FROM GUIDELINES TO PRACTICE: PRACTICAL CONSIDERATIONS OF HYPERTENSION MANAGEMENT

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ABSTRACT

More than 50 million American adults have chronic hypertension, although 1 in 3 adults do not know they have this potentially devastating disease. Current low rates of detection and treatment of hypertension have continued essentially unchanged for 2 decades, and estimates for the cost of treating hypertension in the United States now exceed $50 billion annually. Improved detection and treatment of hypertension will reduce long-term morbidity and mortality related to cardiovascular and renal disease and save billions of dollars in American healthcare costs each year. Patient education and public health approaches recommended in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure can help reduce the incidence of serious complications of hypertension, such as myocardial infarction, stroke, and kidney failure. In addition to nondrug treatment, appropriate early use of combination antihypertensive therapy and modification of risk factors helps to achieve target blood pressure goals. Therefore, potentially devastating consequences of hypertension can be prevented.

improvement in these parameters over the past 20 years strikingly illustrates that millions of Americans remain at risk for serious medical complications related to hypertension—a highly treatable, yet underdiagnosed and undertreated, disease.

**Tangible Benefits of Aggressive Blood Pressure Reduction in the Community**

The main therapeutic objectives of the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) are to reduce cardiovascular disease and renal morbidity and mortality; treat identified hypertension to a target goal of less than 140/90 mm Hg, with a lower target BP of less than 130/80 mm Hg for patients with concomitant diabetes mellitus or chronic kidney disease with proteinuria of more than 1 g/day; and to have a particular emphasis on achieving target systolic blood pressure (SBP) goals, particularly in patients older than 50 years.1

Reaching these goals is of critical nationwide public health significance and of immense economic importance. Public health and patient education approaches, such as the reductions in excess calories, saturated fat, and salt, increased physical activity, and careful clinical vigilance, which are recommended in the JNC-7 report, may also help reduce the rate of serious complications of hypertension, such as myocardial infarction, stroke, kidney failure, and blindness.

**Cardiovascular Risk Reduction**

With regard to reducing cardiac risk in patients, data from recent large population studies convincingly demonstrate the importance of “getting to goal” (ie, aggressively treating patients with hypertension to attain and maintain target SBP and diastolic blood pressure [DBP]). Among patients with stage 1 hypertension (SBP 140–159 mm Hg and/or DBP 90–99 mm Hg) and additional cardiovascular risk factors, a 12-mm Hg decrease in SBP over 10 years prevents 1 death for every 12 patients treated.3 Furthermore, among patients with cardiovascular disease or other target-organ damage, the same sustained BP reduction prevents 1 fatal cardiovascular event for every 9 patients. Also, a recent meta-analysis of clinical trials evaluating data from up to 37 872 patients demonstrated significant and tangible clinical benefits of the use of BP-lowering drugs regarding mortality and cardiovascular morbidity. Specifically, BP reduction with antihypertensive drug therapy was associated with a 35% to 40% reduction in stroke incidence, a 20% to 25% reduction in myocardial infarction rates, and a 50% decrease in the incidence of heart failure.4

Furthermore, intensive lowering of DBP is associated with statistically significant reductions in the incidence of cardiovascular events. In the Hypertension Optimal Treatment trial, 18 790 men and women with hypertension (DBP of 100–115 mm Hg) were randomly assigned to achieve target DBP levels of 90 mm Hg or less (group A), 85 mm Hg or less (group B), or 80 mm Hg or less (group C).5 All of the patients received felodipine as baseline therapy, with other anti-hypertensive agents added as necessary according to an algorithm to reach the designated DBP goals. After an average follow-up period of 3.8 years, DBP was reduced by 20 mm Hg in group A, 22 mm Hg in group B, and 24 mm Hg in group C. Notably, significantly fewer myocardial infarctions occurred among patients in group C (n = 61) versus group A (n = 84; P = .05), with the lowest incidence of major cardiovascular events occurring among patients with a final DBP of 82.6 mm Hg. Overall, these data show us that significant cardiovascular benefits are associated with
reducing DBP to 82.6 mm Hg or lower, particularly in patients with diabetes mellitus.5

Another recent study involving more than 30,000 men and women explored the origin of greater-than-expected cardiovascular mortality that occurred among patients with hypertension who were inadequately treated over a period of at least 8 years. Findings of this study are of particular interest in regard to the effects on patient survival of inadequately treated elevations in SBP. In this study, patients who were treated demonstrated elevated SBP (average increase of +15 mm Hg) and DBP (average increase of +9 mm Hg), and were calculated to have a 2-fold increase in the risk ratio (RR) for cardiovascular mortality (RR, 1.96; 95% confidence interval [CI], 1.74–2.22) and coronary mortality (RR, 1.99; 95% CI, 1.63–2.44) in comparison to patients from the same cohort who were gender-matched, age-matched, and received no treatment.

After additional adjustment for modifiable associated risk factors, increased mortality among these patients persisted at RR 1.52 (95% CI, 1.33–1.74) for cardiovascular mortality and RR 1.49 (95% CI, 1.19–1.86) for coronary mortality. Only after additional adjustment for risk associated with increased SBP were the rates of cardiovascular and coronary mortality similar in the 2 groups of patients: RR 1.06 (95% CI, 0.92–1.23) for patients who received treatment and RR 1.06 (95% CI, 0.85–1.35) for patients who were not treated. Therefore, the increased cardiovascular mortality in patients with hypertension who received treatment versus control subjects without treatment was caused primarily by persistently elevated SBP despite treatment. Significantly, these results demonstrate that excess cardiovascular risk found in patients with inadequately treated hypertension can be drastically diminished if SBP is reduced to target levels (Figure 2).4 Overall, data from these recent large population studies powerfully underscore the importance of reaching and maintaining target BP levels, especially with regard to SBP, in reducing cardiac mortality and morbidity.

Accordingly, isolated systolic hypertension is a significant indicator for increased risk of death caused by coronary heart disease (CHD) and stroke. In a prospective study involving 316,099 men that explored the potential interaction between elevated SBP, CHD, and other factors, the 12-year follow-up clearly confirmed isolated systolic hypertension as an independent risk factor for cardiac mortality.

**Preventing or Delaying Chronic Kidney Disease**

The primary goal of antihypertensive treatment among patients with chronic renal insufficiency is to prevent progression to end-stage renal disease, a serious condition requiring dialysis and/or kidney transplantation. Although dietary protein restriction may slow the progression of renal disease, an important intervention in chronic kidney disease is appropriate BP control. Antihypertensive agents, particularly those agents that block the renin-angiotensin system, produce a reduction in proteinuria, thus not only decreasing BP but also preserving the renal function. In a clinical perspective, dialysis can be delayed by approximately 8 years in a hypothetical case of a 50-year-old man in whom SBP of 144 mm Hg is reduced to and maintained at 134 mm Hg or less.7

**The Case for Combination Antihypertensive Therapy**

The JNC-7 recommendations describe evidence from recent clinical trials (eg, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) demonstrating that most patients with...

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**Figure 2. Cardiovascular Survival in Treated Patients at Goal and Not at Goal**

| Untreated BP <140/90 mm Hg | Treated BP at goal <140/90 mm Hg |
| Untreated BP >140/90 mm Hg | Treated BP not at goal >140/90 mm Hg |

BP = blood pressure.

Adapted from Benetos et al., *J Hypertens.* 2003;21:1635-1640.
Hypertension will initially or eventually require treatment with 2 or more antihypertensive agents to reach target BP levels. Significantly, treatment with a second antihypertensive agent that has a different mechanism of action should be initiated when adequate doses of a single agent fail to achieve target BP goals. In addition, combination therapy should be considered initially for patients who are more than 20 mm Hg above their SBP target and/or 10 mm Hg above their DBP target; one of the components should be a thiazide-type diuretic unless otherwise indicated. In this summation report, an average of 3.2 antihypertensive medications (range of 2.6–4.3 medications) were nec-

Data in support of the above recommendation are provided by several clinical trials demonstrating that 2 or more antihypertensive agents may often be necessary to achieve BP goals in adults with uncomplicated hypertension. For example, in a recent open-label trial involving 179 patients, an antihypertensive algorithm using the selective angiotensin II inhibitor olmesartan as the initial agent controlled BP in most patients, but 66% required concomitant therapy with at least 1 other antihypertensive agent. Primary endpoints of the study were the percentage of the patients attaining a target BP of 140/90 mm Hg or less, as recommended in JNC 7, and the percentage of the patients attaining a more aggressive goal of 130/85 mm Hg or less.

In this study, more than 93% of the patients reached the target BP of 140/90 mm Hg or less with an olmesartan-based regimen, and approximately 88% of the patients reached the more aggressive target of 130/85 mm Hg or less. However, more than 60% of the patients required concomitant treatment with a thiazide diuretic or a thiazide and a calcium channel blocker to meet these target BP goals (Figure 3). These findings identify olmesartan as an effective first-line option for antihypertensive therapy and illustrate that most patients with hypertension will initially or eventually require treatment with 2 or more antihypertensive agents to reach target BP levels.

Furthermore, a summary report of 8 large clinical trials demonstrated the need for treat-

Figure 3. Patients Achieving SBP or DBP Goals on Olmesartan Monotherapy or Combination Therapy

![Figure 3](image_url)

Mean baseline blood pressure: 161/97 mm Hg.
*Percentage achieving goal based on 179 evaluable patients.
DBP = diastolic blood pressure; OLM = olmesartan medoxomil 20 to 40 mg/d; OLM or OLM/HCTZ = olmesartan medoxomil 20 to 40 mg/d or olmesartan medoxomil 40 mg/d plus hydrochlorothiazide 12.5 to 25 mg/d; SBP = systolic blood pressure.
Data from Neutel et al.

Figure 4. Average Number of Antihypertensive Agents Needed Per Patient to Achieve Target Systolic Blood Pressure Goals

![Figure 4](image_url)

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BP = blood pressure; SBP = systolic blood pressure.
ecessary to achieve recommended BP goals of less than 130/80 mm Hg for patients with concomitant diabetes mellitus and for those patients with renal insufficiency. Similarly, in the African American Study of Kidney Disease and Hypertension trial, 2 to 3 drugs were necessary on average to reduce mean arterial BP to less than 92/107 mm Hg in African-American patients with hypertension and mild-to-moderate renal dysfunction.15,16

**Pseudotolerance to Antihypertensive Agents**

Inevitably, with time, pseudotolerance mechanisms limit the sustained effectiveness of a single-drug regimen. Pseudotolerance develops when defense mechanisms (ie, the sympathetic nervous system and the renin-angiotensin-aldosterone system) are activated by single-agent therapy. In these cases, patients often require concomitant therapy with multiple drugs to block the counter-regulatory mechanisms. In addition, hypertensive nephrosclerosis may promote salt/water retention as renal perfusion pressure is reduced, necessitating concomitant administration of diuretics.17 Therefore, combination therapy is inevitable for many patients to reach JNC-7 BP goals.

**Promoting Adherence to Practice Changes Recommended in the JNC-7 Guidelines**

In the United States, several practical issues comprise significant barriers to the attainment of target BP goals identified by the JNC-7 guidelines. Some barriers to successful treatment of hypertension include time constraints during healthcare provider visits, formulary restrictions, and inadequate fluency within healthcare access and cultural obstacles. Among the barriers are several patient-related factors (Table),1 which the physician can identify during office or clinic visits by obtaining an appropriate patient history with close clinical follow-up.

Patient-related issues that may compromise successful treatment of hypertension also include the potentially high cost of antihypertensive medications and their adverse effects, which may affect a patient’s quality of life. Use of generic and less costly antihypertensive agents will reduce treatment costs, and long-acting, once-daily preparations may improve compliance by increasing the convenience of treatment. Furthermore, synergistic use of low-dose combinations of agents can enhance compliance by minimizing drug adverse effects.

The physician must be aware of the comparative cost of available antihypertensive agents, thus treatment costs can be affordable for the patient. For example, in a recent comparative cost analysis of angiotensin II receptor blockers (ARBs), olmesartan, losartan potassium, valsartan, and irbesartan were compared for the treatment of hypertension in a managed care setting.18,19 In this head-to-head, 8-week trial involving 588 patients with mild-to-moderate hypertension, olmesartan was significantly more effective than the ARBs losartan potassium, valsartan, and irbesartan, reducing DBP by 3.3, 3.6, and 1.6 mm Hg more than the other ARBs, respectively. The differences in DBP reductions among the agents were then used to estimate reductions in the annualized risk of cardiovascular and cerebrovascular disease events (using the Framingham model), and related cost savings were estimated. Based on the findings of this comparison, prescribing olmesartan instead of the comparator ARBs may significantly reduce the overall cost of hypertension-related care in managed care settings in the United States. Extrapolated to a 5-year period, savings related to the preferential use of olmesartan could amount to as

<table>
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<tr>
<th>Table. Patient Factors Related to Resistant Hypertension</th>
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<tr>
<td>Excess sodium intake</td>
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<td>Excess alcohol intake</td>
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<td>Inadequate diuretic therapy</td>
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<td>Medication</td>
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<tr>
<td>• Inadequate doses</td>
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<tr>
<td>• Drug actions and interactions (eg, nonsteroidal anti-inflammatory drugs, illicit drugs, sympathomimetics, oral contraceptives, over-the-counter drugs, and herbal supplements)</td>
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<td>Identifiable causes of hypertension</td>
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<td>• Sleep apnea</td>
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<td>• Side effects of prescription or nonprescription drugs</td>
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<td>• Chronic kidney disease</td>
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<td>• Primary aldosteronism</td>
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<td>• Chronic steroid therapy</td>
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<td>• Cushing syndrome</td>
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<td>• Pheochromocytoma</td>
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<td>• Coarctation of the aorta</td>
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<td>• Thyroid or parathyroid disease</td>
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Adapted with permission from Chobanian et al. *JAMA*. 2003;289:2560-2572.
much as a $31 million reduction in the overall cost of treating cardiovascular disease in the United States.

Underdiagnosis and undertreatment of hypertension are the main factors that compromise successful treatment of this dangerous condition. Physicians must maintain a high index of clinical suspicion for the presence of hypertension in all patients with risk factors for the disease. Specifically, as physicians review patients’ medical histories, they should consider the following major risk factors in addition to hypertension: family history of hypertension or heart disease; tobacco use; body mass index of 30 kg/m² or higher; sedentary lifestyle; dyslipidemia; diabetes; albuminuria; and age of 55 years or older for men, 65 years or older for women.

During the patient evaluation, detection of hypertension may also be hampered by improper technique of BP measurement. The following guidelines will help to ensure that BP is measured accurately:

- Patients should avoid nicotine and caffeine for 30 minutes before BP measurements, as these agents cause temporary BP fluctuations.
- Apply the BP cuff to the patient’s bare arm rather than over clothing, which may muffle pulse sounds. For accurate readings, select cuff size so that the bladder of the cuff covers approximately 66% of the height and 75% of the circumference of the patient’s upper arm.
- Palpate the patient’s radial pulse and inflate the cuff until the pulse can no longer be felt. Deflate the cuff and then slowly reinflate to approximately 30 mm Hg higher than the initial pressure reading. Make SBP and DBP determinations as the cuff is slowly deflated (approximately 2–3 mm Hg per second). If the patient’s BP is elevated, repeat the measurement again in 2 to 5 minutes.20

CONCLUSIONS

Improved detection and effective treatment of hypertension will reduce long-term morbidity and mortality related to cardiovascular and renal disease and can save billions of dollars in American healthcare costs. Patient education and public health approaches, such as dietary changes, increased physical activity, and careful clinical vigilance, as recommended in the JNC-7 report, can help to reduce the incidence of serious complications of hypertension, such as myocardial infarction, stroke, and kidney failure. Implementing these measures becomes increasingly important because the incidence of obesity and sedentary lifestyle continues at epidemic levels among adults and, increasingly, among children in the United States. The early implementation of lifestyle modifications to reduce hypertension, informed hypertension treatment with appropriate early use of combination therapy, and consideration of concomitant medical conditions and risk factors will help patients to reach and maintain BP goals and reduce the potentially devastating consequences of hypertension.

REFERENCES
