OPTIMAL RISK MANAGEMENT OF THE HYPERTENSIVE PATIENT WITH MULTIPLE RISK FACTORS*

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ABSTRACT

To determine the risk of cardiovascular disease in patients with hypertension, it is necessary to recognize that the risk with hypertension is increased by the combination of other risk factors, such as smoking, obesity, dyslipidemia, diabetes, and microalbuminuria. This article reviews a series of clinical trials in patients with hypertension to determine appropriate treatment. In clinical practice, diuretics have become the primary source of therapy for patients who have uncomplicated hypertension. Additional agents include calcium-channel blockers, beta blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers based on compelling indications. Compelling indications suggest that if the patient has a condition that has been shown to have cardiovascular, renal, or other secondary effects in clinical trials, these agents should be used, if at all possible, often in combination with other complementary agents. (Adv Stud Med. 2004;4(5A):S382-S389)

Hypertension is a major risk factor for cardiovascular disease (CVD) morbidity and mortality. Despite this fact, detection and treatment of hypertension and high blood pressure among the 50 million persons affected have been inadequate. Indeed, only 27% of hypertensive patients are adequately treated to reach blood pressure below 140/90 mm Hg, although recent data suggest 31% improvement in control rates. In terms of morbidity and mortality, epidemiologic data suggest that the risk of hypertension starts with a threshold down to at least 115/75 mm Hg. If the blood pressure goal is defined as below 130/85 mm Hg, hypertension control rates would be only 10%. The National High Blood Pressure Education Program (NHBEP) of the National Heart, Lung, and Blood Institute is a valued source for practice guidelines to assist primary care providers in approaching hypertension.

Risk

To determine the risk of patients who have hypertension, it is necessary to recognize that high blood pressure is combined with other cardiovascular (CV) risk factors, such as cigarette smoking, obesity (body mass index ≥30 kg/m²), physical inactivity, dyslipidemia, diabetes, microalbuminuria, or estimated glomerular filtration rate 60 mL/min or less. Other risk factors include age 55 years or older for men, 65 years or older for women, and family history of premature CVD. The risk is also present with target-organ damage. This includes left ventricular hypertrophy, angina, prior myocardial infarction (MI), prior coronary revascularization, and heart failure. In the brain, target-organ damage can include stroke or transient ischemic attack.
The Hypertensive Optimal Treatment (HOT) trial found greater reductions in morbidity and mortality at lower blood pressure goals. A recent meta-analysis of more than one million adults with no previous vascular disease demonstrates that in middle-aged and older adults, usual blood pressure levels below the threshold of 120/80 mm Hg are optimal. Studies further indicate that most people in the United States and Western societies are at risk for high blood pressure and CVD, regardless of ethnicity. Much more than cancer, CVD is the primary cause of death in African Americans, Caucasians, Hispanics, Asians, Pacific Islanders, and Native Americans. Indeed, CV risk in women exceeds that of cancer, including breast cancer. Unfortunately, many females present with atypical signs of MI, and recent data indicate that as many as 43% of women did not have chest pain prior to receiving a diagnosis of MI. Women with type 2 diabetes are at greater risk for CVD—even if they are premenopausal. No longer should clinicians be surprised when premenopausal women present to local emergency departments with MIs, especially if they have diabetes.

It is important to continue to intervene aggressively in patients with hypertension and elevated lipids because these are primary causes of CVD. Note that hypertension is often seen as an arbitrary level of 140/90 mm Hg or above, when, in fact, blood pressure higher than 120/80 mm Hg defines the increased level of risk. Elevated blood pressure affects the total body vasculature from the retina to the kidneys, to the heart, and to the peripheral arterial circulation (Figure 1). Cardiologists are increasingly aware of manifestations of heart disease, including heart failure and coronary artery disease. Although heart failure caused by coronary disease predominates in many heart failure trials and academic centers, left ventricular hypertrophy has increasingly been seen as an independent risk factor for coronary heart disease, death, and heart failure. However, hypertension is the primary cause in over 90% of cases.

STROKE

Stroke is a serious and disabling condition. Stroke caused by ischemic disease is related to atherosclerosis in patients, two thirds of whom have high blood pressure prior to presenting with the cerebrovascular event. Yearly it affects over 750,000 Americans, killing over 160,000 and disabling 30%. Indeed, cerebrovascular disease is the leading cause of permanent adult disability. Patients realize the potential risk for CV death from MI, stroke, and serious disability only after hypertension is diagnosed. The patient is then more willing to work with

![Figure 1: Hypertension and Target-Organ Sequelae](image)

![Figure 2: MRFIT: Effect of Systolic BP and Diastolic BP on Age-Adjusted CHD Mortality](image)

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Adapted with permission from Neaton JD, Wentworth D. Serum cholesterol, blood pressure, cigarette smoking, and death from coronary heart disease: overall findings and differences by age for 316,099 white men. Multiple Risk Factor Intervention Trial Research Group. Arch Intern Med 1992;152(1):56-64.
the physician in an effort to control blood pressure and help decrease the risk of stroke.

NHANES

To determine, as a society, how well we are controlling hypertension, we can look to the National Health and Nutrition Examination Survey (NHANES). The latest data from 1999 to 2000 demonstrate that most patients with high blood pressure receive treatment. Moreover, most patients with high blood pressure are aware of their condition. Yet, NHANES suggests that only one third of patients have controlled blood pressures of below 140/90 mm Hg.

NHBEP

An interesting concept is determining the risk of elevated blood pressure prior to the artificial barrier of hypertension at 140/90 mm Hg. The NHBEP, which publishes the Joint National Committee reports, is the committee for the prevention, detection, evaluation, and treatment of high blood pressure, besides hypertension. The optimal blood pressure is below 120/80 mm Hg. In the Framingham data, in patients with what is called high normal blood pressure, there is a 1.6% greater risk of CVD in men and 2.5% increased CV risk in women versus optimal blood pressure.

MRFIT

The most important blood pressure variable for middle-aged and older adults is the systolic versus the diastolic blood pressure. Data from the Multiple Risk Factor Intervention Trial (MRFIT) demonstrate a cohort of more than 360,000 men. The systolic blood pressure exceeds diastolic blood pressure as the primary risk of CV mortality. A low diastolic blood pressure (<70 mm Hg) when combined with a high systolic blood pressure (>160 mm Hg) is the primary marker of decreased arterial compliance and increased risk of coronary heart disease. This is a hard endpoint and suggests that systolic pressure for middle-aged and older adults greatly exceeds diastolic blood pressure as a target for intervention (Figure 2).

Table 1. JNC VII: Components of CV Risk Stratification in Hypertensive Patients

<table>
<thead>
<tr>
<th>Hypertension</th>
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</thead>
<tbody>
<tr>
<td>Smoking</td>
</tr>
<tr>
<td>Obesity (BMI &gt;30 kg/m²)</td>
</tr>
<tr>
<td>Physical inactivity</td>
</tr>
<tr>
<td>Dyslipidemia</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Microalbuminuria or estimated GFR &lt;60 mL/min</td>
</tr>
<tr>
<td>Age (men &gt;55 yr; women &gt;65 yr)</td>
</tr>
<tr>
<td>Family history of premature CVD (men &lt;55 yr; women &lt;65 yr)</td>
</tr>
</tbody>
</table>


Table 2. Key Messages from the JNC VII

| In persons older than 50 years, systolic blood pressure greater than 140 mm Hg is a much more critical CVD risk factor than diastolic blood pressure. |
| The risk of CVD, beginning at a blood pressure of 115/75 mm Hg, doubles with each increment of 20/10 mm Hg; individuals who are normotensive at 55 years of age have a 90% lifetime risk for developing hypertension. |
| Individuals with a systolic blood pressure of 120 to 139 mm Hg or a diastolic blood pressure of 80 to 89 mm Hg should be considered prehypertensive and require health-promoting lifestyle modifications to prevent CVD. |
| Thiazide-type diuretics should be used in drug treatment for most patients with uncomplicated hypertension, either alone or combined with drugs from other classes. Certain high-risk conditions are compelling indications for the initial use of other antihypertensive drug classes, such as ACE inhibitors, ARBs, beta blockers, and calcium-channel blockers. |
| Most patients with hypertension will require 2 or more antihypertensive agents to achieve their goal blood pressure (<140/80 mm Hg or <130/80 mm Hg for patients with diabetes or chronic kidney disease). |
| If blood pressure is more than 20/10 mm Hg above goal blood pressure, consideration should be given to initiating therapy with 2 agents, 1 of which usually should be a thiazide-type diuretic. |
| The most effective therapy prescribed by the most careful clinician will control hypertension only if patients are motivated. Motivation increases when patients trust and have positive experiences with the clinician. |

In the past, patients were told that the systolic blood pressure was normal if it was the person’s age plus 100. For an individual aged 60, a systolic blood pressure of 160 mm Hg was thus considered “normal.” Clinicians and scientists have now learned more about hypertension. Elevated systolic blood pressure with decreased diastolic blood pressure or an increase in pulse pressure is recognized as a sign of decreased arterial elasticity and a hallmark for risk of CV events and deaths.

**JNC VII**

The Seventh Report of the Joint National Committee (JNC VII) guidelines on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure were published in the *Journal of the American Medical Association* in 2003. Highlights of the JNC VII are the components of CV risk stratification in hypertensive patients (Table 1) and a new classification of prehypertension. These data suggest that CV risk increases doubly with every 20/10 mm Hg above a blood pressure of 115/75 mm Hg. Furthermore, everyone at age 55 years with a normal blood pressure reading has a 90% chance of developing hypertension in his or her lifetime. Clinicians should focus on high blood pressure as a target for CV risk control (Table 2).

Figure 3 contains the JNC VII hypertension treatment algorithm. The JNC VII guidelines and supporting documentation are available at www.nhlbi.nih.gov/guidelines/hypertension/. Patients may download these data from the Internet to help them understand their disease and required diet.

**ALLHAT**

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was used in developing the JNC VII guidelines. This landmark trial included 42,418 hypertensive patients and

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**Figure 3. JNC VII: Hypertension Treatment Algorithm**

- **Lifestyle Modifications**
  - Not at Goal BP
    - (<140/90 mm Hg or <130/80 mm Hg for Those with Diabetes or Chronic Kidney Disease)
  - Initial Drug Choices
    - Hypertension Without Compelling Indications
      - Stage 1 Hypertension (Systolic BP 140-159 mm Hg or diastolic BP 90-99 mm Hg)
        - Thiazide-type diuretics for most
        - May consider ACE inhibitor, ARB, beta blocker, CCB, or combination
    - Hypertension With Compelling indications
      - Stage 2 Hypertension (Systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg)
        - 2-drug combination for most
        - Usually thiazide-type diuretic and ACE inhibitor or ARB or beta blocker or CCB
      - Drug(s) for the compelling indications
        - Other antihypertensive drugs
        - Other antihypertensive drugs
      - Other antihypertensive drugs
        - Other antihypertensive drugs
      - Other antihypertensive drugs
        - Other antihypertensive drugs
    - Not at Goal BP
      - Optimize Dosages or Add Additional Drugs Until Goal BP Is Achieved
      - Consider Consultation with Hypertension Specialist

JNC VII = The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; BP = blood pressure; ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CCB = calcium-channel blocker.

reinforced the importance of blood pressure control. Major outcomes were determined in high-risk hypertensive patients randomized to an angiotensin-converting enzyme (ACE) inhibitor (lisinopril) or calcium-channel blocker (amlodipine) versus a diuretic (chlorthalidone). Although several hypertension experts have noted shortcomings and pitfalls in the interpretation of ALLHAT data, it remains to have the greatest impact in treating hypertension to date.

DASH

The Dietary Approaches to Stop Hypertension (DASH) diet is a low-sodium diet that is high in fruits, vegetables, and whole grains, with small amounts of animal protein. As much as the DASH diet may benefit patients in the prehypertensive stage, this diet has also been demonstrated to be effective in African Americans who were included in the DASH trial. Whether these results could be replicated in a free-living community of patients is unclear. Nevertheless, it makes sense that some patients who are able to adhere to the DASH diet have as much as 15-mm Hg systolic blood pressure control or response. Alcohol appears to be related to a decrease in coronary events, perhaps because red wine is rich in flavonoids and has a protective effect in raising high-density lipoprotein cholesterol. However, if a person consumes excessive alcohol (greater than 2 or more drinks daily), it may actually have a blood pressure–elevating effect. Therefore, unless a person is very disciplined to drink moderately, a general recommendation to drink alcohol for CV protection would not be reasonable.

UKPDS

Diabetes remains a significant risk factor for CVD. The United Kingdom Prospective Diabetes Study (UKPDS) has demonstrated that it is better to control blood pressure tightly with either a beta blocker or an ACE inhibitor than with glucose alone in patients with type 2 diabetes. Tight blood pressure control (not necessarily optimal) of 140/82 mm Hg gives better outcomes in CVD and diabetic endpoints than 154/87 mm Hg. In UKPDS, the benefit of tight blood pressure control is demonstrated in decreasing stroke, any diabetic endpoint, diabetes death, retinopathy, and even microvascular complications. For a long time, clinicians and researchers felt that hyperglycemia was the primary hallmark of increased risk for diabetes, but now it remains clear that for diabetics, controlling blood pressure, along with glucose control, is optimal and mandatory. One of the goals of the JNC VII is to lower blood pressure to below 130/80 mm Hg in patients with diabetes. To some extent, this is based on results from the HOT trial, which used felodipine, a calcium-channel blocker, with an ACE inhibitor. The lower the blood pressure in patients with diabetes, the more optimal is the control of CV risks.

Syst-Eur

In European studies of systolic blood pressure, such as Systolic Hypertension in Europe (Syst-Eur), nitrendipine, a calcium-channel blocker not yet available in United States, is shown to decrease CV risk in elderly diabetic patients. Systolic blood pressure is also a powerful risk factor for multi-infarct dementia. One of the teaching points of the Syst-Eur dementia study is that the Mini Mental State Examination and computerized axial tomography can detect definite risks of undiagnosed stroke and ischemic cerebrovascular disease in elderly patients who are not controlled versus those treated with a long-acting dihydropyridine-based therapy. In patients who took placebo, there were 64 cases of dementia and 41 patients who had previously been diagnosed with Alzheimer’s disease versus 21 patients who were in an active control group. Many patients with organic brain syndrome thus have multiple and often undiagnosed small ischemic infarcts of the cerebral vasculature related to poorly controlled high blood pressure. Clinicians may not recognize it, but poorly controlled blood pressure can lead to senility or Alzheimer’s disease.

INVEST

A recent trial called the International Verapamil/Trandolapril Study (INVEST) has shown that the combination of the calcium-channel blocker verapamil plus the ACE inhibitor trandolapril gives similar CV outcomes when compared with the older regimen of atenolol, a beta blocker, and hydrochlorothiazide. Findings from INVEST suggest that ACE inhibitors and calcium-channel blockers, when appropriately used, provide CV protection. The primary outcome of all-cause mortality, nonfatal stroke, and nonfatal MI are comparable. Indeed, one
of the benefits of the calcium-channel blocker and ACE inhibitor arm of INVEST appears to be a lower risk of new-onset diabetes. This result is also seen in ALLHAT when comparing lisinopril with chlorthalidone and amlodipine with chlorthalidone. The long-term clinical significance of preventing new-onset diabetes with ACE inhibitor and calcium-channel blocker–based therapies is not yet clearly defined.

RENNIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

Modulation of the rennin-angiotensin-aldosterone system has proven beneficial in a large number of trials. While many of these trials do not necessarily study hypertension, angiotensin receptor blockers (ARBs) and ACE inhibitors combined with older agents, including diuretics and beta blockers, have been shown to benefit patients who are at a higher risk for heart failure and CVD. Spironolactone and aldosterone antagonists are found to have benefits in patients with higher degrees of heart failure. A newer aldosterone antagonist, eplerenone, has been approved for use in patients with left ventricular dysfunction and heart failure post-MI.

HOPE

The Heart Outcomes Prevention Evaluation (HOPE), while not solely a blood pressure trial, also stresses the benefit of adding the ACE inhibitor ramipril in high-risk patients. This patient cohort of over 9000 with previous vascular disease validated an additional benefit when ramipril was added to conventional medicines versus placebo. The reduction of MI, stroke, and CV death was statistically significant.

IRMA/IDNT

ARBs are the newest antihypertensive agents that specifically prevent progression of diabetic nephropathy. Two outcome trials with patients with diabetes, Irbesartan Microalbumunuria Type 2 Diabetes in Hypertensive Patients (IRMA) study and Irbesartan in Diabetic Nephropathy Trial (IDNT), have shown that diabetic patients with various degrees of renal impairment benefit from the addition of ARBs in preventing progression of microalbuminuria and proteinuria and progression to end-stage renal disease and nephropathy. Nevertheless, cardiologists are concerned about switching from ACE inhibitor to ARB therapy, given the large number of trials showing benefit of ACE inhibitors in preventing CV events, including MI, stroke, and heart failure.

LIFE

A recent ARB trial, the Losartan Intervention For Endpoint Reduction in Hypertension (LIFE) study, has demonstrated that losartan plus diuretics in patients with hypertension and hypertrophy of the left ventricle show benefit in CV events, primarily stroke, versus atenolol with the addition of diuretics. The losartan cohort did not appear to have an increased protection against heart attack versus the beta blocker group. These data suggest that in high-risk hypertensive patients with left ventricular hypertrophy, ARBs have some benefit (primarily stroke prevention) in addition to the ARB benefit in patients with diabetic nephropathy.

AFRICAN AMERICANS

Hypertension in African Americans remains an area of concern. African Americans have one of the highest rates of hypertension in the world. Although some components of the increased risk for hypertension and early onset of high blood pressure in African Americans may be based on genetics, most of it appears to be socioeconomic and lifestyle based. Conditions such as the inability to afford medications or intensive therapy can determine much of the high risk in the African American population. Because the average blood pressure is higher and hypertension starts earlier in life, left ventricular hypertrophy, end-stage renal disease, and heart failure are excessively high in this population. Indeed, there is a 320% increase in end-stage renal disease, an 80% higher mortality stroke rate, and a 50% higher heart disease rate. In most major cities with a large African American population, the dialysis units are seen to have a disproportionately large percentage of African Americans. This is perhaps the most visible effect of poorly controlled blood pressure along with type 2 diabetes. The unfortunate reality is that African Americans have disproportionately high rates of death and disability from diseases unrelated to hypertension, such as infant mortality, breast cancer, colon cancer, prostate cancer, and other conditions. This suggests that it would be difficult to confirm a genetic basis for these various healthcare disparities.
**AASK**

One recent study, the African American Study of Kidney Disease (AASK), evaluates the benefit of the ACE inhibitor ramipril in hypertensive African Americans with nephrosclerosis when compared with the beta blocker metoprolol or the calcium-channel blocker amlodipine in patients with proteinuria. Results showed that no additional benefit of slowing progression of hypertensive nephrosclerosis was observed with the lower blood pressure goal. ACE inhibitors appear to be more effective than beta blockers or dihydropyridine calcium-channel blockers in slowing glomerular filtration rate decline.

**ALLHAT**

As previously mentioned, ALLHAT was the largest antihypertensive trial ever conducted and has provided much of the important data in the understanding of the prevention of CVD in high-risk patients. African Americans comprised one third of the study population, half of the subjects were women, and a large number of diabetic patients were enrolled. Regarding this cohort, the diuretic appeared to give specifically better control of blood pressure than the ACE inhibitor lisinopril. For the patient with compelling indications placed on an ACE inhibitor, the addition of a diuretic for adequate blood pressure control would be dictated. Calcium-channel blockers in the ALLHAT trial yielded outcomes similar to that of chlorthalidone. In this large diverse patient population, the calcium-channel blocker amlodipine showed results comparable to chlorthalidone for fatal coronary heart disease and non-fatal MI. Secondary CV endpoints were also similar to chlorthalidone for stroke, combined coronary heart disease, combined CVD, and total mortality. Calcium-channel blockers do appear to be a protection against the development of new heart failure in patients with chlorthalidone based on the ALLHAT trial versus amlodipine or lisinopril-based therapy. Nevertheless, amlodipine was demonstrated to be safe and effective in a large number of patients based on the ALLHAT cohort, with comparable reduction of end-stage renal disease, comparable rates of cancer, and hospitalized gastrointestinal bleeding. The African American cohort in ALLHAT did not appear to respond to blood pressure lowering with lisinopril. There was a greater fall in systolic blood pressure on chlorthalidone versus the lisinopril cohort, which translated to 40% increased risk of stroke. This result does not mean that ACE inhibitors will not be beneficial for risk reduction, but it suggests that diuretics and, based on the results of amlodipine and ALLHAT, calcium-channel blockers remain effective in blood pressure lowering and reduction of risks in African Americans. One of the important aspects of ALLHAT was to demonstrate the unusual community clinical care. Blood pressure can be controlled to a higher level than what is seen in a national survey. Differences remain, however, in control rates with African Americans, obese patients, patients living in the Southeast, and patients with diabetes.

**SUMMARY**

What agents should we use in patients with hypertension? Diuretics become the primary source of therapy for patients who have uncomplicated hypertension. Additional agents include calcium-channel blockers, beta blockers, ACE inhibitors, and ARBs based on compelling indications. Compelling indications suggest that if the patient has a condition that has been shown to have CV, renal, or other secondary effects in clinical trials, these agents should be used, if at all possible, often in combination with other drugs. The wisdom of ancient Asia has shown that "superior doctors prevent disease, mediocre doctors treat disease before it is evident, inferior doctors treat full-blown disease." It is for the benefit of the patient and the general population that we all become superior clinicians and prevent disease.

**REFERENCES**


