg. This small separation of achieved DBP did not provide the power to detect differences in events between the 3 groups, leaving the controversy of the J-curve still unresolved.
Results from the HOT trial revealed that a DBP of 82.6 mm Hg in nondiabetic hypertensive patients resulted in the lowest incidence of major cardiovascular events. However, statistically significant differences in events were not seen between the 3 treatment groups. The authors thus concluded that the maximum benefit of treatment can be expected when the DBP is between 80 and 85 mm Hg, but most of the benefit is achieved by lowering the DBP to about 90 mm Hg; only a small additional benefit is possible with further reductions in BP. In diabetics, however, a 51% reduction in major cardiovascular events in the ≤ 80 mm Hg target group was observed when compared with the ≤ 90 mm Hg target group, identifying a patient population who do benefit from more aggressive DBP treatment goals.4

LIFE TRIAL

A few studies suggest that specific antihypertensive drugs significantly improve cardiovascular morbidity and mortality when compared with other agents. Clinical trials have shown that most antihypertensive medications provide similar cardiovascular protection when similar levels of BP control are achieved. Recent trials have shown that specific antihypertensives may improve outcomes in patient populations at higher risk for cardiovascular disease; thus, the choice of antihypertensive therapy may be significant. The LIFE trial investigators compared the efficacy of the angiotensin II receptor blocker (ARB) losartan versus atenolol in 9193 patients with hypertension and electrocardiographic (ECG) evidence of LV hypertrophy. The primary composite endpoint of MI, cardiovascular death, and stroke was significantly reduced to 11% in the losartan arm when compared with 13% in the atenolol arm. The benefit of losartan was more pronounced in diabetic patients with hypertension. A significant reduction in the primary composite endpoint to 18% in the losartan arm was seen in comparison with an incidence of 23% in the atenolol group.5

ALLHAT

The ALLHAT trial assessed whether different classes of medications decrease the incidence of fatal CHD and non-fatal MI in hypertensive patients.6 This large trial assessed 45,000 patients with hypertension and one additional cardiac risk factor; patients were randomly assigned to treatment with either a diuretic (chlorothalidone), calcium channel blocker (amlodipine), ACE inhibitor (lisinopril), or α-adrenergic blocker (doxazosin). The doxazosin-based regimen was prematurely discontinued 6 years into the study because of a markedly increased risk of congestive heart failure (ICHF, 8.13%) when compared with patients receiving chlorothalidone (4.45%). Additionally, a marginally significant excess of stroke was noted in the α-blocker group. The study was scheduled to be completed in March of 2002; the data will be analyzed to assess the relative efficacies of specific classes of medications on the incidence of fatal CHD and non-fatal MI in hypertensive patients.7

FUTURE FOCUS

Hydroxymethyl glutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) have been shown to significantly reduce cardiovascular and cerebrovascular events in patients with hypercholesterolemia.8 Small clinical trials have demonstrated a further reduction in BP in both treated and untreated hypertensive patients when a statin is added to the treatment regimen.9 Increasing evidence suggests that the beneficial effects of these agents may be independent of their effects on plasma cholesterol and are probably related to favorable interactions on endothelial function as well as angiotensin II receptors promoting BP reduction.10 If these BP reductions are validated in large trials, statins may have a potentially powerful dual role in treating patients with the combined cardiac risk factors of hypertension and hypercholesterolemia.

As evidence from large clinical trials continues to emerge, the superiority of certain antihypertensive medications in select populations may become apparent. Currently, the treating physician must assess each patient individually. Physicians should focus on assessing the hypertensive patient’s concomitant comorbidities to select the most appropriate pharmacologic regimen to modify multiple risk factors with specific antihypertensive agents.

III. CASE PATIENT 1

PRESENTATION

Patient 1 is a 70-year-old woman who presents to a clinic to establish primary care. She has a history of osteoarthritis and glaucoma. Additionally, she has a family history of hypertension, although she denies having hypertension herself, stating that her “bottom number has always been normal.” A review of systems is unremarkable; specifically, she has neither chest pain nor CHF symptoms. Physical examination reveals an elderly woman with a BP of 188/54 mm Hg and a heart rate of 76 bpm. Lungs are clear, and cardiac examination reveals a regular rate and rhythm, with a normal S1 and S2. An S3 gallop is audible. The apical impulse is in the normal location but is hyperdynamic, and trace peripheral edema is observed. Jugular venous pressure
and peripheral pulses are normal. Laboratory data include normal complete blood count (CBC), electrolytes, and kidney function. A 12-lead ECG shows normal sinus rhythm with left ventricular (LV) hypertrophy and no evidence of prior MI.

- **Does patient 1 have hypertension?**

  Patient 1’s case is a typical example of an elderly individual with isolated systolic hypertension, which is defined as a systolic BP (SBP) of ≥ 140 mm Hg and a DBP of < 90 mm Hg. This patient has not been previously treated because she has not been diagnosed as having hypertension. She mistakenly believes that she has normal BP as reflected by her normal DBP reading.

- **Is isolated systolic hypertension underdiagnosed?**

  **ISOLATED SYSTOLIC HYPERTENSION**

  The most common form of hypertension in patients older than 65 years is isolated systolic hypertension.\(^{11,12}\) This condition will increase as the elderly population continues to grow in the United States. Figure 1 shows the inversion in prevalence of elevated isolated diastolic versus SBP as patients age. This figure demonstrates that if diastolic parameters alone determined the presence of hypertension, a large portion of patients—particularly those who are elderly—would go undiagnosed and untreated. Lloyd-Jones et al recently confirmed that SBP readings are more likely than DBP readings to correctly identify individuals as having hypertension.\(^{13}\) In response to compelling epidemiologic and clinical trial data, the Sixth Report of the Joint National Commission on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-VI) now recommends using both SBP and DBP measurements in hypertension classification and diagnosis.\(^{13}\)

- **Are patients with isolated systolic hypertension at higher risk for adverse events?**

  As early as 1971, the Framingham Heart Study investigators found that SBP is a much more powerful predictor of cardiovascular events than DBP.\(^{14,15}\) Not long afterwards, similar findings were reached for risk of stroke, peripheral arterial disease, and CHF. Based on these findings, SBP elevation (not DBP elevation) is now considered as the major determinant of cardiovascular risk in elderly patients.\(^{11,12,16}\)

  Significant risk reduction after hypertension treatment has been unequivocally demonstrated in epidemiologic studies like Framingham as well as in randomized clinical trials. The SHEP trial has had the greatest effect on the management approach to patients with isolated systolic hypertension. In the SHEP trial, 4736 patients older than 60 years who had isolated systolic hypertension (with SBP between 160 to 219 mm Hg and DBP < 90 mm Hg) were...
randomly assigned to receive either antihypertensive drug therapy with chlorthalidone (12.5 mg per day) or placebo. The dose was doubled if the BP goal was not reached and then atenolol (25 mg per day) or placebo was added. Results showed that antihypertensive treatment reduced the total (ie, fatal and nonfatal) stroke risk by 36% (Figure 2). Further, all cardiovascular events were reduced by 32% in patients receiving treatment. Thus, treating 1000 patients for 5 years using the SHEP trial approach may prevent 30 strokes and 55 major cardiovascular events. Completed in 1991, the SHEP trial was the first to demonstrate that SBP reduction in older patients with an SBP of greater than 160 mm Hg and a normal DBP resulted in reduced morbidity and mortality. All previous trials had focused on DBP.

In the Systolic Hypertension in China (Syst-China) trial, 1255 patients were assigned to either active treatment starting with nitrendipine (10 to 40 mg/day)—with the possible addition of captopril (12.5 to 50 mg/day) and/or hydrochlorothiazide (12.5 to 50 mg/day)—or matching placebo in 1141 control patients. The Syst-China trial confirmed SHEP trial results; subgroup analysis further demonstrated a greater stroke reduction in diabetic patients and a greater reduction of all cardiovascular endpoints in hypertensive smokers. The Systolic Hypertension in Europe (Syst-Eur) trial also demonstrated a significant reduction in stroke incidence in individuals older than 60 years with isolated systolic hypertension. The treatment regimen consisted of either nitrendipine 10 to 40 mg/day (if necessary replaced or combined with enalapril 5 to 20 mg/day, hydrochlorothiazide 12.5 to 25 mg/day, or both) or matching placebo. The goal was a SBP of less than 150 mm Hg, with a reduction of at least 20 mm Hg. The Ethics Committee of the Syst-Eur trial terminated the study at the second of 5 planned interim analyses because the primary end-point of stroke reduction had been achieved with such high significance ($P < 0.001$).12

• Is there an upper age limit when considering treatment for elderly patients?

HYPERTENSION IN ELDERLY PERSONS

The notion that hypertension is a normal part of the aging process and thus does not need to be treated is no longer valid. Elderly populations are at greatest risk for cardiovascular and cerebrovascular events, and evidence shows that hypertension treatment in the elderly confers significant reduction in morbidity and mortality. Significant risk reduction has been demonstrated in patients older than 80 years. Because of these findings, no upper age limit should be set when considering hypertension treatment for the elderly. Evaluation of hypertensive risk and implementation of antihypertensive therapy in the elderly should be based on SBP rather than DBP.

The potential existence of the J-curve discussed earlier may serve as a guide in the future when determining how aggressive therapy should be when treating hypertensive patients. In a reanalysis of the data from SHEP, patients who experienced a cardiovascular event while on antihypertensive therapy had lower DBP than those who did not have an event. A decrease of 5 mm Hg in DBP was associated with statistically significant increases in all cardiovascular events as well as stroke. Although a definite benefit has been shown with controlling SBP, future trials will be needed to further validate or dismiss the presence of a J-curve of adverse events when lowering DBP, thus determining if a lower limit of an acceptable DBP needs to be set when treating systolic hypertension.

IV. CASE PATIENT 2

PRESENTATION

Patient 2 is a 58-year-old man who presents to the emergency department because he has not been “feeling
well" for the past few days. The patient describes fullness in his head and chest without any associated symptoms. His medical history is pertinent only for primary hypertension, and he states that he ran out of his medication 2 weeks before presentation.

Physical examination reveals an anxious man with a BP of 230/134 mm Hg and a heart rate of 108 bpm. Respirations are mildly increased at 22 breaths/minute. No papilledema is seen on funduscopic examination. Lungs have bilateral rales one quarter up from the bases. Cardiac examination reveals a regular tachycardic rhythm with a normal S1 and S2. A summation gallop is heard. Jugular venous pressure is normal but demonstrates sustained fullness with abdominal pressure. The apical impulse is prominent and hyperdynamic. No pedal edema or abdominal bruits are detected. Peripheral pulses are equal.

Laboratory data reveal normal CBC, electrolyte levels, and renal function. Several erythrocytes are seen in the urine. Oxygen saturation is 89% on room air. A 12-lead ECG shows sinus tachycardia, left axis deviation, and 4- to 6-mm ST-segment depressions across the precordium. A chest radiograph is significant for moderate pulmonary venous congestion and cardiomegaly. These findings indicate that patient 2 is in hypertensive crisis and needs immediate attention.

- What characteristics define hypertensive emergency, and how does it differ from hypertensive urgency?

HYPERTENSIVE EMERGENCY

Hypertensive emergency is defined as a sudden increase in SBP and DBP that results in end-organ damage, specifically involving the brain, kidneys, or heart. In contrast, hypertensive urgency occurs when BP is severely elevated without evidence of end-organ damage. Clinical conditions that fulfill diagnostic criteria of hypertensive emergency and necessitate a rapid lowering of BP include acute aortic dissection, hypertensive encephalopathy, pulmonary edema, acute MI, unstable angina, malignant hypertension, and eclampsia. The absolute BP level is not as important as the rate of pressure increase; thus, the presence of hypertensive emergency is not dependent on a specific BP reading but rather on a clinical syndrome. Hypertensive crisis rarely occurs when SBP is lower than 180 mm Hg or DBP is lower than 120 mm Hg. Conversely, most patients with BP readings greater than 180/100 mm Hg have long-standing stage 3 hypertension, are not in crisis, and could face significant morbidity from a rapid reduction in BP. These criteria underscore the importance of differentiating hypertensive emergency from hypertensive urgency during the initial patient evaluation.

In patient 2, the extensive ST-segment depressions seen on ECG indicate the presence of myocardial ischemia. If untreated, he will be at risk for progression to myocardial injury. The patient is also in the beginning stages of pulmonary edema complicated by hypoxia, which, if left untreated, could lead to respiratory failure requiring intubation and mechanical ventilation. The erythrocytes seen in his urine provide additional evidence that patient 2 is in imminent danger.

- Did patient 2 have underlying CHD and poor LV function before presentation?

Hypertensive emergency can elicit myocardial ischemia in the absence of underlying atherosclerotic CHD. Likewise, a person with normal LV function can have florid pulmonary edema during a hypertensive emergency. Afterload, reflected by BP, can be seen as the force against which the heart must work to eject its blood volume. In a hypertensive emergency, the heart must work extraordinarily hard; a normally functioning heart may not be able to promote forward blood flow, a condition that may lead to pulmonary edema. The intense afterload of hypertensive crisis increases wall stress and tension within the heart. Wall tension and heart rate determine myocardial oxygen demand; as wall tension increases in response to increased afterload, blood supply to the myocardium may not be adequate and myocardial ischemia or infarction may result in the absence of underlying CHD.

- Who is at highest risk for developing hypertensive emergency?

Less than 1% of patients with primary hypertension will present with one or more episodes of hypertensive crisis, and almost all patients presenting with hypertensive crisis have a preexisting diagnosis of primary hypertension. The exact cause of sudden and severe hypertension is largely unknown but often indicates uncontrolled primary hypertension, which commonly occurs as the result of interrupted medical therapy, as seen with patient 2. However, patients with secondary hypertension also may present in crisis and should not be overlooked. Elderly and African-American patients are at higher risk of hypertensive crisis than the general population. Other persons at risk include postoperative patients and women who may develop pregnancy-induced hypertension (ie, preeclampsia).

- What is the recommended therapy for patient 2?
TREATMENT

Immediate therapy is indicated to stop the end-organ damage in progress, with the goal of lowering BP while preserving blood flow to vital organs. In the acute setting, normalization of BP is not the immediate goal but should occur over several days. BP should be initially reduced by no more than 25% (within minutes to 2 hours) and then should be decreased toward 160/100 mm Hg within 2 to 6 hours, avoiding excessive falls in BP that may precipitate renal, cerebral, or coronary ischemia. If the patient has an acute aortic dissection, BP reduction should occur within minutes. Patients who have had a major stroke should not have their BP lowered; peristroke hypertension may be a compensatory response to ensure adequate blood supply to an already compromised brain.

The ideal agent for treating hypertensive emergency should be one that is administered intravenously, is easily titratable, has a rapid onset of action, and is characterized by a short half-life for precise rate control of BP reduction. Patient 2 could be started on an intravenous infusion of a short-acting β-blocker in combination with either intravenous nitroglycerin or fenoldopam. Sodium nitroprusside could be considered as another alternative strategy in combination with an intravenous loop diuretic to treat the pulmonary edema. Patient 2 should be admitted to an intensive care unit for close monitoring including intra-arterial BP monitoring.

- What is the mechanism of action of fenoldopam? Is there any head-to-head comparison for its efficacy and safety versus nitroprusside?

Fenoldopam

Fenoldopam is a new intravenous antihypertensive medication recently approved for the treatment of hypertensive emergencies in the United States. The agent is a dopamine agonist that is highly specific for the D₁-receptor and, because of this affinity, is not associated with α- or β-adrenergic effects, as seen with intravenous dopamine infusion. In addition to BP reduction, fenoldopam offers a 10-fold increase in renal vasodilation compared with low-dose dopamine. Fenoldopam also inhibits sodium reabsorption, which results in diuresis and natriuresis. Panacek et al compared fenoldopam with nitroprusside and found equal efficacy between the 2 medications, although patients treated with fenoldopam demonstrated improved renal function and an increase in creatinine clearance. Shusterman et al later confirmed the effects of fenoldopam on improving renal function in severely hypertensive patients. Based on this data, fenoldopam is the drug of choice for patients presenting with hypertensive crisis and renal insufficiency.

No adequate, well-controlled studies have assessed the use of fenoldopam in pregnant women. Hydralazine has been used traditionally in the treatment of eclampsia. Labetalol or nicardipine is preferred; however, once the patient is admitted to an intensive care unit. Both oral and intravenous formulations of labetalol and nicardipine appear to be safe and effective agents in pregnant hypertensive patients.

- What is the safety profile of nitroprusside?

Nitroprusside

Sodium nitroprusside is perhaps the most powerful and immediate antihypertensive agent, with an onset of action within seconds. Adverse effects are common, including profound hypotension with reflex tachycardia, cyanide toxicity, increased intracranial pressure, lipid peroxidation, and ototoxicity. The drug also requires normal liver/renal function for adequate clearance and can decrease coronary blood flow in patients with preexisting CHD, a phenomenon referred to as coronary steal or the Venturi effect. Mann et al, who compared nitroglycerin with nitroprusside in patients with CHD, demonstrated that nitroprusside can result in the redistribution of blood flow away from ischemic areas, potentially worsening ischemia or causing myocardial injury. Sodium nitroprusside is highly effective in patients with hypertensive crisis; however, the drug should be administered only for a short time to reduce risk of cyanide toxicity and should not be used in patients with liver or renal insufficiency. Cyanide detoxification can be achieved by providing a sulfide donor with sodium thiosulfate infusion.

- Are there any particular drugs or drug classes that should be avoided when treating hypertensive crisis?

Short-acting calcium channel blockers should not be used in hypertensive crisis. Splitting open a nifedipine capsule and administering the liquid sublingually has been a longstanding practice. However, virtually none of the drug is absorbed sublingually; nifedipine is absorbed via the intestinal mucosa. Evidence and a review of the biomedical literature have shown that the rapid and uncontrolled BP drop associated with nifedipine and other short-acting calcium channel blockers can result in cerebrovascular ischemia, stroke, repeated episodes of symptomatic hypotension, acute MI, conduction disturbances, fetal distress, and death. Therefore, short-acting calcium channel blockers—especially nifedipine—should be avoided in the treatment of hypertensive crisis.
V. CASE PATIENT 3

PRESENTATION

Patient 3 is a 60-year-old African-American man who presents to an outpatient clinic for a follow-up visit 3 weeks after hospitalization for an acute anterior MI. He has type 2 diabetes mellitus requiring insulin and primary hypertension, for which he is taking a calcium channel blocker and a diuretic. He is a nonsmoker and is currently in phase 2 of cardiac rehabilitation. Although he has not experienced recurrent chest pain during his exercise program, he does describe significant dyspnea on exertion and occasional paroxysmal nocturnal dyspnea that began after his hospital stay.

Physical examination reveals a mildly overweight man with a BP of 180/90 mm Hg and a heart rate of 90 bpm. Lungs are clear, and cardiac examination reveals a regular rate and rhythm, with a normal S1 and S2. S3 and S4 gallops are heard. The apical impulse is laterally displaced and sustained. His abdomen is without bruits, and peripheral pulses are equal.

Laboratory results are significant for a non-fasting glucose of 163 mg/dL. Patient 3’s blood urea nitrogen and serum creatinine are 26 mg/dL and 1.8 mg/dL, respectively; microalbuminuria is present. A 12-lead ECG reveals normal sinus rhythm, LV hypertrophy with secondary ST changes, and anterior Q-waves. A transthoracic echocardiogram performed in the office shows a dilated LV cavity with anterior akinesis. Ejection fraction is estimated to be 30%.

• What aspects of patient 3’s presentation are important in his further management?

Patient 3 has hypertension, diabetes, proteinuria, and new-onset CHF after a recent anterior MI. His hypertension has likely been longstanding and poorly controlled; consequently, he has experienced adverse effects that could have been prevented with adequate treatment.

• Does patient 3’s hypertension require a different approach because he also has diabetes?

DIABETES AND BLOOD PRESSURE CONTROL

More than 11 million North Americans have both diabetes and hypertension, with a higher prevalence of both disorders seen in African Americans and Native Americans. Diabetes alone increases the risk for cardiovascular mortality 2-fold, hypertension escalates this risk, and these patients also have both macrovacular (eg, MI, stroke, and peripheral arterial disease) and microvascular (eg, retinopathy and nephropathy) sequelae. Managing diabetic patients with hypertension is a complex task because of concerns about the metabolic effects of several antihypertensive agents, including worsening lipid profile and decreasing insulin sensitivity. Evidence suggests that tighter BP control imparts greater benefit than tighter glycemic control, however, both are crucially important. Furthermore, early antihypertensive treatment in diabetic patients, especially those with microalbuminuria, is important. Achieving a lower target BP than what is usually recommended appears to preserve more kidney function for a longer period of time and to decrease the incidence of cardiovascular events. Based on these observations, the JNC-VI guidelines recommend a target BP of < 130/85 mm Hg in hypertensive patients with type 2 diabetes and < 125/75 mm Hg in hypertensive patients with diabetes and nephropathy (eg, proteinuria > 1 g per day). If these guidelines are followed, polypharmacotherapy will most likely be necessary. More than 65% of patients with diabetes and hypertension require a regimen of 2 or more antihypertensives.

• Is a calcium channel blocker the drug of choice in African-American patients?

HYPERTENSION IN AFRICAN AMERICANS

Different characteristics of hypertension are seen in African-American patients, including a higher prevalence than in the overall US population and a tendency to be more refractory to traditional therapies. In addition, African-American patients present with hypertension at a younger age and therefore have target organ damage earlier than non–African-American patients. Because of these variations, researchers have attempted to differentiate specific classes of antihypertensive drugs based on their relative efficacy in subpopulations of hypertensive patients. Calcium channel blockers have subsequently been found to be more effective in reducing BP in African Americans with hypertension when compared with other therapies, specifically β-blockers and ACE inhibitors. Table 1 summarizes the proportion of African-American patients who responded to low-dose and high-dose therapy with atenolol, captopril and verapamil during 4-week treatment periods. Based on available data, calcium channel blockers are appropriate first-line therapy for the treatment of uncomplicated hypertension in African-American patients.

• Are calcium channel blockers indicated for patient 3?
Calcium Channel Blockers

Low ejection fraction and proteinuria are 2 comorbid conditions that should caution against the use of calcium channel blockers in patient 3. In addition to their vasodilatory properties, calcium channel blockers also have direct myocardial depressant effects (negative inotropy). Clinical trials have shown an increase in mortality associated with the use of short-acting calcium channel blockers in patients with CHD and reduced LV function. Newer long-acting calcium channel blockers differ from the older prototypical short-acting blockers in terms of pharmacokinetic, pharmacodynamic, and tolerability profiles and do not impart the same risks.45

New concerns have recently been raised regarding the use of calcium channel blockers in African Americans with hypertension and proteinuria. Preliminary results from the African American Study of Kidney Disease (AASK) trial demonstrated an increased mortality in African Americans with proteinuria who were treated with long-acting calcium channel blockers, prompting early termination of that study arm. The AASK study investigators assessed for an optimal treatment strategy to prevent renal failure in African Americans with hypertension by randomly assigning 1094 patients to a calcium channel blocker (amlodipine), an ACE inhibitor (ramipril), or a β-blocker (metoprolol XL). In September 2000, the data and safety monitoring board recommended terminating the amlodipine study arm because interim analysis showed that over 3 years, the ramipril group had a 36% slower decline in glomerular filtration rate and a 48% reduction in clinical end points (rapid decline in renal function, end stage renal disease, and death) compared with the amlodipine group.46 The ramipril and metoprolol XL comparisons remain in progress. These data suggest that calcium channel blockers do not slow progression of renal disease despite a substantial reduction in BP and should not be used to treat hypertension in African Americans with proteinuria. The data confirm the results of previous clinical trials citing ACE inhibitors as first-line therapy in such patients.

- What would be the most appropriate pharmacologic treatment for patient 3?

TREATMENT FOR CASE PATIENT 3

Patient 3’s hypertension is complicated by diabetes mellitus with proteinuria and by reduced LV function manifesting clinically as CHF from a recent anterior MI. The ideal antihypertensive regimen for patient 3 would include an ACE inhibitor, a β-blocker, and an increased dose of his diuretic for CHF symptoms.

ACE Inhibitors and ARBs

In addition to antihypertensive effects, ACE inhibitors improve endothelial function, retard experimental atherogenesis, and decrease ischemic events and mortality in patients with LV dilatation and reduced LV function, especially after an anterior wall MI (as seen with patient 3).47,48 The benefits seen with ACE inhibitors are partly caused by their ability to halt or limit LV remodeling after an MI, although survival is increased in patients who have LV dysfunction, both related and unrelated to MI.47,48 Finally, ACE inhibitors slow progression of nephropathy in diabetic patients with proteinuria or microalbuminuria. In some patients, complete remission of nephropathy has been observed with ACE inhibitor treatment.49-52 For the rapidly increasing population of diabetic hypertensives, an ACE inhibitor should usually be the initial choice, with diuretics and calcium channel blocker as needed for adequate BP control.

Table 1. Response to Antihypertensive Treatment in African-American Patients*

<table>
<thead>
<tr>
<th>Treatment Period</th>
<th>Antihypertensive Agent</th>
<th>Atenolol</th>
<th>Captopril</th>
<th>Verapamil SR</th>
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<td><strong>Initial therapy</strong></td>
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<td></td>
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<tr>
<td>Patients, n = 345</td>
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<tr>
<td>Patients, n</td>
<td>118</td>
<td>112</td>
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</tr>
<tr>
<td>Success, %</td>
<td>55.1</td>
<td>43.8</td>
<td>65.2</td>
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<tr>
<td>Failure, %</td>
<td>44.9</td>
<td>56.3</td>
<td>34.8</td>
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<tr>
<td><strong>Forced titration/maintenance (low and high dose)</strong></td>
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<tr>
<td>Patients, n = 307</td>
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<tr>
<td>Patients, n</td>
<td>109</td>
<td>98</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Success, %</td>
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<td>57.1</td>
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<tr>
<td>Failure, %</td>
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<tr>
<td><strong>Forced titration/maintenance (high dose only)</strong></td>
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<tr>
<td>Patients, n</td>
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<tr>
<td>Success, %</td>
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<td>61.7</td>
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<td>Failure, %</td>
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<td>38.3</td>
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</tr>
</tbody>
</table>

*Treatment response is measured by success or failure in reaching target blood pressure for low-dose and high-dose drug treatments for 2 active treatment periods, each lasting 4 weeks. Numbers of patients given indicate those for whom data could be evaluated.

The Heart Outcomes Prevention Evaluation (HOPE) and LIFE trials are 2 large clinical trials that demonstrated a benefit in treating high-risk patients with hypertension with ramipril and losartan, respectively. In the HOPE trial, 9541 patients older than 55 years at high risk of having cardiovascular events were randomly assigned either to ramipril (5 to 10 mg/day) or to placebo. High risk was defined as having vascular disease (peripheral vascular disease, coronary heart disease, or previous stroke) or diabetes along with hypertension, hypercholesterolemia, microalbuminuria, or cigarette smoking. The trial was prematurely terminated after a 4.5-year follow-up because of a 14.0% versus 17.8% rate of cardiovascular events in the ramipril versus placebo groups.53 As discussed earlier, the LIFE trial sought to compare the efficacy of losartan versus atenolol in 9193 patients with hypertension and ECG evidence of LV hypertrophy. The primary composite endpoint of MI, cardiovascular death, and stroke was significantly reduced to 11% in the losartan arm as compared with 13% in the atenolol arm. The results of the HOPE and LIFE trials support administration of an ACE inhibitor or ARB in high-risk patients such as patient 3. Head-to-head comparisons between ARBs and ACE inhibitors in high-risk populations are not currently available. However, early BP control with losartan or an ACE inhibitor in this patient with ECG evidence of LV hypertrophy and diabetes may have significantly reduced the likelihood of developing the adverse cardiac events.5

**Beta-Blockers**

Results of large clinical trials—including the Norwegian Multicenter Study (NMS)54 and the Beta-Blocker Heart Attack Trial (BHAT)55—showed the value of β-blockers after MI. These antihypertensive agents are used for secondary prevention of CHD, improving exercise tolerance, and decreasing the incidence of sudden cardiac death. Patient 3 also would benefit from β-blocker therapy because of improved hemodynamics, symptom reduction, and increased survival in patients with reduced LV function and CHF.56

**VI. SUMMARY POINTS**

- Randomized clinical trials have provided the basis for diagnosis, treatment, and determination of risk and prognosis for patients with hypertension.
- Earlier clinical trials established the benefits of multiple risk factor intervention as well as diuretic-based and β-blocker-based therapies. Recent trials have documented the equal overall effectiveness of ACE inhibitor or calcium channel blocker therapy.
- The initial choice of drug therapy should be individualized based on concomitant conditions and risk factors.
- Isolated systolic hypertension is defined as a systolic BP > 140 mm Hg and a diastolic BP < 90 mm Hg; it is the most common form of hypertension in patients older than 65 years.
- The JNC-VI recommends using both systolic BP and diastolic BP measurements in hypertension classification and diagnosis. Systolic BP is a more powerful predictor of cardiovascular events than diastolic BP.
- Elevated BP and hypertension are not inevitable processes of aging; no upper age limit should be set when considering treatment.
- Clinical conditions that fulfill the diagnostic criteria of a hypertensive emergency and necessitate a rapid lowering of BP include: acute aortic dissection, hypertensive encephalopathy, pulmonary edema, acute MI, unstable angina, malignant hypertension, and eclampsia.
- In hypertensive emergencies, BP should be reduced by no more than 25% (within minutes to 2 hours), avoiding excessive falls in BP that may precipitate renal, cerebral, or coronary ischemia. Patients who have had a stroke usually should not have their BP lowered.
- Short-acting calcium channel blockers should be avoided in the treatment of hypertensive crisis.
- The presence of both hypertension and diabetes mellitus escalates risk. Therefore, the target BP is lower in these patients (< 130/85 mm Hg) and even lower (< 125/75 mm Hg) if proteinuria (> 1 g per day) also is present.
- African-American patients present earlier and with more severe hypertensive disease than non–African-Americans. Calcium channel blockers are acceptable first-line therapy for African-American patients but should not be used if proteinuria is present.

**REFERENCES**

point beyond which pressure reduction is dangerous? JAMA 1991;265:489–95.


