HYPERTENSION

• Prevalence and economic implications
• Summary of JNC-7 guidelines
• Trials underlying JNC-7 guidelines
• Implications of uncontrolled hypertension
• Drug-therapy review
• Recommendations for combination therapy
• NCQA standards and quality measurement
• Adherence to therapy
• Formulary status of antihypertensive agents

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Hypertension is a major driver of health care resource utilization and expenditures in the United States. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) recognizes several contributing factors to the epidemiology of hypertension and provides evidence-based guidelines for reducing blood pressure levels in patients with hypertension. Practitioners and health care organizations that follow these recommendations ultimately will contribute to reduced rates of morbidity and mortality from hypertension.

Hypertension is a serious public health threat, and by extension, a threat to the health of populations for which managed care organizations bear responsibility. The authors of JNC-7 note that many health care professionals often do not employ the practices advocated in the report. JNC-7 includes a comprehensive set of recommendations for appropriate pharmaceutical treatment of hypertension.

This publication places JNC-7 recommendations into perspective for managed care decision makers. Thus, it serves as a valuable tool for formulary committees and is an important contribution to the medical literature.

A Tool for Formulary Decision Makers

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This publication is made possible by an unrestricted educational grant from AstraZeneca
Hypertension

Continuing education objectives and accreditation statements

OVERVIEW

Hypertension: Prevalence and Economic Implications

Hypertension, which affects about 50 million Americans, is undetected in 30 percent of those who have it and is controlled in only 34 percent. The sequelae resulting from poor control is a major contributor to health care resource utilization.

MICHAEL D. DALZELL

GUIDELINES

Management of Hypertension in Light of the New National Guidelines

The JNC-7 treatment recommendations, if followed by a majority of physicians, should help to reduce the number of resistant hypertensives in the United States, resulting in increasing numbers of patients with controlled blood pressure.

MARVIN MOSER, MD

PERSPECTIVE

Outcomes Trials Underlying the JNC-7 Guidelines

Guidelines have become useful instruments to improve outcomes. The JNC-7 guidelines put the available data into perspective for physicians and health plans and provide a blueprint for improving care of populations and individuals. They are based on sound scientific evidence.

MARVIN MOSER, MD

DISEASE MANAGEMENT

Progression of Uncontrolled Hypertension and Implications for Managing Its Sequelae

Cardiovascular risk is most closely related to systolic blood pressure, which is a predominant component of uncontrolled hypertension. Because hypertension seldom occurs in isolation from other atherogenic risk factors, global risk assessment is mandatory for evaluating the hazard.

WILLIAM B. KANNEL, MD, MPH
PHARMACOTHERAPY

Hypertension: a Review of Therapeutic Options

Excellent clinical outcomes trial data support the use of several classes of drugs for reducing and controlling hypertension. This review covers the classes discussed in the JNC-7 report, including ACE inhibitors, ARBs, beta blockers, CCBs, and diuretics.

BARRY L. CARTER, PHARMD

PHYSIOLOGY

Fixed Low-Dose Combination Therapy: Current Recommendations

JNC-7 acknowledges that blood pressure can be difficult to control with one drug and provides guidelines for initiating combination therapy. Because hypertension involves numerous body systems, interrupting only one of these with monotherapy frequently is insufficient to achieve control.

L. MICHAEL PRISANT, MD

QUALITY MEASUREMENT

Measuring Hypertension Control: NCQA and Beyond

Using tools developed by the National Committee for Quality Assurance, Rand, and others, health plans and providers can take an aggressive stance toward the management of hypertension. This effort has led to gains in blood pressure control in some populations.

NANCY HOUSTON MILLER, RN

IMPROVING OUTCOMES

Compliance – and Improving It – in Hypertension

Compliance with hypertension therapy is a key component to achieving target blood pressure control rates. Clinicians can take practical steps to improve patients’ adherence to recommended regimens. Physician compliance with national treatment guidelines is also an important factor in efforts to reduce the prevalence of uncontrolled hypertension.

WILLIAM J. ELLIOTT, MD, PhD

CONTINUING EDUCATION

Post-test

Physician CME answer sheet/evaluation form

Pharmacist CPE answer sheet/evaluation form

DECISION-MAKING FOCUS

Formulary Status of Antihypertensive Drug Classes

Data reported in this section reflect aggregate national formulary statuses of classes of prescription drugs for hypertension, as well as trends with respect to the same.

DATA COMPILATION BY MEDIIMEDIA INFORMATION TECHNOLOGIES
P&T DIGEST

Hypertension

Continuing education credit is offered to physicians and pharmacists who read pages 6 through 61 of this publication, complete the post-test on pages 62 and 65, and fill out the appropriate evaluation form on either page 63 (physicians) or 64 (pharmacists).

PURPOSE AND OVERVIEW
Medical and pharmacy directors and other decision makers in managed care organizations seek state-of-the-art information about evidence-based guidelines, emerging therapies, and other best-practice information. This publication places the recommendations of the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) into perspective for managed care decision makers, who can use this information when deliberating treatment guidelines and formulary recommendations and who can disseminate it to providers to improve the collective health of their populations. The subject matter in this publication was selected on the basis of literature searches and faculty perceptions of significant issues.

EDUCATIONAL OBJECTIVES
After reading this publication, the participant should be able to:

• Describe JNC-7 risk stratification for prehypertensive and hypertensive patients.
• Illustrate the prevalence of both hypertension and prehypertension, as well as the clinical and economic implications thereof.
• Explain the importance of controlling isolated systolic hypertension.
• Identify appropriate pharmacotherapeutic treatments for a given hypertensive patient, depending on the patient’s disease state and treatment history.
• Discuss the value of combination therapy in controlling hypertension.
• Elucidate strategies for therapeutic compliance and the consequences of noncompliance.

TARGET AUDIENCES
Managed care organization medical directors and pharmacy directors; practicing primary care physicians, cardiologists, nephrologists, endocrinologists, and pharmacists; members of pharmacy and therapeutics committees; and other senior-level decision makers at MCOs.

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Hypertension: Prevalence And Economic Implications

MICHAEL D. DALZELL

Hypertension affects about 50 million Americans and is the most common reason that people visit their physicians (Cherry 2002). The relationship between hypertension and increased risk of myocardial infarction, congestive heart failure, stroke, and end-stage renal disease is clear and consistent. Nevertheless, many patients with this disease are under-treated. Hypertension is undetected in 30 percent of those who have it (JNC-7 2003).

The financial and public health consequences of both hypertension and the failure to control it are enormous. While the annual economic toll of the disease in the United States (direct and indirect costs) is about $1,000 per hypertensive patient (AHA 2002), its sequelae result in more than $3,700 in direct medical expenditures alone, per patient per year (Hodgson 2001).

The next several pages provide a statistical snapshot of hypertension: prevalence, populations at risk, implications for morbidity and mortality, demands the condition places on health care utilization, and ramifications for payers.

1Michael D. Dalzell is also managing editor of MANAGED CARE, a peer-reviewed journal.

EPIDEMIOLOGY

Rates of hypertension (defined as systolic blood pressure [SBP] ≥ 140 mm Hg or diastolic blood pressure [DBP] ≥ 90 mm Hg) peaked in the late 1970s and early 1980s (Figure 1). The 1970s and 1980s marked the advent of the development of many newer antihypertensive medications and an intensive public-awareness campaign, which together contributed to dramatic reductions in the incidence of, and morbidity and mortality from, hypertensive diseases (Moser 1997).

FIGURE 1  Historical prevalence of hypertension
Percentage of U.S. population age 20–74, age-adjusted


41.3% 43.9% 45.2% 26.4% 29.8%

35.0% 35.8% 35.8% 21.4% 27.5%

Male Female†

†1999–2000 figures are based on smaller sample sizes and are subject to greater sampling error.
†Excluding pregnant women.
SOURCE: NCHS 2002
Demographic characteristics
As the population ages, the prevalence of hypertension increases. Data emerging from the Framingham Heart Study suggest a 90-percent residual lifetime risk of developing hypertension for individuals 55 and older with normal blood pressures (Vasan 2001).

Figure 2 provides a demographic breakdown of hypertension prevalence. The share of women with high blood pressure lags that of men until middle age, at which point incidence becomes higher in females. Prevalence among blacks, while higher than that in the white population, varies significantly; the highest rates in the black population represent individuals who are older, less educated, overweight, or who have type 2 diabetes mellitus. Less detailed information is available for other ethnicities (Table 1).

**FIGURE 2** Prevalence of hypertension: white and black populations
*Percentage of Americans, 1988–1994*

![Graph depicting prevalence of hypertension by age and race.](source: Wölz 2000)

**TABLE 1** Prevalence of hypertension: Hispanic, Asian, and American Indian populations
*Percentage of Americans, 18 or older, who have been told that they have hypertension*

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Indians/Alaska natives</td>
<td>20.7</td>
</tr>
<tr>
<td>Asian/Pacific Islanders</td>
<td>16.3</td>
</tr>
<tr>
<td>Hispanics</td>
<td>18.6</td>
</tr>
</tbody>
</table>

*Source: AHA 2002*

Prevalence of hypertension tends to be higher in lower-income populations, as well as in those with fewer years of education. Figure 3 illustrates differences in mean SBP (mm Hg) for women on the basis of educational status.

**FIGURE 3** The educational gap and systolic blood pressure*
*Mean SBP (mm Hg), American women, age 25–64, 1988–1994*

![Graph showing mean SBP by years of education and race.](source: Winkleby 1998)

*Rates for men suggest a similar trend but are of lesser magnitude.*

*Source: Winkleby 1998*
EPIDEMIOLOGY, continued

Awareness, treatment, and control
The benefits of controlling hypertension have been appreciated for decades. Ogden (2000) estimated that a sustained 12 mm Hg reduction in SBP will prevent 1 death for every 11 patients treated. While control rates are improving, they still are well below the 50-percent goal outlined in Healthy People 2010 (Figure 4).

FIGURE 4 Trends in hypertension treatment
Percentage of hypertensive Americans age 18–74 (NHANES data)

![Graph showing trends in hypertension treatment from 1976-1980 to 1999-2000.](image)

Among the elderly in the Cardiovascular Health Study, treatment and control improved significantly during the 1990s. The share of the study population treated for hypertension increased from 35 percent to 51 percent. Accordingly, control increased from 37 percent in 1990 to 49 percent in 1999 (Psaty 2002).

Control in managed care populations
Managed care plans are optimally designed to improve hypertension control within their populations. With their sophisticated repositories of data, third-party payers can track treatment and control rates, analyze segments of the population that are responding to treatment, identify subpopulations that warrant special attention, and influence clinicians toward aggressive treatment of affected patients.

Yet, managed care plans are still struggling to meet the challenges that hypertension presents. Early reports of blood pressure control among commercial managed care populations were relatively low; in the late 1990s, researchers at a large Northern California health plan found “substantial room for improvement” (Alexander 1999), while an Upstate New York payer reported that 35 percent of hypertensive patients were controlled to target levels, despite a 68-percent treatment rate (DiTusa 2001).

In 2000, the National Committee for Quality Assurance (NCQA) introduced a HEDIS hypertension-performance measure that was intended to assess the rate at which HMOs achieve JNC-6 recommended control rates. Since then, commercial managed care plans have reported rapid improvement in hypertension control, from a median rate of 40 percent in 2000 to 57 percent in 2002 — a level higher than the Healthy People 2010 goal (NCQA 2002).

CAUSES OF HYPERTENSION

One objective of the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of Hypertension (JNC-7) was to improve clinicians’ awareness of national treatment guidelines and to encourage them to integrate up-to-date recommendations into everyday practice. Understanding that treatment begins with awareness, JNC-7 identified known causes of hypertension and urged practitioners to monitor patients for these conditions.

The cause of 90 percent of hypertension cases is unknown (AHA 2002). In general, however, groups at risk for cardiovascular disease also are candidates for hypertension — the elderly, smokers, individuals with dyslipidemia or diabetes mellitus, and people who are obese, overweight, or physically inactive. These people should be screened routinely. In addition, the following conditions may cause hypertension:

- Sleep apnea
- Chronic kidney disease
- Primary aldosteronism
- Renovascular disease
- Chronic steroid therapy and Cushing’s syndrome
- Pheochromocytoma
- Coarctation of the aorta
- Thyroid or parathyroid disease
- Iatrogenic disease, nonadherence, and other drug-related causes

SOURCE: JNC-7 2003
Isolated systolic hypertension

JNC-7 stresses that in people older than 50, elevated SBP is a much more important risk for cardiovascular disease than DBP. The Framingham Heart Study established elevated SBP as a primary risk factor for cardiovascular disease (Kannel 2000). As early as 1992, evidence from the Multiple Risk Factor Intervention Trial suggested that SBP elevation was a stronger predictor of death from coronary heart disease than DBP (Figure 5).

Isolated systolic hypertension (ISH), in which SBP is elevated (≥140 mm Hg) but DBP is normal (<90 mm Hg), is a major contributor to poor hypertension control, in part because physicians historically have been trained to focus on DBP (Sennett 2000). ISH is common, particularly in patients with untreated hypertension (Figures 6 and 7).

FIGURE 5 Effect of hypertension on mortality

Source: Neaton 1992

FIGURE 6 Blood pressure of individuals with hypertension

From NHANES III data

FIGURE 7 Isolated systolic hypertension in individuals with untreated hypertension

Source for Figures 6 and 7: Lapuerta 1999
OVERVIEW

UTILIZATION AND ECONOMIC IMPLICATIONS

Office visits and hospitalizations
Hypertension is responsible for 457,000 hospital admissions per year (AHA 2002). It also is the number one reason, in terms of primary diagnosis, for visits to physician offices. Of the more than 823 million office visits in 2000, essential hypertension accounted for more than 1 of every 25 (Table 2).

TABLE 2 Office visits, 2000

<table>
<thead>
<tr>
<th>Primary diagnosis</th>
<th>Number of visits (millions)</th>
<th>Share of visits (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>35.1</td>
<td>4.3</td>
</tr>
<tr>
<td>Routine well-child visit</td>
<td>33.9</td>
<td>4.1</td>
</tr>
<tr>
<td>Acute upper-respiratory infections</td>
<td>30.7</td>
<td>3.7</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>23.6</td>
<td>2.9</td>
</tr>
<tr>
<td>Arthritis/related disorders</td>
<td>23.2</td>
<td>2.8</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>22.4</td>
<td>2.7</td>
</tr>
<tr>
<td>Cancer</td>
<td>21.8</td>
<td>2.6</td>
</tr>
<tr>
<td>General medical examination</td>
<td>18.3</td>
<td>2.2</td>
</tr>
<tr>
<td>Rheumatism (excluding back)</td>
<td>16.5</td>
<td>2.0</td>
</tr>
<tr>
<td>Ear infections</td>
<td>16.3</td>
<td>2.0</td>
</tr>
</tbody>
</table>

SOURCE: CHERRY 2002

The hidden costs of hypertension are in its complications. Hodgson (2001) estimated that the cost of health services for treatment of hypertension alone account for but a fraction of expenditures for hypertension-related disease (Figure 8). This aggregate estimate — $108.8 billion in 1998 — accounts for one eighth of total national health care expenditures, suggesting that substantial reductions in health spending could result from better control of hypertension.

FIGURE 8 Share of expenditures for hypertension-related illness
In billions. All ages, both sexes.

**Total spending:** $108.8 billion

Hypertension ($22.8)  Other diagnoses ($56.4)  Cardiovascular complications ($29.7)

Economic impact of hypertension
In terms of direct and indirect costs, hypertension carries a $50.3 billion annual price tag in the United States (Figure 9).

FIGURE 9 Estimated cost of hypertension

<table>
<thead>
<tr>
<th>Direct costs</th>
<th>(billions)</th>
<th>(per capita, annual)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs/medical durables</td>
<td>$17.8</td>
<td>$23</td>
</tr>
<tr>
<td>Physicians/other professional services</td>
<td>$9.2</td>
<td>$21</td>
</tr>
<tr>
<td>Hospital care</td>
<td>$5.1</td>
<td>$13</td>
</tr>
<tr>
<td>Nursing home care</td>
<td>$3.6</td>
<td>$10</td>
</tr>
<tr>
<td>Home health care</td>
<td>$1.5</td>
<td>$4</td>
</tr>
<tr>
<td><strong>Total direct expenditures</strong></td>
<td><strong>$37.2</strong></td>
<td><strong>$70</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Indirect costs</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Lost productivity/ morbidity</td>
<td>$7.0</td>
<td></td>
</tr>
<tr>
<td>Lost productivity/ mortality</td>
<td>$6.1</td>
<td></td>
</tr>
<tr>
<td><strong>Total indirect costs</strong></td>
<td><strong>$13.1</strong></td>
<td></td>
</tr>
</tbody>
</table>

*2003 estimates (AHA 2002).
†1995 expenditures (Hodgson 1999). Components add to $71, due to rounding.
‡ Lost future earnings of people who will die this year, discounted at 3 percent. The overall death rate from hypertension alone in 2002 was 16.2 people per 100,000 (AHA 2002).

*Slices of pie add to $108.9 billion due to rounding.

SOURCE: HODGSON 2001
Implications for MCOs
The financial goal of hypertension management is to prevent expensive clinical sequelae. Paramore (2001) studied the relationship between hypertension control and health care resource utilization among managed care patients in New Mexico, concluding that poor control of hypertension is associated with greater numbers of office visits (Table 3).

<table>
<thead>
<tr>
<th>TABLE 3</th>
<th>Relationship between hypertension control and office visits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure</td>
<td>Mean number of visits</td>
</tr>
<tr>
<td>Systolic &lt;120</td>
<td>4.1</td>
</tr>
<tr>
<td>Systolic ≥180</td>
<td>9.7</td>
</tr>
<tr>
<td>Diastolic &lt;85</td>
<td>5.5</td>
</tr>
<tr>
<td>Diastolic ≥100</td>
<td>10.0</td>
</tr>
</tbody>
</table>

SOURCE: PARAMORE 2001

Poor control also correlated with higher drug costs; in the Paramore cohort, the higher the patient’s blood pressure, the greater the medication expenditure (Figure 10).

FIGURE 10 Relationship between hypertension control, medication costs 1996–1997; study period, 1 year. BP in mm Hg.

<table>
<thead>
<tr>
<th>Blood pressure</th>
<th>Medication costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;130/85</td>
<td>$325.92</td>
</tr>
<tr>
<td>130/85–139/89</td>
<td>$407.66</td>
</tr>
<tr>
<td>140/90–159/99</td>
<td>$430.76</td>
</tr>
<tr>
<td>≥160/100</td>
<td>$577.95</td>
</tr>
</tbody>
</table>

SOURCE: PARAMORE 2001

CONCLUSION
Hypertension affects nearly 1 in 6 Americans and accounts for a large proportion of health care resource utilization. The relationship between hypertension and increased risk of cardiovascular disease is unequivocal. Health plans and practitioners that place an emphasis on detection and aggressive treatment will benefit from improved clinical and financial outcomes.

REFERENCES
Cherry DK, Woodwell DA. National Ambulatory Medical Care: 2000 Summary. Advance Data From Vital and Health Statistics. 2002(328); Table 12.
Management of Hypertension
In Light of the New National Guidelines

MARVIN MOSER, MD
Yale University School of Medicine

SUMMARY

The JNC-7 treatment recommendations, if followed by a majority of physicians, should help to reduce the number of resistant hypertensive patients in the United States and should result in an improved proportion of patients with controlled blood pressure.

National guidelines for hypertension management have been issued periodically over the past 26 years. These guidelines summarize available data on the diagnostic evaluation and treatment of hypertension. Committees appointed by the National Heart, Lung, and Blood Institute — whose members represent most major medical organizations in the United States — formulate them. Periodically, other groups also issue guidelines for management of hypertension and other cardiovascular (CV) risk factors. The model for these guidelines has been the reports of the Joint National Committees on Prevention, Detection, Evaluation and Treatment of High Blood Pressure.

The first JNC report (JNC-1), in 1977, was published at a time when a limited number of effective antihypertensive drugs were available and only a few long-term clinical treatment trials had been completed. Data regarding the relative merits of various antihypertensive medications were limited. The committee evaluated treatment results and published an algorithm based on the available information. This algorithm suggested that the “first-step drug should usually be a thiazide diuretic … starting with less than a maximal dose.”

The JNC-1 report stated, “If a diuretic proved ineffective and the therapeutic goal is not achieved, an additional drug should be added as the second step to the therapeutic program.” At that time, “second-step” drugs included reserpine, methyldopa, or propranolol (a beta blocker). The concept of adding one drug to another if the first was ineffective was labeled stepped care. The report noted that when a third drug was needed, “hydralazine or clonidine may be added to the regimen.”

Criticism of the report followed, some of which was based on the use of diuretics as initial therapy, despite data demonstrating their effectiveness. The committee was also criticized for recommending a “cookbook” approach to treatment. Critics noted that physicians should not be advised to follow a protocol-driven program; findings from numerous trials over the years, however, have reinforced the concept that controlling hypertension is more achievable when guidelines are followed.

Over the next 20 to 25 years, many large-scale, randomized blinded trials were completed, and many better-tolerated, more-effective medications were introduced — but the concept of stepped care continued to represent a reasonable approach to treatment. Nevertheless, the arguments about stepped care continued. Irvine Page, MD, a pioneer in the treatment of hypertension, commented on this in a 1985 editorial in Modern Medicine:

“We must not get snarled in nonproblems such as whether stepped care is good or bad. Stepped care is merely a way of presenting an orderly scenario in what otherwise threatens to join the New Yorker’s “Department of Utter Confusion.”

Subsequent reports were issued approximately every few years until 1997 (Table 1). These reports continued to stress lifestyle modifications as initial therapy, but
some changes were made in the recommendations for initial pharmacotherapy. For example, the 1984 JNC suggested diuretics and beta blockers as initial therapy. The 1988 JNC again recommended diuretics and beta blockers, but it suggested that angiotensin-converting enzyme (ACE) inhibitors and calcium channel blockers (CCBs) also could be used as initial treatment because they were widely prescribed at the time (despite their lack of long-term outcome data). JNC-6 (1997) advised a diuretic or a beta blocker with a diuretic as initial therapy for the elderly, and elaborated special reasons for the use of other agents. Studies continued to vindicate recommendations of diuretics as a preferred initial treatment.

**Updating clinical practice**

In 1997, the JNC departed from previous recommendations by suggesting that combination therapy might be appropriate as initial treatment in some patients. Concerns about this approach were raised repeatedly, primarily in academic centers, where the belief lingered that it would be difficult to determine which drug had been effective in lowering blood pressure (BP) and, if side effects occurred, which medication produced which side effect. Yet, numerous studies since 1997 have reported greater efficacy with low-dose combinations of two drugs from classes with different mechanisms of action than with higher doses of monotherapy, and without significant side effects (Moser 1997, Moser 1998).

Since 1997, clinical trial evidence has demonstrated a need to update JNC-6. Studies have confirmed that thiazide diuretics with or without a beta blocker are at least as effective as newer medications, such as ACE inhibitors and CCBs, in controlling BP and reducing CV and cerebrovascular events (Hansson 1999, VHAS 1998, INSIGHT 2000, ALLHAT 2000). In addition, studies have validated the concept that a majority of patients require more than one drug to reach goal BP (a beta blocker, ACE inhibitor, CCB, or angiotensin II receptor blocker (ARB), usually in combination with a diuretic (LIFE 2002, Agodoa 2001, Brenner 2001, Lewis 2001). Short-term studies had indicated that diuretics or CCBs were more effective in reducing BP in black patients and in the el-

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**TABLE 1** Evolution of the Joint National Committee recommendations prior to the JNC-7 report

<table>
<thead>
<tr>
<th>Step 1</th>
<th>Step 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>JNC-1 (1977) Stepped care</td>
<td>Diuretic</td>
</tr>
<tr>
<td>JNC-3 (1984) Stepped care</td>
<td>Less than full dose of diuretic or beta blocker</td>
</tr>
<tr>
<td>JNC-4 (1988) Individualized stepped care</td>
<td>Diuretic, beta blocker, calcium channel blocker, or ACE inhibitor</td>
</tr>
<tr>
<td>JNC-5 (1993) Modified stepped care</td>
<td>Diuretic or beta blocker</td>
</tr>
<tr>
<td></td>
<td>Substitute another drug or add second agent</td>
</tr>
</tbody>
</table>

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

SOURCE: MOSER 2002

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**TABLE 2** JNC-7 blood pressure classification

<table>
<thead>
<tr>
<th>BP classification</th>
<th>SBP (mm Hg)</th>
<th>DBP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;120</td>
<td>&lt;80</td>
</tr>
<tr>
<td>Prehypertension</td>
<td>120–139</td>
<td>80–89</td>
</tr>
<tr>
<td>Stage 1 hypertension</td>
<td>140–159</td>
<td>90–99</td>
</tr>
<tr>
<td>Stage 2 hypertension</td>
<td>≥160</td>
<td>≥100</td>
</tr>
</tbody>
</table>

SBP=systolic blood pressure; DBP=diastolic blood pressure.

SOURCE: JNC-7 2003
derly, while a beta blocker or an ACE inhibitor might be more effective in younger white patients (Materson 1995). Only about one half of patients will respond to any monotherapy, regardless of how carefully patients are evaluated and initial treatment is selected. Hence, the need for a stepped care approach, especially for patients with hypertension and other CV risk factors, such as diabetes or renal disease. Such patients often require two or three medications to produce goal BP levels and reduce CV events (Bakris 2002).

THE JNC-7 REPORT

JNC-7 recognizes and reemphasizes many issues raised in previous JNC reports. In addition, definitions of hypertension have been updated and modified, based on recent analyses of epidemiologic data (Table 2, page 13). The new definitions indicate increased risk for CV disease when systolic blood pressure (SBP) rises above 120 mm Hg. The designation of prehypertension for people with BP levels of 120–139 mm Hg (systolic) or 80–89 mm Hg (diastolic) does not imply that these individuals should be considered hypertensive or should be treated with medications. Some physicians disagree with this new designation, which may affect more than 22 million people. There may be merit to their argument, because there are no data to suggest that reducing BP from, for example, 135/88 to 120/80 mm Hg improves outcomes. Nonpharmacologic lifestyle modifications may, however, help prehypertensives to reduce their CV risk.

The JNC-7 report summarizes newer data on the benefits of nonpharmacologic approaches to reducing BP (e.g., weight loss, exercise, modification of alcohol intake, and consuming a low-sodium diet). A summary of possible BP-lowering effects of each of these interventions is presented in Table 3.

All JNC reports have recommended lifestyle modifications for all patients as initial and concurrent therapy. Yet, with lifestyle modifications alone, only about 20 percent of patients will achieve goal pressures (<140/90 mm Hg for most patients, <130/80 mm Hg for patients with diabetes or chronic kidney disease). BP levels may decline, but not enough. The majority of patients will have to take some medication.

It is of interest to review results of the only trial that compared nutritional (nonpharmacologic) intervention alone and nonpharmacologic therapy plus medication — the Treatment of Mild Hypertension Study (TOMHS). In this 4-year trial, all subjects were placed on a nonpharmacologic intervention that included an exercise and weight-loss program, nutritional guidance, and smoking cessation. There was a reduction of approximately 9/9 (systolic/diastolic) mm Hg in the nonpharmacologic intervention group. In subjects who received antihypertensive medications in addition to lifestyle interventions, a further BP reduction of 7/3 mm Hg was noted. At the end of the study, there was no difference in overall CV events among the five different drugs used (the study was not powered to show individual medication differences or spe-
cific event differences); lifestyle change plus medication, however, was superior to lifestyle intervention alone. The addition of medication further decreased BP and reduced the occurrence of overall CV events (Neaton 1993).

One question that guidelines committees address is, “How long should a patient be maintained on lifestyle interventions before specific medications are prescribed?” In a 45-year-old woman with a BP of 145–150/90–95 mm Hg and with no other risk factors, it might be appropriate to try lifestyle modifications alone for 3 to 6 months. On the other hand, a 45-year-old male smoker with hyperlipidemia and obesity should probably be put on medication either initially or after confirming the elevated BP and 3 to 4 weeks of nonpharmacologic therapy, even if he has the same BP as the 45-year-old woman (Moser 2002). Patients with diabetes should be put on medication at the same time as lifestyle interventions.

**JNC-7 THERAPEUTIC RECOMMENDATIONS**

Based on evidence from numerous controlled clinical trials, including the recently reported Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) (2002), JNC-7 has recommended that “thiazide diuretics be used as initial drug therapy for most patients with hypertension” (Figure 1). The report recognizes that many patients will require a second or even a third drug but that in any multiple-drug treatment program, a diuretic should be one of the medications used: “Addition of a second drug from a different class should be initiated when the use of a single drug in adequate doses fails to achieve goal blood pressure.” Emphasis is placed on the use of two or more medications in many situations — either as separate drugs or in fixed-dose combinations.

According to JNC-7, in patients with stage 2 hypertension (BP >160/100 mm Hg), “consideration should be given to initiating therapy with two agents, one of which should be a diuretic (e.g., beta blocker/diuretic, ACE inhibitor/diuretic, ARB/diuretic, or CCB/diuretic).” In addition, multiple drugs as initial therapy may be indicated in patients with stage 2 hypertension if they have diabetes, or if there is evidence of renal disease or coronary heart disease.

What are the justifications for these recommendations? It is well recognized that no matter how good a therapist is, no matter how carefully medication is titrated, and no matter which antihypertensive drug is used, BP will not be controlled with monotherapy in more than 50 to 60 percent of patients. Often, a second or a third medication is necessary to reduce BP to goal levels, especially in high-risk patients, such as those with diabetes or renal disease. If medications with different actions on different parts of the hypertension cascade are used, results will improve. Diuretics are underutilized. When more than one drug is used, a diuretic should be one of them, either as a first- or a second-line agent. Many of the so-called resistant hypertensives achieve control when a diuretic is added to their regimens.

Combination therapy makes physiologic sense. For example, a diuretic may raise plasma renin levels and increase the activity of the renin-angiotensin-aldosterone system (RAAS); a beta blocker decreases them. With a

### Table 3: Effect of lifestyle modifications on hypertension

<table>
<thead>
<tr>
<th>Modification</th>
<th>Recommendation</th>
<th>Approximate SBP reduction (range), mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight reduction</td>
<td>Maintain normal body weight*</td>
<td>5–20 per 10 kg lost</td>
</tr>
<tr>
<td>Adopt DASH† eating plan</td>
<td>Consume a diet rich in fruits, vegetables, and low-fat dairy products with a reduced content of saturated and total fat</td>
<td>8–14</td>
</tr>
<tr>
<td>Dietary sodium reduction</td>
<td>Reduce dietary sodium intake to no more than 100 mmol per day (2.4 g sodium or 6 g sodium chloride)</td>
<td>2–8</td>
</tr>
<tr>
<td>Physical activity</td>
<td>Engage in regular aerobic physical activity, e.g., brisk walking (at least 30 minutes per day, most days of the week)</td>
<td>4–9</td>
</tr>
<tr>
<td>Moderation of alcohol consumption</td>
<td>Limit consumption to 2 drinks (1 oz or 30 mL ethanol, 20 oz beer, 10 oz wine, or 2 oz 80-proof whiskey) per day in most men; ≤1 drink in women and lighter-weight people</td>
<td>2–4</td>
</tr>
</tbody>
</table>

* Body mass index 18.5–24.9 kg/m². † DASH=Dietary Approaches to Stop Hypertension. The effects of implementing these modifications are dose- and time-dependent and could be more dramatic for some individuals.

SOURCE: JNC-7 2003
diuretic/beta blocker combination, renin levels remain essentially at baseline. Aldosterone levels may also rise with a diuretic but are reduced with a beta blocker. When the two agents are used together, aldosterone levels remain essentially unchanged.

The rise in renin or aldosterone may not negate the BP-lowering effects of the diuretic, but adding an agent that neutralizes the effects of activation of the RAAS, such as a beta blocker, ACE inhibitor, or ARB, increases effectiveness. Response rates go from 40 to 50 percent for monotherapy to as high as 75 to 80 percent.

Racial differences in response also disappear with combination therapy when combining ACE inhibitors or ARBs with a diuretic. Black patients do not respond very well to ACE inhibitors or ARBs as monotherapy; this population responds better to diuretics. In a black patient, therefore, using a diuretic with either of these other classes or with a beta blocker will increase response. JNC-7 recognized these facts in advancing the new treatment algorithm.

Low-dose combination therapy has withstood the test of time. There are no outcome studies with specific combinations, but it is clear that most patients require more than one drug to achieve goal BP. Low-dose combinations also have compliance advantages over the use of two drugs separately (Moser 2000).

**Compelling indications**

This new report also recognized compelling reasons for the use of specific medications (Table 4). For example, in patients with heart failure and hypertension, use of an ACE inhibitor, ARB, beta blocker, or aldosterone antagonist along with a diuretic is indicated.

In patients with diabetic nephropathy, an ACE inhibitor or an ARB are medications of choice, but it is often necessary in these patients to use a diuretic to achieve goal BP. The report notes that the use of an ACE inhibitor or an ARB in a treatment program may reduce the occurrence of new-onset diabetes.

**Blood pressure treatment goals**

In 1997, JNC-6 emphasized the importance of SBP in estimating risk and guiding therapy. This point is reemphasized in JNC-7. Most physicians would not hesitate to treat a patient with a persistent diastolic BP (DBP) 95–100 mm Hg, but — based on recent treatment data — many do not treat SBP 150–159 mm Hg. However, the relative risk of a cardiac event with this level of SBP is considerably greater than when DBP is 95–100 mm Hg (Figure 2).

A majority of hypertensive patients who are uncontrolled are those with elevated SBP. Framingham Heart Study data indicate that over time, people with SBP 140–159 mm Hg have a poorer prognosis when compared to those with SBP <140 mm Hg (Table 5).
the benefit or if specific medications affect outcomes.

In 1999, a World Health Organization committee reviewed the available data on the treatment of hypertension and concluded that reducing BP, as opposed to the choice of medication, accounted for most of the benefit (WHO 1999). The committee recommended diuretics, beta blockers, ACE inhibitors, CCBs, or alpha blockers as initial therapy. But is there is at least some difference in outcome with different medications? Most available medications—diuretics, beta blockers, ACE inhibitors, ARBs, and CCBs—reduce BP with appropriate doses. There may be a slight difference in the degree of reduction, but this may not be of great significance.

Another pertinent question is, “Is there a difference in the effect of various medications on certain organs, such as the heart?” What about left ventricular hypertrophy (LVH)? All available medications except for hydralazine and minoxidil, the direct vasodilators, reduce left ventricular mass if LVH was present before instituting therapy. Two carefully conducted prospective placebo-controlled studies have compared the effects of multiple medications on LVH over a 2 to 4 year period (Figure 5, page 18). All the drugs resulted in regression of LVH, with the ACE inhibitor and diuretic somewhat more effective than the CCB (Gottdiener 1997). If blood pressure is reduced with any of the available antihypertensive agents (except the vasodilators), LVH will be reduced.

Numerous comparative trials have indicated that a diuretic or diuretic/beta blocker-based treatment regimen reduces CV events to a greater degree than a CCB- or ACE inhibitor-based program. Meta-analyses suggest that while a CCB-based regimen reduces strokes to a greater or greater degree, the occurrence of myocardial infarction or coronary heart failure is less with other therapies, such as diuretics or ACE inhibitors (Pahor 2000).

In addition to data reporting a dramatic reduction in stroke incidence through the treatment of hypertension, a recent trial of a diuretic/ACE inhibitor combination reported reduced incidence of recurrent cerebrovascular events in patients who had had a previous stroke (Figure 4, page 18). In the ACE inhibitor-alone group, results

### TABLE 4 Compelling indications for specific medications

<table>
<thead>
<tr>
<th>Condition</th>
<th>Diuretic</th>
<th>BB</th>
<th>ACE</th>
<th>ARB</th>
<th>CCB</th>
<th>AA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart failure</td>
<td></td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Postmyocardial infarction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High coronary disease risk</td>
<td></td>
<td>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td>*</td>
<td></td>
<td>*</td>
<td></td>
<td>*</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent stroke prevention</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>*</td>
<td></td>
</tr>
</tbody>
</table>

BB=beta blocker; ACE=angiotensin-converting enzyme inhibitor; ARB=angiotensin II receptor blocker; CCB=calcium channel blocker; AA=aldosterone antagonist.

SOURCE: JNC-7 2003

### TABLE 5 Long-term risk for CV disease morbidity and mortality

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Increase in risk (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular disease</td>
<td>47</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>44</td>
</tr>
<tr>
<td>Stroke or transient ischemic attack</td>
<td>42</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>60</td>
</tr>
<tr>
<td>Cardiovascular disease death</td>
<td>57</td>
</tr>
</tbody>
</table>

CV=cardiovascular; SBP=systolic blood pressure; TIA=transient ischemic attack.

*Adjusted for age, sex, cholesterol level, body mass index, glucose intolerance, and cigarette use.

SOURCE: SAGIE 1993

At the end of a long follow-up period, the incidence of CV disease, coronary heart disease, transient ischemic attack (TIA), heart failure, and CV-disease death were statistically significantly higher in individuals who originally had this degree of SBP elevation compared with those whose SBP was <140 mm Hg. The message of both JNC-6 and JNC-7 is to treat even minimal elevations of SBP. Elsewhere in this publication, Kannel reviews data on the relative importance of SBP and DBP.

Trial results have indicated that even patients with a less-severe degree of hypertension (stage 1, 140–159/90–99 mm Hg) should be treated to prevent progression to more severe hypertension or organ damage (Figure 3).

### Specific medications, different outcomes?

A key question in formulating guidelines is: “Is it the blood pressure alone that makes a difference in outcome, or should more attention be paid to specific medications or specific interventions?”

Until 1997, most outcome data in hypertensive patients had been obtained with diuretics and beta blockers; one study in the elderly used CCBs. In recent years, this has changed. In establishing an algorithm for treatment, the JNC scrutinized newer studies to answer the question of whether reductions in BP alone account for

### Note

JNC-7 GUIDELINES
were not significantly better than those of the control group. These results indicate that if a hypertensive patient has a history of cerebrovascular attack or TIA, then blood pressure should be lowered. Multiple medications may be necessary to achieve this.

JNC-7 bases its conclusions on more data than were available for previous JNC reports. Some conclusions, however, are similar: a thiazide diuretic remains preferred initial therapy in a majority of patients; other medications should be added if goal BP is not achieved; emphasis is placed on multiple-drug therapy, even as a first step in some patients. This is an effective way to treat many hypertensive patients. Abundant data demonstrate that when a specific treatment plan is followed, outcomes improve.

**Improving outcomes**

What have we accomplished and how can we improve outcomes? The percentage of hypertensive Americans who have achieved goal BP (<140/90 mm Hg) is only 34 percent (JNC-7 2003), despite the availability of safe and effective medications and considerable effort on the part of many organizations. I believe, however, that the control rate is improving more rapidly than national data suggest.

Poor control of SBP accounts for much of the poor statistics on BP control. This is illustrated by a 2-year Veterans Administration study in the elderly (Berlowitz 1998). At the study’s end, 40 percent of subjects still had SBP >140 mm Hg. These patients had been seen an average of 5 to 6 times a year. It appeared that poor physician implementation of a treatment program, rather than poor patient adherence, was an important cause of the results. Medication had been increased in only 25 percent of patients with SBP >155 mm Hg and even less often in patients with SBP >165 mm Hg. Patients are often singled out for lack of adherence, but many physicians do not pay as much attention to achieving goal BP, especially SBP, as they should (Moser 2001).

Some specific ways to improve outcomes:

1. Emphasize that SBP elevations are important and treat them more effectively.
2. Publicize the benefits of the treatment trials in the young, middle-aged, and especially the elderly.
3. Use medication more effectively. There are many effective and safe medications available; the newest drug on the market is not always the best one to use.
4. Use multiple medications in more patients and include a diuretic as one of the medications.

**CONCLUSIONS**

The treatment of hypertension is rewarding but often dull. It is neither like the TV program *ER* nor as dramatic as treating a diabetic coma, but over time it is exciting to realize that many more people with hypertension today...
will not experience strokes, die prematurely of end-stage renal disease, or experience a CV event.

There is little doubt about the benefits of ACE inhibitors, CCBs, ARBs, beta blockers, and diuretics in improving outcomes. There also is little doubt that these drugs should and will be used more frequently in the future if we set appropriate treatment targets. There is good evidence that blocking the renin-angiotensin system should be an integral part of therapy in many patients, especially those with diabetes or renal disease. It may also be true that using an ACE inhibitor or an ARB may prevent some cases of new-onset diabetes, especially in patients with the metabolic syndrome. The present guidelines take these factors into consideration and recognize the need for more than one medication in many cases.

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MRFIT. Mortality rates after 10.5 years for participants in the Multiple Risk Factor Intervention Trial. JAMA. 1990;263:1795–1801.


Outcomes Trials Underlying The JNC-7 Guidelines

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SUMMARY

Guidelines in medicine have become useful instruments to improve outcomes for many diseases. The JNC-7 report puts the available data into perspective and provides suggestions to physicians and health plans for improving treatment. The JNC-7 guidelines are based on sound scientific evidence.

Comparative outcomes trials influenced the development of the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7). Many of these results have been reported within the past 3 to 5 years. Some of these include the Verapamil in Hypertension and Atherosclerosis Study (VHAS), the United Kingdom Prospective Diabetes Study (UKPDS), the Swedish Trial in Older People (STOP-2), the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), the Hypertension Optimal Treatment (HOT) study, the Reduction of End Points in type 2 Diabetes With the Angiotensin II Antagonist Losartan (RENAAL) study, and the Australian National Blood Pressure Study (ANBP 2). The JNC-7 panel carefully analyzed each of these studies in formulating the present medical consensus.

The VHAS trial

Verapamil, a nondihydropyridine calcium channel blocker (CCB), was compared to chlorthalidone, a diuretic. At the end of this 2-year study, there was no difference in adverse events, no difference in fatal or nonfatal cardiovascular (CV) events, and no difference in total cholesterol or glucose levels between the two medications (VHAS 1998). What did this trial demonstrate? A nondihydropyridine CCB appeared to be as effective in reducing CV events as a diuretic. Studies and meta-analyses had reported that the use of some CCBs, especially the shorter-acting dihydropyridines, had resulted in an increase in CV events (Pahor 2000). The VHAS trial reported equivalency with a nondihydropyridine CCB and a diuretic.

The UKPDS

An ACE inhibitor-based treatment group was compared to a beta blocker-based treatment group. More than 1,100 diabetic patients were followed for 8.5 years. A majority of patients in both groups also received a diuretic. There was no difference in CV events between the groups (UKPDS 1998).

Nevertheless, outcomes differed, due to differences in blood pressure (BP). In the UKPDS, there was a difference of 10/5 mm Hg between “tight” and “less tight” BP groups — 144/82 mm Hg compared to 154/87 mm Hg, respectively. The difference in BP between these groups resulted in a significantly lower incidence of stroke (44 percent), heart failure (56 percent), and microvascular disease (proteinuria or retinopathy) (37 percent) in the diabetic patients (UKPDS 1998).

Prior to this trial, there had been concern that, because beta blockers may increase insulin resistance, these agents should not be used in type 2 diabetes patients. The results of this trial indicate, however, that beta blockers can be used in these patients. Repeated cautions about using these agents in CHF had also arisen because beta blockers decrease the effect of catecholamines on cardiac function. But catecholamines may be toxic to a failing myocardium, and beta blockers, which block their action, have been found to be effective in the treatment of CHF.

As in the VHAS study, the UKPDS trial suggests that the lowering of BP, not the use of specific medications, improves outcome. (It should be emphasized that this trial — like most that determine recommendations — did not compare two monotherapies; multiple medications were used in both groups).
Additionally, while glycemic control in diabetes patients is helpful in correcting endothelial dysfunction and in reducing microvascular events, the benefits of lowering BP in the UKPDS study were greater than those achieved through glycemic control (although HbA1c levels were not reduced to <7 percent, the goal level advocated by most diabetes experts (Figure 1, page 22).

STOP-2

This study compared older conventional drugs (diuretics and beta blockers) to ACE inhibitors and CCBs. After 5 years, there was no difference in outcomes in terms of CV events between the diuretic/beta blocker and ACE inhibitor/CCB groups (Figure 2, page 23). Blood pressures were reduced to an equivalent degree in the two groups (Hansson 1999). This study again appears to suggest that it is the reduction in BP, not the use of specific medications, that make the difference in outcomes. While there was no difference in CV events between the beta blocker/diuretic group and the ACE inhibitor/CCB group, there were some differences in some subsets of patients. There were fewer MIs and episodes of CHF in the ACE inhibitor group compared to the CCB group (Figure 3, page 24).

Different outcomes with different drugs — the ALLHAT trial

The World Health Organization (WHO) guidelines in 1999 recommended that alpha blockers, as well as other classes of medications, could be used as initial therapy (WHO 1999). The JNC-6 (1997) and JNC-7 (2003) reports did not make this recommendation. ALLHAT results helped to clarify this issue.

At the end of 3 years of a comparative study of an alpha blocker (doxazosin) in 9,064 patients and chlorthalidone in 15,266 patients as part of the antihypertensive antilipid study in the United States, it was noted that chlorthalidone decreased BP more than doxazosin and, most importantly, that the number of combined CV events was reduced by 25 percent with chlorthalidone as compared to the alpha blocker (ALLHAT 2002). This did not suggest that the use of the alpha blocker caused more CV events; rather, results indicated that a diuretic was more effective in reducing them. Recommendations followed (even before the JNC-7 report) suggesting that alpha blockers should not be considered as preferred initial therapy. On the basis of these data, a change in the WHO recommendations seems warranted.

Target blood pressures

Target blood pressures are also addressed in guidelines. In the HOT study, three different DBP goals were set: 90, 85, and 80 mm Hg. Achieved DBP levels were actually 85, 83, and 81 mm Hg. Diabetics who achieved lower DBP levels had fewer CV events. Most of the benefit, however, occurred in the overall group of patients by lowering BPs to <140/90 mm Hg (Hansson 1998). Thus, target BPs established in recent recommendations for patients other than diabetes patients appear to be appropriate.

The J-curve

The J-curve is another consideration when setting BP goals. The J-curve implies that if the DBP is decreased to <85 mm Hg or <80 mm Hg, especially in a patient with a plaque or evidence of ischemic heart disease, coronary filling (which occurs during diastole) will be decreased and an ischemic episode might occur. There was no evidence of a J-curve phenomenon in the HOT study, even in patients with DBP <80 mm Hg.

In the Systolic Hypertension in the Elderly Program (SHEP), a decrease in benefit was not noted until the DBP decreased to <55–60 mm Hg (SHEP 1991). A message from the SHEP trial might be this: In an older person whose DBP decreases to <50–60 mm Hg, therapy might be moderated. Fortunately, this does not happen often. Recent guidelines do not set a level below which BP should not be lowered.

The event rate in the HOT trial was lower than rates in other clinical trials. While it is difficult to compare trial A to trials B or C due to different demographics and study protocols — HOT results may be of importance. In the HOT study, more patients achieved goal BP than in other outcomes trials. In this study, only 8.5 percent of people maintained a DBP >90 mm Hg. In most other trials, about 20–25 percent continue to have DBP of >90 mm Hg. This may account for the fewer events in this trial. Certainly, JNC-7 considered these facts.

ANGIOTENSIN II RECEPTOR BLOCKERS (ARBs)

Where do ARBs fit into the new treatment algorithm? Consideration of these newer agents was important in the JNC-7 deliberations. Some long-term trial data are available for these agents, which decrease BP as well as ACE inhibitors do. Their use will result in regression of left ventricular hypertrophy (LVH), if present, and they have the same hemodynamic effects in CHF as ACE inhibitors. Even before results of recent trials, many experts believed that the ARBs could probably be used interchangeably with ACE inhibitors, especially in patients who developed an ACE inhibitor-induced cough, but sufficient data were lacking to lead to this recommendation.

Several recent trials have clarified the role of these agents, especially in diabetes patients and, in particular, diabetes patients with evidence of renal disease. The Irbesartan Diabetic Nephropathy Trial (IDNT) study included more than 1,700 type 2 diabetes patients with pro-
teinuria, many of whom had significant proteinuria. In this trial, an ARB-based treatment group was compared with two other groups of patients. One group (the control group) received medications other than an ARB, and the other group was treated with a CCB-based regimen. There was a decrease in progression of renal disease and a lengthening of the time to doubling of creatinine in the ARB group compared to the control group or the group of patients on a CCB (amlodipine). Type 2 diabetes patients with evidence of nephropathy clearly benefited from treatment with the ARB (in addition to other medications) (Lewis 2001).

The RENAAL study with losartan also demonstrated the benefits of using an ARB in a treatment program in type 2 diabetes patients with nephropathy. A statistically significant reduction in end-stage renal disease in patients on the ARB was noted when compared to a group of patients who were not receiving losartan. As in all the other trials, a large majority of people were also receiving either a diuretic or a diuretic and a beta blocker (Brenner 2001).

These trials have provided evidence that the addition of an ARB to a treatment regimen reduces progression of renal disease in diabetes patients.

The Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study in patients with LVH was an investigation among more than 9,000 patients with an average age of 67, who predominantly had systolic hypertension (baseline BP=174/98 mm Hg). Many subjects in this study had vascular disease. In this trial, patients being treated with an ARB (losartan) were compared to a beta blocker group (atenolol). More than 70 percent in each group required the use of multiple medications to achieve goal pressures. Final BPs were 144/82 mm Hg in each group (LIFE 2002).

Results indicated that a regimen that included the use of losartan reduced overall primary end points (primarily stroke) more than a beta blocker-based regimen. There was no difference in outcome between the beta blocker-based and the ARB-based groups in terms of MI, CV disease, or total mortality. These data suggest that, in addition to preventing progression of proteinuria in patients with type 2 diabetes and preventing progression in more severely hypertensive patients with nephropathy, an ARB-based regimen also may be more protective than a beta blocker-based treatment program in reducing strokes in hypertensive patients with LVH.

ALLHAT

ALLHAT was a strong influence on the JNC-7 guidelines and warrants some discussion. This landmark trial was the largest single study of hypertensive individuals ever undertaken (ALLHAT 2000, ALLHAT 2002). It was the first major long-term outcomes trial directly comparing a diuretic-based treatment with a CCB, ACE inhibitor, and an alpha blocker.

More than 40,000 hypertensive patients with at least one other coronary heart disease risk factor were entered into the trial and followed for more than 5 years. The mean age was 67; 36 percent of patients were diabetic; 35 percent were black. After all previous medications were stopped, patients were randomly assigned blinded treatment with a diuretic (chlorthalidone), a beta blocker (atenolol), a CCB (amlodipine), an ACE inhibitor (lisinopril), or an alpha blocker (doxazosin). Doses could be increased and additional drugs from other classes could be added in an effort to achieve goal BP levels.

In ALLHAT, there were, however, some limitations to add-on therapy. The additional drugs were limited to nonstudy drugs, meaning that if a patient had not reached goal pressures on increasing doses of a diuretic, another drug could be added — a beta blocker, clonidine, methyldopa, reserpine, or hydralazine, but not an ACE inhibitor or a CCB. If patients failed to respond to the ACE inhibitor, a beta blocker or other drugs could be added, but a diuretic or a CCB could not. The ALLHAT

**FIGURE 1** Effects of tight glucose control vs. tight blood pressure control (UKPDS)

DM=Diabetes mellitus.

ADAPTED FROM UKPDS 1998, UKPDS 2000
protocol, therefore, may not reflect what physicians do in actual practice.

At the beginning of the study, less than 30 percent of hypertensive patients had been controlled to ≤140/90 mm Hg, despite the fact that more than 90 percent of them were receiving some kind of antihypertensive therapy prior to entering the study.

As noted, after 3 years, the alpha blocker/diuretic comparison arm of the trial was stopped. Results had indicated that patients in the alpha blocker group had experienced 25 percent more CV events and double the incidence of CHF, compared to those in the thiazide diuretic group.

After 5 years of follow-up, of the remaining 33,000 patients, more than 90 percent had attained goal DBP of <90 mm Hg, and 67 percent had achieved SBP of <140 mm Hg (Cushman 2002). These results were achieved by following a fixed protocol that included a careful follow-up. The findings demonstrated that hypertensive patients can be controlled better in a practice setting with some established guidelines than national statistics suggest. Previous data had suggested control of DBP in 60–70 percent of patients with a lesser degree of control of SBP (<30–35 percent of patients controlled below 140/90 mm Hg). ALLHAT data indicated that more careful attention to the achievement of goal pressures, even with the use of potentially suboptimal add-on medication, would still control BP at goal levels in a relatively high percentage of patients — an important message.

The final ALLHAT results indicated that, while there were no differences in the primary outcome of fatal or nonfatal coronary heart disease events and no mortality difference among the ACE inhibitor, CCB, and diuretic groups, patients receiving the diuretic experienced fewer overall CV events than those on the other agents. There were some differences in outcomes on selected end points. For example, patients on diuretics had a lower incidence of heart failure and strokes than the group randomized to receive lisinopril. This was especially true in black patients. The risk of hospitalized/fatal heart failure was not, however, significantly different. Diuretics were also more effective in reducing the occurrence of heart failure (hospitalized or fatal) than the amlodipine group.

**Second-step drugs in ALLHAT**

The choice of second-step drugs in ALLHAT could have made a difference in outcomes. There was some difference in achieved BPs in ALLHAT among the three drugs tested. On average, SBP were 4 mm Hg lower with diuretics than with lisinopril in black subjects and 3 mm Hg lower in patients at least 65 years old. Overall, SBP levels were 2 mm Hg higher in the ACE inhibitor group when compared to the diuretic cohort. These results were not unexpected, given the demographics of the patients studied; as noted, black subjects and the elderly generally experience a greater decrease in BP on diuretics compared to medications that block the renin-angiotensin-aldosterone system.

The SBP was 0.8 mm Hg higher and the DBP was 0.8 mm Hg lower with amlodipine compared to chlorthalidone. These results are similar to those noted in other comparative studies.

The ALLHAT protocol may have contributed, at least partially, to the difference in outcomes. For example, if a diuretic had been routinely added to the ACE inhibitor, the difference in BPs between groups probably would have been less; this combination usually reduces or eliminates differences in response to ACE inhibitors between black and white patients. It is also possible that any difference in outcomes between the ACE inhibitor and diuretic-based treatment groups would have been minimized or eliminated, especially regarding heart failure events. In addition, an ACE inhibitor/CCB combination might have minimized differences in heart failure outcomes. Despite this lack of more logical choices of second-step medications, a large number of patients achieved goal BP.

**FIGURE 2**

 Patients who reached primary endpoint (STOP-2)

ACE=angiotensin-converting enzyme.

SOURCE: HANSSON 1999
and the ALLHAT and ANBP-2 results might have been similar. But there were some problems with the ANBP 2 study. It was not blinded and only 60 percent of patients remained on the initial study drug. More than 25 percent of patients crossed over from diuretics to the ACE inhibitor, and vice versa. Although the ACE inhibitor-based group in this trial experienced fewer CV events than the diuretic group, the benefit occurred only in male patients. There were no statistically significant differences in outcome between the ACE inhibitor and the diuretics in women — a point that is difficult to explain.

While it is easy to criticize the ANBP 2 trial, faults also can be found with ALLHAT. A perfect trial has never been designed or carried out. But are the results of ALLHAT and ANBP 2 truly different? Can both results be believed with some qualifications? These are questions for guideline committees to ponder further.

**CONCLUSIONS**

The recent JNC-7 guidelines appear to reflect a reasonable approach to the debate over the best agents for improving cardiovascular outcomes. The recommendations rely on evidence not only from ALLHAT but also from many other trials. It is reasonable to continue to suggest the use of diuretics as one of the cornerstones of treatment. The European Society of Hypertension guidelines are less specific with regard to the uses of a particular medication as initial therapy (European Society 2003). The belief that BP lowering, and not a particular medication choice, makes most of the difference in outcomes is what led this group to conclude that any one of the drug classes could be used as initial treatment. This
report from Europe emphasizes the use of monotherapy, but noted that most patients will require multiple drugs to achieve goal BP levels. Specific indications for particular agents are similar to those in JNC-7. The debate relative to the treatment of hypertension should not be about “My drug is superior to your drug,” or “My study is better than your study.” It should be about getting as many people to goal BP levels as possible with the least intrusion on their life or their pocketbook. Numerous trials prior to ALLHAT had reported that ACE inhibitors and CCBs reduced morbidity and mortality in hypertensive patients with or without diabetes and with or without renal disease. The ALLHAT study did not report that these agents should not be used, nor that they were dangerous or ineffective.

Guidelines in medicine have become useful instruments to improve outcomes for many diseases besides hypertension. The JNC-7 guidelines represent an attempt to put all the available data in perspective, and they offer suggestions to physicians for improving treatment. They are based on good scientific evidence.

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Progression of Uncontrolled Hypertension and Implications For Managing Its Sequelae

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SUMMARY

Cardiovascular risk, which increases incrementally with blood pressure, is most closely related to systolic pressure. Isolated systolic hypertension and increased pulse pressure are hazardous. Because hypertension seldom occurs in isolation from other atherogenic risk factors that augment its risk, global risk assessment is mandatory for evaluating the hazard and the nature and intensity of treatment required. The predominant component of uncontrolled hypertension resides in systolic blood pressure.

One in four adult Americans is hypertensive. Hypertension, and in particular systolic hypertension, is a powerful independent predictor of cardiovascular disease (CVD), the leading cause of death in the United States. Among the elderly in the general population, 27 percent of CVD in women and 32 percent in men is attributable to hypertension. The major portion of CVD promoted by hypertension relates to atherosclerotic progression of uncontrolled or inadequately controlled hypertension (Table 1). Among elderly persons with hypertension, as much as 33 percent of the CVD in men and 64 percent in women occurs in those who are already on treatment (Kannel 1998a).

The JNC-7 guidelines acknowledging epidemiologic data now emphasize that even modest increases in marginally elevated blood pressure (BP) within the “high-normal” range significantly elevate the risk of CVD (Kannel 1985, Neaton 1995, JNC-7 2003). Framingham Study investigation of the CVD risk associated with high-normal BP (130–139/85–89 mm Hg), compared with optimal BP (<120/80 mm Hg), found it imposed a 2.5-fold hazard ratio in women and 1.6 in men. Risk of myocardial infarction (MI), heart failure, stroke, renal disease and peripheral vascular disease rises incrementally with BP elevations (Kannel 1985, Neaton 1995). In fact, a recent meta-analysis of data for 1 million adults in 61 prospective studies, contributing 56,000 vascular deaths for analysis, indicates that hypertension-related cardiovascular damage begins at BP levels as low as 115/75 mm Hg (Prospective studies collaboration 2002). Data suggest that these perceived hazardous BP levels have continued to decrease over recent decades (MacMahon 1990).

By restructuring the hypertension guidelines, the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC), has responded to the perceived urgency for treatment at...
Early intervention is not yet standard clinical practice, however, despite guidelines that recommend intervening early, focusing on systolic blood pressure (SBP), and treating to aggressive goals, even in patients whose BP is in the high-normal range. We need to abandon out-of-date hypertension diagnostic and treatment practices.

Despite periodic improvements in diagnosis and treatment of elevated BP, hypertension remains the most prevalent vascular disease in the United States and a dominant cause of death in the American population. Besides causing suffering from organ diseases and premature death, hypertension and resultant CVD are responsible for excessive health care costs.

Consider these statistics: uncontrolled hypertension costs the United States health care system an estimated $964 million annually. Costs to treat individuals with established CVD who fail to attain goal BP adds $467 million in direct medical expenditures (Flack 2002). Yet 30 percent of individuals with hypertension are unaware that they have the disease, and only 34 percent of those on treatment are adequately controlled (<140/90 mm Hg) (JNC-7 2003). These statistics reflect the unacceptably high cost of hypertension-induced CVD that contributes to exorbitant health care spending. To improve antihypertensive treatment for a substantial portion of adult Americans is not an easy task, requiring subtle but crucial shifts in diagnosis and treatment.

One important shift is that of using SBP rather than diastolic blood pressure (DBP) as the chief hypertensive risk marker for patients over age 50. Most of the uncontrolled hypertension observed in the Framingham Heart Study was concentrated in patients with isolated systolic hypertension (ISH); this pattern holds true particularly for the elderly, blacks, the obese, and diabetics (Lloyd-Jones, 2000). Isolated systolic hypertension denotes a wide pulse pressure, reflecting a dangerous stiffening of the arterial vasculature that is associated with increased risk of CVD (Franklin 1997).

Second, while keeping in mind that SBP is a predominant marker for CVD risk, clinicians must also discern the hypertensive patient’s risk profile as a whole, taking into consideration all risk factors such as those comprising the “metabolic syndrome” that globally affect an individual’s risk for the development of hypertensive CVD sequelae.

This article describes the risks conferred by progressive uncontrolled hypertension, with special emphasis on the increasingly important role of SBP in defining a new treatment framework that incorporates new clinical evidence.

### TABLE 1 Population-attributable risk for cardiovascular disease, by blood pressure category

<table>
<thead>
<tr>
<th>Framingham Heart Study subjects, age 65–94</th>
<th>% of population (total) CVD attributable to elevated BP</th>
<th>Proportion of total hypertension risk attributable to stages of high blood pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal</td>
<td>Stage 1</td>
</tr>
<tr>
<td>Men</td>
<td>31.6%</td>
<td>6.6%</td>
</tr>
<tr>
<td>Women</td>
<td>26.5%</td>
<td>2.3%</td>
</tr>
</tbody>
</table>

*High normal=130–139/85–89 mm Hg; stage 1=140–159/90–99 mm Hg; stage 2=160–179/100–109 mm Hg; stage 3=≥180/110 mm Hg.

SOURCE: KANNEL 1998

### PREVALENCE AND INCIDENCE

Approximately one quarter of the United States adult population has hypertension, defined as a BP of >140/90 mm Hg (Burt 1995, JNC-6 1997). The prevalence of hypertension increases with advancing age. While approximately 4 percent of Americans under age 30 are affected, prevalence rates escalate to 71 percent beyond age 80 (NHLBI 2000). Men are more likely than women to have CVD attributable to hypertension; blacks have higher age-adjusted prevalence rates (32.4 percent) compared with non-Hispanic whites (23.3 percent) and with Mexican-Americans (22.6 percent) (Burt 1995).

After age 30, the age-related prevalence of hypertension increases in relation to baseline BP. Vasan assessed the rate of progression from normotension (<140/90 mm Hg) to hypertension (≥140/90 mm Hg) among 4,200 men and 5,645 women participating in the Framingham Study. Participants were assigned to optimum (<120/80 mm Hg), normal (120–129/80–84 mm Hg), or high-normal (130–139/85–89 mm Hg) groups, according to baseline BP. The investigators followed the increasing rate of hypertension for 4 years and then computed the probability of developing hypertension for the three groups. Investigators observed a stepwise increase in risk across the three baseline BP groups (Figure 1), with the likelihood of developing hypertension at different ages remaining 2 to 3 times greater among those with higher baseline BP. This increase in risk is highly modifiable, and effective treatment has been shown to result in significant reductions in occurrence of stroke, coronary heart disease (CHD) heart failure, and renal insufficiency (Collins 1990, Shulman 1989, Hebert 1993).

The $	extast{normal}$ normal child has a blood pressure that is in the high-normal range. We need to abandon out-of-date hypertension diagnostic and treatment practices.

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One important shift is that of using SBP rather than diastolic blood pressure (DBP) as the chief hypertensive risk marker for patients over age 50. Most of the uncontrolled hypertension observed in the Framingham Heart Study was concentrated in patients with isolated systolic hypertension (ISH); this pattern holds true particularly for the elderly, blacks, the obese, and diabetics (Lloyd-Jones, 2000). Isolated systolic hypertension denotes a wide pulse pressure, reflecting a dangerous stiffening of the arterial vasculature that is associated with increased risk of CVD (Franklin 1997).

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This article describes the risks conferred by progressive uncontrolled hypertension, with special emphasis on the increasingly important role of SBP in defining a new treatment framework that incorporates new clinical evidence.
with higher baseline BP levels within the nonhypertensive range. Normotensive persons at age 55 years had a 90 percent chance of developing hypertension in their lifetimes (Vasan 2001).

**CLINICAL IMPACT: HAZARDS OF UNCONTROLLED HYPERTENSION**

As a major precursor to the leading causes of death, hypertension is known as the “silent killer” because it, per se, does not usually produce symptoms; this may contribute to nonadherence to prescribed treatment regimens. Clinicians should no longer wait until frank hypertension is evident to insist on compliance. Based on meta-analysis of a massive amount of data, it has been determined that there is a continuous graded increment in risk of CVD mortality beginning at blood pressures as low as 115/75 mm Hg (Prospective Studies Collaboration 2002). Lewington (2002) estimates the incremental risk after age 40 such that each 20/10 mm Hg increment in BP (up to 185/115 mm Hg) doubles the risk of CVD. In the Framingham Study, the average BP preceding development of CHD was only 141/81 mm Hg among men and 142/79 mm Hg among women; corresponding pulse pressures were 59.2 mm Hg and 62.8 mm Hg, respectively.

**Disease progression**

**Atherosclerosis and coronary heart disease**

Statistically, heart failure is the greatest outcome of uncontrolled hypertension (when expressed as a risk ratio), but CHD is actually the most prevalent hazard of hypertension progression; the incidence of CHD equals that of all other hypertensive CVD sequelae combined (Kannel 2000a). The cumulative incidence of coronary events among hypertensive men is generally double that of women, but the risk ratios are higher among women.

Individuals, especially those over age 65 years, with BP levels ≥140/90 mm Hg or on treatment for hypertension, are prone to angina pectoris, MI, and sudden death at a rate that is 2 to 3 times greater than their normotensive counterparts (Wilson 1995). The presence of left ventricular hypertrophy (LVH) on electrocardiogram or echocardiography is considered a strong marker of progressive hypertensive target organ damage and an ominous predictor of hypertensive CVD morbidity and mortality: subjects with echocardiographic LVH have been shown to have a two- to fourfold increase in cardiovascular events, independent of other risk factors (Devereux 1996, Brown 2000).

The progression of hypertension to atherosclerotic CVD is a complex process involving arterial stiffening, endothelial dysfunction, and cardiac remodeling. Elevated BP alters cardiac structure and function and accelerates atherogenesis, thereby compromising blood supply to the heart, brain, kidneys, and limbs. As a result, the hypertensive patient is at high risk for all major atherosclerotic CVD, including CHD, heart failure, stroke, peripheral arterial disease, renal disease, and retinal damage.

**Renal damage**

Hypertensive renal involvement generally progresses slowly, but in some patients severe (malignant) hypertension can lead to renal insufficiency within a few years as a consequence of severe arteriolar damage. Warning signs of renal damage in hypertension are proteinuria (urinary protein excretion of >300 mg/d) or microalbuminuria — an abnormal elevated urinary albumin excretion (30–300 mg/d) in the absence of clinical proteinuria. These
markers are recognized to be independent risk factors for all-cause and cardiovascular mortality (Kannel 1984). Proteinuria can be reduced effectively by vigorously lowering the BP (<125/75 mm Hg), particularly using a regimen that includes angiotensin-converting enzyme inhibitors (ACE inhibitors) and angiotensin II receptor blockers (ARBs) (JNC-6 1997, Ruilope 1993).

Ocular effects
Hypertension also can affect the ocular microvasculature, causing microinfarcts and superficial hemorrhages. A direct relationship has been noted between elevation of the diastolic pressure and the degree of narrowing of the optic arterioles. Progressive narrowing of the optic vasculature has been observed, and this narrowing has been found to predict a tripled risk of CHD in patients with hypertension. Hypertensive retinopathy can be reversed with effective BP control, although there may be a delay to full regression of the narrowing. Untreated over time, hypertensive optic vascular disease can lead to macular degeneration, serious retinal detachment, nerve damage, and permanent impairment or loss of vision.

Insulin resistance syndrome
Elevated blood pressure tends to occur concurrently with other major CVD risk factors (Kannel 1981, Kannel 1992). A particular risk profile — marked by the presence of hypertension, obesity, dyslipidemia, glucose intolerance, diabetes, and/or LVH — is called the insulin resistance syndrome (Reaven 1988). Two or more of these metabolically linked CVD risk factors can be found to accompany approximately half of all hypertension; indeed, less than 20 percent lack all these risk-enhancing factors (Figure 2) (Kannel 2000a).

This tendency for atherogenic risk factors to cluster with hypertension greatly affects the rate of progression of hypertension to overt CVD. The extent of risk-factor clustering determines the hypertensive individual’s atherogenic potential. Only 14 percent of coronary events in hypertensive men occur in the absence of concomitant risk factors, as do only 5 percent of events in hypertensive women (Kannel 2000a). Diabetes alone has been shown to double the risk of cardiovascular events associated with hypertension (ADA 2002).

Systolic hypertension and pulse pressure
Systolic hypertension
The JNC-7 guidelines advise using SBP as a risk factor for CVD in patients older than 50. Historically, DBP was considered the chief measure of hypertensive risk, until Rutan (1989), in a thorough review of prospective population-based hypertension studies, pointed out a stronger association between CVD events and systolic — rather than diastolic — blood pressure. Prior to and since Rutan’s review, evidence from epidemiologic surveys and clinical trials repeatedly showed a greater role for elevated SBP than DBP in the development of CVD (Lichtenstein 1985; Deubner 1980; Kannel 1980; Wilson 1995; Neaton 1995). Further, successful treatment of elevated SBP has been shown to reduce the risk of cardiovascular events (SHEP 1991, Staessen 1997, Dahlof 1991). There is compelling evidence from trials that effective treatment of ISH (SBP >160 mm Hg and DBP<90 mm Hg) leads to marked reductions in CVD events, further highlighting the importance of SBP control (SHEP 1991, Staessen 1999). Framingham Study data show that the relationship between each standard deviation increase in BP and the risk of CVD is greater for SBP than DBP, particularly in the elderly (Kannel 1971). Similar findings relating SBP more closely to cardiovascular mortality than DBP have been reported from the huge data set of the

FIGURE 2 Concurrence of multiple metabolically linked CVD risk factors

Framingham Offspring Study, subjects age 18–74, who had hypertension in combination with one or more of the following risk factors:

- Glucose intolerance
- Hyperinsulinemia
- High triglycerides or LDL
- Low HDL
- Adverse total/HDL-C ratio
- Obesity
- Left ventricular hypertrophy

SOURCE: KANNEL 2000
Multiple Risk Factor Intervention Trial. Reinforcing the clinical trial evidence for the importance of SBP as a treatment cutpoint, epidemiologic data have complemented the findings, showing that the relative risk of cardiovascular events is consistently greater with each decile increase in SBP compared with DBP (Neaton 1995).

Coronary events can occur even at normal to high-normal SBP (Figure 3). Significant additional risk is observed with each standard deviation increase of SBP in both men and women (51 percent and 23 percent, respectively); the relationship between DBP and cardiovascular events, on the other hand, is significant only among men (30 percent in men, 9 percent in women) (Table 2, Kannel 2003). Earlier clinical studies in samples of younger persons showed increases in DBP to be positively and independently associated with the risk for major cardiovascular disorders (Reid 1976, Kagan 1974, Dawber 1980).

Advancing age confers a disproportionate rise in ISH, particularly after diastolic pressure peaks at about age 60. ISH is seen in approximately two thirds of hypertensive individuals older than 60. In the elderly patient with systolic hypertension, DBP actually confers an inverse relation to CVD risk; thus, use of diastolic values in risk stratification can obscure the true risk for stroke, MI, heart failure, and kidney damage. At any age and in either sex, ISH increases risk of CVD to a greater extent than isolated diastolic hypertension. In the Framingham Study, among patients with SBP >160 mm Hg, CVD events such as CHD, stroke, heart failure, and peripheral arterial disease were only weakly or inversely dependent on the accompanying DBP. In contrast, CVD event rates among persons with diastolic hypertension were strongly influenced by the accompanying SBP (Lloyd-Jones 1999, Kannel 1980, Wilson 1995).

JNC-7 places primary emphasis on achieving SBP goals, stating that “Most persons with hypertension, especially those aged 50 years or older, will reach the DBP goal once SBP is at goal.”

### Pulse pressure

Another consideration is the impact of pulse pressure in the elderly as a predictor of CVD (Franklin 1997). Pulse pressure (the difference between SBP and DBP) increases with age as the DBP declines and SBP rises. It was unclear in the past whether the CVD risk associated with high pulse pressure resulted directly from the stiff atherosclerotic arteries producing the wide pulse pressure or the increased pulse pressure per se. Nevertheless, clinical trials demonstrating that CVD risk is reduced in patients receiving treatment for ISH make it clear that pulse pressure itself contributes to increasing CVD risk, rather than the underlying damaged artery itself (SHEP 1991, Staessen 1997).

Further, the effect of widening pulse pressure has been statistically estimated: each 10 mm Hg increase in pulse pressure increases CVD risk by 20 percent in men and 21 percent in women under age 65, and by 23 percent in men and 11 percent in women at age 65 and beyond (Kannel 2000b). Preferential control of SBP, particularly in the elderly, should often achieve a decrease in pulse pressure and, as a result, reduce the risk for cardiovascular events.

### Knowledge/treatment gap

The clinical approach to control and treatment of hypertension is clearly several steps behind the understanding of the disease and the role of SBP. Berlowitz (1998) found that in actual practice, clinicians are more likely to increase antihypertensive medications in response to DBP ≥90 mm Hg than to SBP ≥165 mm Hg. In an analysis of treatment at five hos-
pitals, increased medication dosage occurred in only 22 percent of patients with a noted ISH of >160/<90 mm Hg.

The information-treatment gap is especially apparent among older patients. Older patients are most likely to have ISH and to be at the highest risk for CVD sequelae, yet they consistently do not reach goal BP levels (Burt 1995). Undertreatment of the elderly may arise from a misperception about the safety and efficacy of aggressive antihypertensive therapy in the elderly or from fear of the J-curve phenomenon (a theory of potential negative effects accruing at exceptionally low DBPs); this notion, however, has been disproved (Forette 1998). In addition, the historical precedent to focus on DBP and the fact that progression of SBP over time often is still erroneously considered a normal aging process might be responsible for the finding that elevated SBP in the presence of a normal DBP is too often considered controlled in the elderly and therefore undertreated (Franklin 1997).

IMPLICATIONS FOR DISEASE MANAGEMENT

Emphasis on hypertension control

BP control can result in significant reductions in the rate of CVD occurrence, including stroke (35–40 percent), MI (20–25 percent), and heart failure (>50 percent) (Neal 2000). The greatest risk associated with hypertension occurs in individuals with a constellation of other risk factors. Thus, the threshold for and the nature of treatment for hypertension depends on understanding the full spectrum of an individual’s metabolic derangements and their relative influences on the outcome. Thus, JNC-7 emphasizes integrated management that is based on a global risk profile, as determined by the burden of concomitant risk factors and prior CVD (Table 3, page 32). The guidelines designate “compelling” indications defined by high-risk conditions that require more aggressive BP reduction or treatment with specific drug classes (see page 17). This integration also may be accomplished by using computer-based multivariate risk assessment programs or risk factor scoring charts that have been derived from Framingham Study data (Wilson 1998).

Treatment strategies

To improve BP control in the United States and decrease related cardiovascular morbidity and mortality, it is important that health care professionals encourage healthful lifestyle adjustments for all Americans and individualize therapeutic strategies, aiming for complete BP control. With some additional simple preventive practices, the vast majority of individuals with uncomplicated hypertension can reach appropriate goals.

Diuretics are widely considered first-line therapy for hypertension as a result of convincing clinical trial data indicating the safety and efficacy of these drugs. An interim analysis from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) described the benefit of the diuretic chlorthalidone (n=15,268) compared with the alpha-receptor blocker doxazosin (N=9,067) when administered to patients with established hypertension (SBP >140 mm Hg or DBP >90 mm Hg), or receiving antihypertensive medication and at least one other CHD risk factor (ALLHAT 2000). In addition, the ALLHAT data concluded that a diuretic was just as effective in reducing the primary endpoint of CHD events as amlodipine, a calcium channel blocker, and lisinopril, an ACE inhibitor. This study, described by Moser elsewhere in this publication, concluded that diuretics are safe and effective therapy for hypertension, and equal to or superior in some endpoints to other agents for first-line treatment of older hypertensive patients with other CHD risk factors.

Although the implications of the ALLHAT study are limited by the lack of individualizing of medication assignment based on concomitant conditions (e.g. diabetes, dyslipidemia, angina, prostate hypertrophy) or the global risk profile, the study nonetheless reestablished the safety and efficacy of diuretic therapy in a hypertensive population. This attitude is reflected in the JNC-7 report, which acknowledges that diuretics are underused (Psaty 2000).
DISEASE MANAGEMENT

2002). The JNC-7 report also asserts that most patients with hypertension will need two or more antihypertensive medications to achieve goal BP, necessitating combination of an initial diuretic with an ARB, beta blocker, calcium channel blocker, or ACE inhibitor — the choice is based on coexisting conditions and indications from a global risk profile. Following selection of appropriate medication(s), ensuring adherence to appropriate lifestyle modifications and drug regimens is the most important component of hypertension control.

The threshold for treating ISH is still 160 mm Hg. Because half the patients with mild ISH also have two or more additional risk factors, however, most are candidates for treatment. The goal for ISH should be to reduce SBP to below the average for their age (i.e., <140/90 mm Hg).

CONCLUSION

Hypertension is a precursor of many devastating conditions, including CHD, heart failure, stroke, end-stage renal disease, and peripheral arterial disease. Evidence of target organ damage occurs even within the high-normal blood pressure range (part of a broader range that JNC-7 now defines as prehypertension). Current control rates for hypertension are rather poor, overwhelmingly due to lack of SBP control (Lloyd-Jones 2000). The number of patients who remain undiagnosed or inadequately treated remains below expectation. Clinicians must accept the challenge posed by JNC-7 to identify hypertension in their patients, look at the global risk factors, and focus on SBP in patients over 50 years old. Thus, we can improve diagnosis, individualize therapy, manage the disease appropriately, ensure adherence to aggressive treatment goals, and reduce the clinical and economic burdens of hypertension in the United States.

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Hypertension: A Review Of Therapeutic Options

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SUMMARY

Excellent clinical trial data support the use of several classes of drugs for reducing and controlling hypertension. This review covers the classes discussed by JNC-7, including angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, beta blockers, calcium channel blockers, and diuretics.

The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) differs significantly from previous reports regarding blood pressure classifications and treatment cutpoints. These differences are described by Moser elsewhere in this publication; one significant change is the establishment of a new stage, prehypertension, for individuals with a systolic blood pressure (SBP) of 120–139 mm Hg and/or a diastolic blood pressure (DBP) of 80–89 mm Hg. For this population, as well as for individuals with established hypertension, JNC-7 recommends lifestyle modification as a valuable tool for controlling blood pressure (JNC-7 2003).

However, pharmacotherapy is necessary for prehypertensive persons with target-organ damage, clinical cardiovascular disease, or diabetes, and for hypertensive patients.

Providing the most appropriate antihypertensive therapy requires some investigation, including comprehensive patient and family history details, a medical examination, and diagnostic tests. The clinical evaluation should detect known causes of hypertension, as well as identify other cardiovascular risk factors, determine whether the patient has any blood pressure (BP) related target-organ damage, and identify relevant comorbidities (see page 32).

To develop baseline data prior to starting antihypertensive therapy, the examination should include at least the following tests (Carter 2002, JNC-7 2003):

• Urinalysis
• Complete blood cell count
• 12-lead electrocardiogram
• Serum chemistries (sodium, potassium, creatinine, fasting glucose, total cholesterol, high-density lipoprotein cholesterol)

Treatment goals

Reducing cardiovascular and renal morbidity and mortality is the primary public health goal of antihypertensive therapy. The major objectives are to reduce the risk of cardiovascular injury, cerebrovascular events, heart failure, kidney disease, and other damage to organs at risk from hypertension.

Although there are no guarantees, the most appropriate correlation in hypertension therapy is the simplest: the higher the patient’s BP, the higher the risk for morbidity and mortality; as the patient’s BP approaches normal, the risk falls.

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JNC-7 has established SBP/DBP goals of <140/90 mm Hg to decrease cardiovascular disease complications. In hypertensive patients with diabetes or renal insufficiency, target BP measurements are <130/80 mm Hg. JNC-7 has determined that most hypertensive patients, especially those age 50 and older, will reach their DBP goal after achieving their SBP goal. It follows that the clinician and hypertensive patient should focus primarily on achieving the SBP goal (Rocella 2003).

PHARMACOTHERAPY FOR UNCOMPLICATED HYPERTENSION

Currently, first-line treatment of most patients with hypertension typically consists of a thiazide diuretic — the oldest class of antihypertensive agents — to reduce morbidity and mortality. While thiazide diuretics are generally preferred as initial therapy, many patients will require two or more medications to control BP. Depending on other risk factors and coexisting conditions, JNC-7 supports the use of four additional classes of medication as possible therapy for hypertension (usually following a thiazide diuretic):

- Beta blockers
- Angiotensin-converting enzyme (ACE) inhibitors
- Angiotensin II receptor blockers (ARBs)
- Calcium channel blockers (CCBs)

The JNC-7 report singles out thiazide diuretics as most appropriate for initial therapy of hypertension and discusses high-risk conditions that serve as “compelling indications” for beginning therapy with an agent from one of the four classes above rather than a diuretic (see page 17). JNC-7 also advises combination therapy — typically with a thiazide diuretic and a second agent — if the patient’s hypertension is severe or if BP is above the target level by more than 20/10 mm Hg; the new report suggests that most patients with hypertension will need at least two medications for first-line therapy (JNC-7 2003).

If the intent of therapy is to reduce BP to JNC-7 goal pressures, then any antihypertensive medication on the market will effectively control BP in only 40–50 percent of cases. This suggests that many patients will require a regimen of two or three medications. The need for multiple medication is supported by numerous clinical trials (Carter 2000, Carter 2001). All antihypertensives are generally safe and fairly well tolerated, but each has specific side effects requiring patient monitoring (Carter 2002).

Diuretics

When first initiated, thiazide diuretic therapy induces natriuresis, decreasing plasma volume. With chronic use of some agents, diuresis decreases; however, in the long term, thiazide diuretics lower BP by decreasing peripheral vascular resistance (Saseen 2001, Moser 1987).

Selected diuretics are summarized in Table 1, page 36.

Thiazide diuretics

The use of thiazide diuretics in long-term clinical trials reduces strokes (by 40–45 percent), congestive heart failure (CHF) (by 40–50 percent), and coronary artery disease (by 16–25 percent) (Moser 1996). Only one study found diuretics to be slightly less effective than ACE inhibitors among men, but this did not include many black patients (Wing 2003).

These agents are well tolerated and effective; most are administered once daily. Diuretics can cause biochemical alterations (including hypokalemia, hyperuricemia, hyperglycemia, and hypercholesterolemia); however, these problems are dosage-related and may not be of major clinical significance (ALLHAT 2002). For example, the former standard of care called for the administration of 100 mg to 200 mg of hydrochlorothiazide (HCTZ) per day. In contrast, the current standard is 12.5 mg to 25 mg per day (maximum daily dosage 50 mg). At the lower doses, adverse effects are much less common. Dietary modifications often minimize biological changes associated with the use of these medications, especially hypokalemia (by lowering salt intake). Patients receiving diuretics, even at low dosages, should be monitored for potassium, serum creatinine, lipids, glucose, and uric acid at about 4 weeks after diuretic therapy starts.

Thiazide diuretics are effective first-line medications, but adding almost any other antihypertensive agent to a thiazide diuretic should substantially improve the regimen’s efficacy. If it is not used as initial therapy, a thiazide diuretic should be the second drug added to the regimen (Carter 2001, Saseen 2001).

Loop diuretics

Loop diuretics provide more pronounced diuresis than thiazide diuretics (Saseen 2001), and are valuable for treating patients with renal insufficiency or CHF, or when creatinine clearance is <25 mL to 30 mL/min (Carter 2001). Loop diuretics have a shorter duration of action than thiazide diuretics and are generally less effective than a thiazide in reducing BP.

Thus, loop diuretics should be reserved for patients who have more significant renal insufficiency (Saseen 2001).

Potassium-sparing diuretics

Potassium-sparing diuretics can be used to treat patients who develop clinically significant hypokalemia (less than 25 percent of patients) while taking thiazide diuretics.
Beta blockers

Beta blockers lower BP by the following mechanisms (Saseen 2001):

- Decreasing cardiac contractility and output
- Lowering heart rate
- Diminishing sympathetic reflex (in combination with exercise)
- Reducing central release of adrenergic substances
- Inhibiting peripheral epinephrine release
- Decreasing renin release

Like thiazide diuretics, beta blockers are generally well tolerated; they are suitable for initial therapy in some patients. Generally, beta blockers are used as monotherapy for specific indications such as coronary heart disease or post-myocardial infarction (MI).

Beta blockers are commonly used to treat patients with mitral valve prolapse who develop tachycardia and then show symptoms of anxiety. Beta blockers can also be used to treat hypertension in patients with paroxysmal supraventricular tachycardia, atrial fibrillation, or ventricular arrhythmias that result from idiopathic hypertrophic subaortic stenosis. Patients on beta blockers should be monitored for bradycardia, fatigue, central nervous system (CNS) adverse effects, and symptoms of asthma (Carter 2001).

Beta blockers can benefit hypertensive patients with angina pectoris, and can be considered initial anti-hypertensive therapy for patients with stable angina. Unless they are absolutely contraindicated, beta blockers should be used to prevent secondary MIs in hypertensive patients who have suffered an acute MI. Clinicians should use caution when they find it necessary to prescribe beta blockers to diabetic patients, especially if the disease is tightly controlled or if the patient is vulnerable to hypoglycemia; cardioselective beta blockers are preferred in these cases. However, a beta blocker-based treatment program has been found to reduce both micro- and macrovascular events in type 2 diabetes (UKPDS 1998).

Selected beta blockers are listed in Table 2. Different types of beta blockers demonstrate differences not only in cardioselectivity, but also in intrinsic sympathomimetic activity (ISA) and relative lipid solubility; depending on the patient, some of these differences may be clinically significant.

Cardioselectivity

Some beta blockers are relatively cardioselective, demonstrating beta₁-blocking activity at low doses. Use of a sustained-release formulation, which avoids the high plasma peaks seen with conventional beta blocker formulations, may enable cardioselectivity at higher doses. Generally, most beta₂-adrenergic receptors are in the heart, while beta₂-adrenergic receptors are in the lungs, kidneys, and peripheral arterial endothelium. Selective beta blockers may be somewhat better tolerated in patients with asthma, peripheral vascular disease, or Raynaud’s disease (Saseen 2001).

Intrinsic sympathomimetic activity

Beta blockers with ISA may increase the heart rate of

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Trade name(s)</th>
<th>Typical total daily dosage (mg)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiazide</td>
<td>Chlorothiazide†</td>
<td>Diuril</td>
<td>125–500</td>
</tr>
<tr>
<td></td>
<td>Chlorthalidone</td>
<td>Hygroton</td>
<td>12.5–25.0</td>
</tr>
<tr>
<td></td>
<td>Hydrochlorothiazide</td>
<td>Esidrix, Hydrodiuril, Microzide</td>
<td>12.5–50.0</td>
</tr>
<tr>
<td></td>
<td>Indapamide</td>
<td>Lozol</td>
<td>1.25–2.50</td>
</tr>
<tr>
<td></td>
<td>Metolazone†</td>
<td>Mykrox</td>
<td>0.5–1.0</td>
</tr>
<tr>
<td></td>
<td>Metolazone</td>
<td>Zaroxolyn</td>
<td>2.5–5.0</td>
</tr>
<tr>
<td></td>
<td>Polythiazide†</td>
<td>Renese</td>
<td>2–4</td>
</tr>
<tr>
<td>Loop</td>
<td>Bumetanide</td>
<td>Bumex</td>
<td>0.5–2.0 (≤1.0 bid)</td>
</tr>
<tr>
<td></td>
<td>Furosemide</td>
<td>Lasix</td>
<td>20–80 (≤40 bid)</td>
</tr>
<tr>
<td></td>
<td>Torsemide</td>
<td>Demadex</td>
<td>2.5–10.0</td>
</tr>
<tr>
<td>Potassium-sparing</td>
<td>Amiloride</td>
<td>Midamor</td>
<td>5–10 (can be given ≤5 bid)</td>
</tr>
<tr>
<td></td>
<td>Triamterene</td>
<td>Dyrenium</td>
<td>50–100 (can be given ≤50 bid)</td>
</tr>
</tbody>
</table>

* Once daily, unless otherwise noted. Bumetanide, for instance, is given twice daily. An individual dose, therefore, would be ≤1.0 mg, given bid for a maximum total daily dosage of 2.0 mg.

Sources: Saseen 2001; †JNC-7 2003
patients with slow resting heart rates, or may slow rates in patients with normally high or exercise-induced rapid heart rates. These agents can trigger asthma or, in patients with coronary artery disease, can worsen heart failure and angina. In patients who suffer severe bradycardia from other beta-agonists, ISA beta blockers may be indicated; however, they should not be used as prophylaxis against MI. Agents with ISA have generally not been shown to reduce morbidity and are not recommended.

**Lipid solubility**
Lipid solubility should be considered in a hypertensive patient with renal or hepatic impairment. Less lipophilic (more hydrophilic) beta blockers are less influenced by hepatic metabolism and are excreted to a greater extent by the kidney; thus, when these types of beta blockers are given to renally impaired patients, dose adjustments may be required. A beta blocker with higher lipid solubility may be appropriate for a patient with a history of migraine headaches, as this type of beta blocker has CNS properties that may provide better prophylaxis than other agents.

**Alpha-beta blockers**
As the name suggests, alpha-beta blockers combine the actions of alpha and beta blockers, acting as a vasodilator while slowing the heartbeat. The dual effect reduces the pressure of blood flowing through vessels. Table 3, on page 38, lists selected alpha-beta blockers.

<table>
<thead>
<tr>
<th>Relative selectivity</th>
<th>Drug</th>
<th>Trade name(s)</th>
<th>Typical total daily dosage (mg)*</th>
<th>Lipid solubility</th>
<th>ISA level</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Atenolol</td>
<td>Tenormin</td>
<td>25–100</td>
<td>Low</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Acebutolol</td>
<td>Sectral</td>
<td>200–800 (≤400 bid)</td>
<td>Moderate</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>Bisoprolol</td>
<td>Zebeta</td>
<td>2.5–10</td>
<td>Low</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Betaxolol</td>
<td>Kerlone</td>
<td>5–20</td>
<td>Low</td>
<td>None</td>
</tr>
<tr>
<td>Moderate</td>
<td>Metoprolol</td>
<td>Lopressor</td>
<td>50–100 (can be given 50 bid)</td>
<td>Moderate to high</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Metoprolol extended release*</td>
<td>Toprol XL release*</td>
<td>50–100</td>
<td>Moderate to high</td>
<td>None</td>
</tr>
<tr>
<td>Low</td>
<td>Nadolol</td>
<td>Corgard</td>
<td>40–120</td>
<td>Low</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Penbutolol</td>
<td>Levatol</td>
<td>10–40</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>Pindolol</td>
<td>Visken</td>
<td>10–40 (≤20 bid)</td>
<td>Moderate</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>Propranolol</td>
<td>Inderal</td>
<td>40–160 (≤80 bid)</td>
<td>High</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Timolol</td>
<td>Blocadren</td>
<td>20–40 (≤20 bid)</td>
<td>Low to moderate</td>
<td>None</td>
</tr>
</tbody>
</table>

*Lipid solubility should be considered in a hypertensive patient with renal or hepatic impairment. Less lipophilic (more hydrophilic) beta blockers are less influenced by hepatic metabolism and are excreted to a greater extent by the kidney; thus, when these types of beta blockers are given to renally impaired patients, dose adjustments may be required. A beta blocker with higher lipid solubility may be appropriate for a patient with a history of migraine headaches, as this type of beta blocker has CNS properties that may provide better prophylaxis than other agents.

Labetalol may be used alone or in combination with other antihypertensive agents, particularly thiazide and loop diuretics. Labetalol appears to increase the risk of hyperkalemia in renal transplant patients who experience postoperative hypertension (McCauley 2002).

Carvedilol, a relatively expensive therapy for hypertension, can be used alone or in combination with other antihypertensive agents, particularly thiazide-type diuretics. Carvedilol is extensively metabolized; thus, it should not be given to patients with severe hepatic impairment. Due to its high degree of plasma protein binding, carvedilol does not appear to be cleared significantly during hemodialysis. Carvedilol has been found to be beneficial in the treatment of heart failure.

**ACE inhibitors**
ACE inhibitors lower BP by inhibiting the conversion of angiotensin I to angiotensin II (AT-II), reducing vasoconstriction and decreasing aldosterone secretion (Saseen 2001). These agents impede the degradation of bradykinin, thus promoting vasodilation; however, ACE inhibitors also can induce coughing in some patients. Patients with hypertension due to high renin often respond to ACE inhibitor therapy, although many patients with lower renin levels may have partial response (Carter 2001). All ACE inhibitors lower BP through peripheral arterial vasodilation, but cause no significant changes in cardiac output, heart rate, or glomerular filtration rate (Saseen 2001).
Compared with other anti-hypertensives, ACE inhibitors are protective in renal insufficiency, and are one of the preferred agents in the treatment of hypertensive diabetic patients, especially those who exhibit evidence of microalbuminuria. Because they also reduce cardiac remodeling, ACE inhibitors should be considered as an option for hypertensives with a history of MI. Patients with atherosclerosis — including smokers and diabetics — are at elevated risk of renal artery stenosis; ACE inhibitors should be used with caution in these cases.

ACE inhibitors are of particular benefit to patients with CHF, reducing both fatal and nonfatal events. ACE inhibitor-based treatment regimens also prevent cardiovascular events in diabetics who are being treated for hypertension. Because most ACE inhibitors are excreted in the urine, dose adjustments may be necessary for patients with renal dysfunction. Fosinopril does not require dose adjustment with renal insufficiency, due to extensive hepatic elimination.

When initiated, ACE inhibitor therapy may induce acute hypotension, especially in patients who are severely sodium-depleted or volume-depleted; therefore, the clinician should consider reducing diuretic therapy and perhaps reduce the dose of other antihypertensives before starting the ACE inhibitor (Carter 2002).

Patients receiving ACE inhibitors should be monitored frequently for cough, as well as skin rash and taste disturbances, though these two are rare. Laboratory tests should include serum creatinine, potassium, urinalysis, and — if warranted — hematology, to test for neutropenia (also rare). Patients with CHF or other complications, as well as those who are frail, should be monitored every 1 to 3 months, as necessary. Serious adverse effects due to ACE inhibitors are rare but can include angio-neurotic edema, which is more common in black patients (Carter 2002).

Table 1 lists selected ACE inhibitors.

Most ACE inhibitors are given once daily, except for captopril, which is given twice daily in hypertension. Studies in heart failure used captopril 3 times a day; twice-daily dosing of ACE inhibitors is often necessary to provide 24-hour blood pressure control. Time-to-onset and duration of efficacy vary. For most ACE inhibitors, onset requires 1 hour. Exceptions are captopril (15 to 30 minutes), moexipril and perindopril (90 minutes), ramipril (1 to 2 hours), and trandolapril (2 to 4 hours). For most ACE inhibitors, duration of action is 12 to 24 hours. Exceptions are the following: captopril (8 to 12 hours) and quinapril (longer than 30 hours). Lower initial doses may be appropriate for patients who are elderly, volume-depleted, or taking diuretics (Saseen 2001).

**Angiotensin II receptor blockers**

ARBs bind to AT-II receptors in tissues, including adrenal glands and vascular smooth muscle. Blocking access of AT-II to its receptors prevents AT-II–mediated vasoconstriction and aldosterone release, thereby reducing BP. ARBs do not alter the metabolism of bradykinin, norepinephrine, or substance P.

Some BP-lowering effects of ACE inhibitors may stem from increased bradykinin levels. Because ARBs do not block the breakdown of bradykinin, there is some question as to whether these agents are as effective as ACE inhibitors in lowering BP. The addition of a low-dose thiazide diuretic to an ARB significantly improves antihypertensive efficacy (Carter 2002).

ARBs cause cough much less frequently than ACE inhibitors. The benefits of these agents in diabetic neuropathy and albuminuria are firmly established; studies have found them to reduce renal complications in these patients (Brenner 2001, Lewis 2001).

Although the JNC-7 report suggests that ARBs be considered as first-line therapy, these agents are currently used more often as second-line alternatives for patients — such as those with heart failure or diabetes — who would benefit from an ACE inhibitor but who suffer from an ACE-induced cough (Saseen 2001).

ARBs are more expensive than ACE inhibitors, and their effect on mortality risk is not as well established, although one study found that losartan reduced morbidity better than atenolol, especially in diabetics (Dahlof 2002). In patients with angio-neurotic edema caused by ACE inhibitors, some reports have described cross-reactivity between ACE inhibitors and ARBs (Carter 2001). Like ACE inhibitors, these agents may cause renal insufficiency and hyperkalemia.

The ARBs that are now available primarily block subtype-1 (AT₁) receptors. When these are stimulated, they cause vasoconstriction, vascular remodeling, and the retention of salt and water. Subtype-2 receptors, on the
other hand, are not known to affect cardiovascular homeostasis and their stimulation causes a beneficial antiproliferative action and promotes cell differentiation and tissue repair (Saseen 2001). In theory, if the AT1 receptors are blocked and the subtype-2 became overreactive, a more beneficial effect on the vasculature will result.

Table 5, on page 40, lists selected ARBs.

ARBs vary in their ability to antagonize subtype-1 receptors; candesartan, irbesartan, and telmisartan block AT-II receptors more effectively than losartan or valsartan, but the clinical significance of this is not established.

**Aldosterone receptor blockers**

Ongoing research provides evidence of aldosterone’s role in the pathophysiology of hypertension, heart failure, MI, and renal disease. Aldosterone is primarily synthesized from cholesterol, a process stimulated by AT-II, potassium, and catecholamines. Research largely has been concentrated on efforts to reduce production of AT-II by blocking AT-II receptors or by ACE inhibition. Fewer studies have focused on blocking aldosterone receptors.

Table 6, on page 40, lists selected aldosterone receptor blockers.

Spironolactone, a nonselective aldosterone antagonist, has been available in the United States since the 1970s. It has been shown to be efficacious in the treatment of hypertension via its antimineralocorticoid receptor effect (Corvol 1981, Laragh 1987). Spironolactone may be particularly useful for patients with salt sensitivity or those with heart failure, but some side effects, such as gynecomastia, limit its usefulness.

**Calcium channel blockers**

Intracellular free calcium concentrations increase arteriolar smooth muscle tone, which in turn increases peripheral vascular resistance. CCBs promote vasodilation by preventing the intracellular influx of calcium. There are two main subtypes of CCBs: dihydropyridines and nondihydropyridines. Dihydropyridines are potent vasodilators of peripheral and coronary arteries. Nondihydropyridines are less potent arterial vasodilators, but they also directly decrease arteriovenous nodal conduction and demonstrate negative chronotropic and inotropic actions. Neither subtype of CCB alters serum lipids, glucose, uric acid, or electrolytes, nor do CCBs aggravate asthma or peripheral vascular disease. Older patients and blacks may experience greater BP-lowering response to CCBs than do younger or white patients. If response to the CCB is inadequate, efficacy may be increased by adding a diuretic (Saseen 2001).

The use of CCBs may reduce the risk of cardiovascular events in both isolated systolic and diastolic/systolic hypertension. In comparison with diuretics, beta blockers, and ACE inhibitors, dihydropyridines may not provide as much protection against MI and other cardiac events, although they may be more effective than ACE inhibitors in preventing stroke.

Selected CCBs are summarized in Table 7 on page 41.

In the management of hypertension, clinicians should avoid the use of immediate-release dihydropyridine CCBs, particularly nifedipine, because of evidence of possible serious side effects, such as myocardial ischemia.
Most dihydropyridines are formulated as sustained-release medications because of their short duration of action. Previously, immediate-release nifedipine had been used to reduce BP quickly in hypertensive emergencies, but it is not approved for this indication because of side effects that include severe hypotension, cerebral ischemia, acute MI, conduction abnormalities, and death.

Every CCB except amlodipine has a short half-life. However, half-life can be extended significantly (up to 15 hours) in elderly patients because of reduced hepatic elimination (Carter 1993). Because immediate-release formulations must be administered multiple times daily, sustained-release CCBs are preferred for hypertension therapy. However, generic verapamil can be given twice daily in older patients and is less expensive than sustained-release products (Carter 1993).

When interchanging sustained-release CCBs, the clinician should monitor the patient’s BP within 2 weeks of the dosage conversion, to guard against variable BP reduction. Special sustained-release verapamil formulations, such as Covera HS and Verelan PM, are designed to take advantage of the body’s circadian BP pattern (Saseen 2001).

**Combination therapy**

If initial monotherapy fails to lower BP to the established goal, the clinician has three options: increase the dosage of the first agent, replace the first agent, or add a second agent and, later, a third agent if necessary. Increasing the dosage of a first-line antihypertensive to high dosages may generate problems, such as the metabolic changes associated with a higher-dose thiazide diuretic. Switching medications may also be suboptimal; if the first drug is working but BP is still not controlled, switching to a different class of antihypertensive may prove to be less effective. In such cases, combination therapy is often successful (Saseen 2001, JNC-7 2003).

As noted earlier, if a thiazide diuretic is not used initially, it should be added to the regimen. The combination of a diuretic and an ACE inhibitor or beta blocker has an additive BP-lowering effect without sodium retention or volume increase. Combining a diuretic with an ARB, alpha blocker, or CCB such as verapamil or diltiazem also has an additive effect (Saseen 2001). Interestingly, the combination of diltiazem or verapamil (nondihydropyridine CCBs) with nifedipine (a dihydropyridine CCB) has an additive effect, but should be reserved for cases of refractory disease or multiple contraindications or drug intolerances (Carter 2001, Saseen 1996, Bakris 2000).

JNC-7 suggests the use of combination therapy as initial treatment in patients with stage 2 hypertension. Table 8, on page 42, lists selected fixed-combination antihypertensives.

Before choosing a fixed-combination antihypertensive product, the clinician should titrate to the optimal dose of each component and then select the combination medication that corresponds. Fixed-combination agents simplify the regimen for the patient (i.e., the patient takes only one medication according to one schedule, rather than multiple medications according to multiple schedules).

Additionally, fixed-combination antihypertensives are typically less expensive than the same multiple medications at the same doses, purchased individually, and tend to generate fewer side effects because of low initial doses.

The article by Prisant that begins on page 45 provides a detailed description of various combination therapies, their indications, and contraindications.

### TABLE 5 Selected ARBs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trade name(s)</th>
<th>Typical total daily dosage (mg)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candesartan</td>
<td>Atacand</td>
<td>4 8–32 (can be given 16 bid)</td>
</tr>
<tr>
<td>Eprosartan</td>
<td>Tevetan</td>
<td>400 400–800 (can be given 400 bid)</td>
</tr>
<tr>
<td>Irbesartan</td>
<td>Avapro</td>
<td>75–150 150–300</td>
</tr>
<tr>
<td>Losartan</td>
<td>Cozaar</td>
<td>25 25–100 (can be given 50 bid)</td>
</tr>
<tr>
<td>Telmisartan</td>
<td>Micardis</td>
<td>20 20–80</td>
</tr>
<tr>
<td>Valsartan</td>
<td>Diovan</td>
<td>80 80–320</td>
</tr>
</tbody>
</table>

* Once daily, unless otherwise noted.

SOURCE: JNC-7 2003

### TABLE 6 Selected aldosterone receptor blockers

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trade name(s)</th>
<th>Typical total daily dosage (mg)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spironolactone</td>
<td>Aldactone</td>
<td>25–50 (can be given ≤25 bid)</td>
</tr>
<tr>
<td>Eplerenone</td>
<td>Inspra</td>
<td>50–100 (can be given ≤50 bid)</td>
</tr>
</tbody>
</table>

* Both are administered once or twice daily.

SOURCE: JNC-7 2003
SPECIFIC CONCERNS

Clinicians must take into consideration specific medical and demographic factors that influence — or even dictate — the choice of antihypertensive medication for particular patient populations, especially for some high-risk conditions. In other situations, certain agents demonstrate potential favorable or unfavorable effects.

Table 9 recommends antihypertensive medications for selected situations, comorbidities, and populations. Table 10 shows potential unfavorable conditions for specific drugs. These two tables are on page 43.

Difficult-to-control hypertension

Other agents used to control hypertension typically are reserved for specific purposes.

Peripheral alpha1-receptor blockers. Prazosin, terazosin, and doxazosin cross the blood-brain barrier and may cause adverse CNS effects. Occasionally, in the first 3 hours after the initial dose, patients may experience faintness, dizziness, palpitation, or syncope, which may make these agents inappropriate for use in elderly patients. When giving peripheral alpha1-receptor blockers for the first time, clinicians should warn patients to rise with caution from a sitting position; the first dose should be given at bedtime. Orthostatic dizziness can persist with chronic use.

Because these agents effectively reduce blood pressure and provide symptomatic relief to patients with benign prostatic hypertrophy, they may be used in low dosages to treat hypertension in these patients who are already receiving diuretics, beta blockers, or ACE inhibitors. They should not be used as monotherapy because they are not as effective as other agents in reducing cardiovascular events (ALLHAT 2002). Because fluid and sodium accumulate with their prolonged use and at higher dosages, peripheral alpha1-receptor blockers should be given concurrently with diuretics (Carter 2002).

Central alpha2-receptor antagonists. Clonidine, guanabenz, guanfacine, methyldopa, and reserpine inhibit sympathetic outflow to the heart, kidneys, and peripheral vasculature by stimulating alpha2 receptors in the CNS. The result is peripheral vasodilation. These agents are not

---

**TABLE 7** Selected calcium channel blockers

<table>
<thead>
<tr>
<th>CCB subtype</th>
<th>Drug</th>
<th>Trade name(s)</th>
<th>Typical total daily dosage (mg)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dihydropyridines</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate release</td>
<td>Amlodipine (t)</td>
<td>Norvasc</td>
<td>2.5–10</td>
</tr>
<tr>
<td></td>
<td>Isradipine (c)</td>
<td>DynaCirc</td>
<td>2.5–10 (≤5 bid)</td>
</tr>
<tr>
<td>Extended release</td>
<td>Felodipine (t)</td>
<td>Plendil</td>
<td>2.5–20</td>
</tr>
<tr>
<td></td>
<td>Nisoldipine (t)</td>
<td>Sular</td>
<td>10–40</td>
</tr>
<tr>
<td>Controlled release</td>
<td>Isradipine (t)</td>
<td>DynaCirc CR</td>
<td>2.5–10 (≤5 bid)</td>
</tr>
<tr>
<td>Sustained release</td>
<td>Nifedipine (t)</td>
<td>Procardia XL, Adalat CC</td>
<td>30–60</td>
</tr>
<tr>
<td><strong>Nondihydropyridines</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate release</td>
<td>Diltiazem (t)</td>
<td>Cardizem, generic</td>
<td>120–360 (120 tid)</td>
</tr>
<tr>
<td></td>
<td>Verapamil (t)</td>
<td>Calan, Isoptin, generic</td>
<td>80–320 (≤160 bid)</td>
</tr>
<tr>
<td>Sustained release</td>
<td>Diltiazem (c)</td>
<td>Cardizem SR, Tiamate</td>
<td>120–360 (≤180 bid)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dilacor XR</td>
<td>180–480</td>
</tr>
<tr>
<td></td>
<td>Verapamil (t)</td>
<td>Cardizem CD, Tiazac</td>
<td>180–480</td>
</tr>
<tr>
<td></td>
<td>Verapamil (c)</td>
<td>Calan SR, Isoptin SR, generic</td>
<td>120–360 (can be given ≤180 bid)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Verelan</td>
<td>120–360 (can be given ≤180 bid)</td>
</tr>
<tr>
<td>Controlled onset, extended release</td>
<td>Verapamil (t)</td>
<td>Covera HS</td>
<td>120–360</td>
</tr>
<tr>
<td>Chronotherapeutic oral drug absorption system</td>
<td>Verapamil (c)</td>
<td>Verelan PM</td>
<td>120–360</td>
</tr>
</tbody>
</table>

* Once daily, unless otherwise noted.

SOURCE: SASEEN 2001
first-line antihypertensives because they cause more side effects than other agents, including sedation, dry mouth, and (with abrupt cessation) nervousness, palpitations, headache, perspiration, nausea, and agitation. In some cases, sudden withdrawal can cause a rapid rise in BP to dangerous levels. When giving these drugs, clinicians should warn patients about the possibility of rebound hypertension.

Generally, these agents should be used in combination with agents that have different mechanisms of action (vasodilators), agents that do not affect central adrenergic receptors (beta blockers), and — because they foster fluid retention —concurrently with diuretics (Saseen 2001). Reserpine is relatively inexpensive and is effective in lowering BP, and has been a second-step agent for many large pivotal clinical studies in hypertension.

**Arterial vasodilators.** Hydralazine and minoxidil are potent arterial vasodilators, relaxing arteriolar smooth muscle, reducing perfusion pressure, and increasing sympathetic output from the vasomotor center; increased heart rate, cardiac output, and renin release result. Because their hypotensive effectiveness diminishes as fluid

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**TABLE 8  Selected fixed-combination antihypertensives**

<table>
<thead>
<tr>
<th>Classes combined</th>
<th>Components (dose in mg)</th>
<th>Trade name(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiazide diuretic and potassium-sparing diuretic</td>
<td>Hydrochlorothiazide/amiloride (50/5)</td>
<td>Moduretic</td>
</tr>
<tr>
<td></td>
<td>Hydrochlorothiazide/spironolactone (25/25, 50/50)</td>
<td>Aldactone</td>
</tr>
<tr>
<td></td>
<td>Hydrochlorothiazide/triamterene (25.0/37.5, 25/50, 50/75)</td>
<td>Dyazide, Maxzide</td>
</tr>
<tr>
<td>Thiazide diuretic and beta blocker</td>
<td>Chlorthalidone/atenolol (25/50, 25/100)</td>
<td>Tenoretic</td>
</tr>
<tr>
<td></td>
<td>Hydrochlorothiazide/bisoprolol fumarate (6.25/2.50, 6.25/5.00, 6.25/10.00)</td>
<td>Ziac</td>
</tr>
<tr>
<td></td>
<td>Hydrochlorothiazide/propranolol (25/40, 25/80)</td>
<td>Inderide</td>
</tr>
<tr>
<td></td>
<td>Hydrochlorothiazide/metoprolol tartrate (25/50, 50/100, 50/100)</td>
<td>Lopressor HCT</td>
</tr>
<tr>
<td></td>
<td>Bendroflumethiazide/nadolol (5/40, 5/80)</td>
<td>Corzide</td>
</tr>
<tr>
<td></td>
<td>Hydrochlorothiazide/timolol maleate (25/10)</td>
<td>Timolide</td>
</tr>
<tr>
<td>Thiazide diuretic and ACE inhibitor</td>
<td>Hydrochlorothiazide/benazepril (6.25/5.00, 12.5/10.0, 12.5/20.0, 25/20)</td>
<td>Lotensin HCT</td>
</tr>
<tr>
<td></td>
<td>Hydrochlorothiazide/captopril (15/25, 25/15, 50/25, 50/50)</td>
<td>Capozide</td>
</tr>
<tr>
<td></td>
<td>Hydrochlorothiazide/enalapril maleate (12.5/5.0, 25/10)</td>
<td>Vaseretic</td>
</tr>
<tr>
<td></td>
<td>Hydrochlorothiazide/lisinopril (12.5/10.0, 12.5/20.0, 25/20)</td>
<td>Prinzide</td>
</tr>
<tr>
<td></td>
<td>Hydrochlorothiazide/moexipril HCl (12.5/5.75, 12.5/15.0, 25/15)</td>
<td>Uniretic</td>
</tr>
<tr>
<td></td>
<td>Hydrochlorothiazide/quinapril HCl (12.5/10.0, 12.5/20.0, 25/20)</td>
<td>Accuretic</td>
</tr>
<tr>
<td>Thiazide diuretic and ARB</td>
<td>Hydrochlorothiazide/candesartan cilexetil (12.5/16.0, 12.5/32.0)</td>
<td>Atacand HCT</td>
</tr>
<tr>
<td></td>
<td>Hydrochlorothiazide/epranosartan mesylate (12.5/600.0, 25/600)</td>
<td>Teveten HCT</td>
</tr>
<tr>
<td></td>
<td>Hydrochlorothiazide/irbesartan (12.5/75.0, 12.5/150.0, 12.5/300.0)</td>
<td>Avalsde HCT</td>
</tr>
<tr>
<td></td>
<td>Hydrochlorothiazide/losartan potassium/potassium (12.5/50.0, 24.25, 25.00/100.00/8.48)</td>
<td>HyaRaz</td>
</tr>
<tr>
<td></td>
<td>Hydrochlorothiazide/telmisartan (12.5/40.0, 12.5/80.0)</td>
<td>Micardis HCT</td>
</tr>
<tr>
<td></td>
<td>Hydrochlorothiazide/valsartan (12.5/80.0, 12.5/160.0, 12.5/160.0)</td>
<td>Diovan HCT</td>
</tr>
<tr>
<td>Thiazide diuretic and centrally acting agent</td>
<td>Hydrochlorothiazide/methyldopa (15/250, 25/250, 35/500, 50/500)</td>
<td>Aldoril</td>
</tr>
<tr>
<td></td>
<td>Chlorothiazide/reserine (250.000/0.125, 500.000/0.250)</td>
<td>Diupres</td>
</tr>
<tr>
<td></td>
<td>Hydrochlorothiazide/reserine (250.000/0.125, 500.000/0.125)</td>
<td>Mylan</td>
</tr>
<tr>
<td>ACE inhibitor and CCB</td>
<td>Amlodipine/benazepril HCl (2.5/10.0, 5/10.0, 5/20, 10/20)</td>
<td>Lotrel</td>
</tr>
<tr>
<td></td>
<td>Enalapril maleate/felodipine (5.0/5.0, 5.0/2.5)</td>
<td>Lexxel</td>
</tr>
<tr>
<td></td>
<td>Trandolapril/verapamil (1/240, 2/180, 2/240, 4/240)</td>
<td>Tarka</td>
</tr>
</tbody>
</table>

SOURCE: JNC-7 2003; DRUG FACTS AND COMPARISONS 2003
When pharmacotherapy is indicated for hypertension, there are many drug classes and agents that can be used to initiate and maintain BP control. Each class has specific advantages and disadvantages for a given situation. The appropriate medication(s) are clarified by the new JNC-7 guidelines both for general use and for specific situations.

For the future, a simplified approach to choosing antihypertensives will improve achievement of BP control by narrowing pharmacotherapeutic options for each patient type and clinical condition. The most important goal in managing hypertension is to achieve BP control as specified by JNC-7.

CONCLUSION

REFERENCES


Fixed Low-Dose Combination Therapy: Current Recommendations

L. MICHAEL PRISANT, MD, FACC, FACP
Medical College of Georgia

SUMMARY

JNC-7 recommends initiating combination therapy in specific circumstances. Hypertension involves numerous body systems; interrupting only one of these systems with monotherapy is frequently insufficient to achieve control. Altering two systems by combining drugs with different mechanisms of action increases the likelihood of control.

The current rate of hypertension control in the United States, 34 percent (JNC-7 2003), is unacceptably low. Therefore, the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC), in its seventh report (JNC-7), revised its guidelines regarding mono- and combination therapy as first- and second-line treatment modalities, based on data from large clinical studies. JNC-7 recommends initiating combination drug therapy if blood pressure (BP) is >20/10 mm Hg above goal blood pressure (<140/90 mm Hg). Combinations of two or more drugs for diabetic patients and three or more drugs for chronic renal disease are often required to achieve BP <130/80 mm Hg, the level of control that JNC-7 advises for these populations (JNC-7 2003).

Updates in JNC guidelines have lowered target BP levels and have concentrated on systolic hypertension. Systolic blood pressure (SBP) is an independent and accurate marker of cardiovascular disease and is much more difficult to control than diastolic blood pressure (DBP).

It is clear that one of the most important and overlooked reasons for low rates of response to BP therapy, particularly regarding SBP, is that safe and adequate control with one drug is difficult or impossible in the majority of patients. Hypertension is a multifactorial disease with many physiological pathways involved in the disease process. The body systems involved include the vasculature, heart, kidneys, and the nervous system’s pressor response. Interrupting only one of these systems is usually insufficient to control blood pressure. However, chemically altering two body systems by combining drugs with different mechanisms of action increases the likelihood of controlling blood pressure. Several such approaches are listed in Table 1 on page 46.

NONRESPONSIVE INITIAL DRUG THERAPY

Combination therapy should be considered for patients with an incomplete therapeutic response to an initial agent. The theoretical requirements of combination therapy are: (1) The combination must have superior efficacy to monotherapy; (2) Each component must contribute to the therapeutic effect; and (3) Dosage forms must be satisfactory regarding bioavailability, absence of unwanted interactions, and careful selection of doses for each component (Oster 1987).

The rationale for combination therapy is to maximize hypotensive effect (using two complementary antihypertensive agents to achieve additive results while blocking opposing homeostatic mechanisms) and to minimize side effects by permitting lower doses. Combination therapy must be approached with care, however.
Considerations include tailoring the combination to the patient and patient type; additive effects of the agents and their bioavailability must be foreseen. Finally, dose selection for each component is key to success (Bakris 1998, Hannson 1998).

Figure 1 depicts responder rates for six antihypertensives used as monotherapy in the Veterans Administration Cooperative Study (Materson 1995). The definition of responder was DBP <90 mm Hg at titration of therapy and <95 mm Hg after 12 months. A placebo-corrected response occurs in less than half of patients on monotherapy without taking SBP into consideration.

In the Hypertension Optimal Treatment (HOT) Study, 68 percent of subjects required more than one agent. Almost 75 percent of patients in the group who had a DBP goal of ≤80 mm Hg required two or more drugs to achieve control (Hansson 1998). In the United Kingdom Prospective Diabetes Study, 29 percent of subjects required three or more agents to achieve a BP of 144/82 mm Hg at 9 years after randomization (UKPDS 1998).

Figure 2 shows evidence from five large placebo-controlled trials in which multiple agents were needed to control blood pressure.

Unfortunately, there is a tendency among physicians often to leave BP inadequately controlled for fear of increasing doses and side effects. Results of an Argentine study (Kuschnir 1996), however, indicate that when two appropriate agents are combined, side effects are often reduced, especially when compared with escalating the dose of a single agent.

**HIGH-RISK HYPERTENSIVES**

New products that combine antihypertensive agents (usually with a diuretic) make it possible to administer one pill and achieve aggressive BP goals in high-risk patients. High-risk populations include diabetics, the elderly, blacks, and the renally impaired. Successful blood pressure reductions in patients with diabetes or renal in-
sufficiency has been shown to reduce target organ damage.

**Diabetic patients**

In the HOT study, for the diabetic cohort, the end-of-study blood pressure levels showed that despite differences of only 2 mm Hg, there were significant reductions in cardiovascular disease between treatment groups. The group with the lowest DBP target (<80 mm Hg) had significantly better outcomes than those whose DBP was reduced to <85 mm Hg or <90 mm Hg (Hansson 1998).

In diabetic patients, there is some information based on clinical trials relating to long-term cardiovascular morbidity and mortality outcomes with certain drugs. Blood pressure reductions with angiotensin II receptor blockers (ARBs) appear to be equivalent to those of ACE inhibitors. ARBs are well tolerated, and their use results in regression of left ventricular hypertrophy; there are positive hemodynamic effects in congestive heart failure and decrease in the progression of diabetic nephropathy and proteinuria compared with regimens that do not contain an ACE inhibitor or an ARB (Moser 2002). There is a direct correlation between systolic blood pressure and the decline in glomerular filtration rate.

**The elderly**

The treatment of hypertension in older persons requires consideration of polypharmacy, altered drug metabolism, and also changes in physiological characteristics. In this population, it is important to avoid the debilitating complications of stroke, heart failure, angina, myocardial infarction (MI), and renal failure.

Elderly patients may have comorbidities, for which specific drug mechanisms of action aside from BP lowering is necessary. For these high-risk patients, the target BP is lower and the approach to therapy more aggressive, yet balanced with caution (Bakris 1998).

A target SBP of <140 mm Hg is reasonable in patients over 65 unless diabetes or renal insufficiency is present. The Systolic Hypertension in the Elderly Program (SHEP) study found a 36-percent reduction in fatal and nonfatal strokes with treatment (chlorothalidone with either atenolol or reserpine added if needed). Forty-four percent of subjects received combination therapy to attain the BP goal. Although there were statistically significant changes in levels of glucose, total cholesterol, creatinine, and triglycerides, these increases were not clinically significant (SHEP Cooperative Research Group 1991).

Comorbidities in the elderly can include reduced myocardial contractility and renal function. Hepatic metabolism is slightly altered because of a decline in hepatic mass and blood flow. Further, because of the aging process, total body water is reduced, and there is often impaired baroreceptor responsiveness with possible postural hypotension; cognitive function may be impaired, negatively affecting adherence to therapy. In the elderly, body fat increases and gastric absorption decreases. Thus, the volume of distribution of water-soluble drugs may be smaller in the elderly, resulting in higher plasma drug concentrations. Also, lipid-soluble drugs have greater volume distribution and longer elimination time.

Many elderly patients are on multiple medications that may interfere with the efficacy of hypertension drugs. An example is the use of NSAIDs for arthritis, which blocks the action of many antihypertensive agents, especially diuretics and ACE inhibitors (Prisant 2000). Fixed incomes may limit drug choices in the elderly. All of these factors may increase the likelihood of adverse drug reactions and/or nonadherence.

Combination therapy, particularly combinations that include low-dose diuretics, often achieves BP control in the elderly. Volume depletion or orthostatic hypotension is unusual when diuretics are combined with another hypotensive agent in the elderly. The basic approach for drug therapy in this population is to “Start low and go slow” (Prisant 2000).

**Black patients**

The prevalence of hypertension in blacks older than
50 is 50–70 percent (Burt 1995). However, the African-American Study of Kidney Disease (AASK) trial and the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) study showed that blacks can achieve adequate antihypertensive response when treated with appropriate agent(s) (ALLHAT 2002). Used as monotherapy, ACE inhibitors, ARBs, and beta blockers do not achieve BP goals in this population because of the high prevalence of salt-sensitivity and suppressed renin activity. However, this effect is eliminated by concomitant diuretic use in combination therapy. Adverse effects, such as edema, diminish with certain combinations. Low-dose diuretics, such as 6.25 to 12.5 mg of hydrochlorothiazide (HCTZ), decrease the probability of metabolic side effects from the diuretic (Prisant 1995). Edema accompanying calcium channel blockers may decrease with the addition of an ACE inhibitor or a diuretic. The hypotensive effect of diuretics combined with ACE inhibitors, ARBs, or beta blockers in blacks can alleviate such comorbid conditions as angina, congestive heart disease, heart failure, diabetic nephropathy, and migraine (Douglas 1998).

### SPECIFIC DRUG COMBINATIONS

The U.S. Food and Drug Administration has approved five combinations for an indication as first-line therapy: bisoprolol/HCTZ, captopril/HCTZ, and the double diuretics (e.g., amiloride with HCTZ). Because of new evidence from ALLHAT (ALLHAT 2002), an appropriate protocol for a patient without comorbidities would be to use a diuretic then switch to a single-pill combination drug. Diuretics are additive to all agents, including such second-line drugs as alpha, stimulants, alpha, blockers, and reserpine. The classes to use as combination therapy depend on patients’ comorbidities, such as MI history or angina (beta blocker), or kidney disease (ACE inhibitor or ARB).
Antihypertensive drugs are generally complementary; however, there are some combinations that tend to be more favorable (Figure 3). Favorable combinations are shown in the figure by the blue lines. Although drug combinations shown by other colors can be used, they tend to be less complementary and frequently do not result in additive reductions in BP (Chalmers 1993).

Tables 2 and 3 give examples of beneficial and non-beneficial combinations.

Under special circumstances, adding certain drugs may be useful not only in reducing BP, but in controlling concurrent illnesses. Using a dihydropyridine calcium antagonist with a beta blocker is effective for treating angina. An ACE inhibitor in combination with a diuretic is well-suited first-line therapy for hypertension with systolic heart failure. In hypertensive patients with either hypertrophic cardio-myopathy or hyperkinetic heart syndrome, a beta blocker and a nondihydropyridine calcium antagonist (verapamil or diltiazem) can be used cautiously (Prisant 2001).

Dihydropyridine and nondihydropyridine calcium channel blockers are additive for reducing blood pressure (Kaesemeyer 1994, Saseen 1996). This combination can be used in select patients who have difficult-to-control hypertension. One study found that the combination of nifedipine plus diltiazem was slightly more effective than nifedipine plus verapamil, but both combinations had at least additive effects (Saseen 1996).

Table 4, on page 50, lists combinations for specific situations.

### CONCLUSION

Because information is rapidly forthcoming in the hypertension field and some algorithms are still controversial, there is a disconnect between the approved labeling for antihypertensive classes and expert-recommended protocols and guidelines.

If there were a single agent that could achieve the following, it would:

- Effectively reduce BP

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**TABLE 3** Controversial antihypertensive combinations

<table>
<thead>
<tr>
<th>Combination</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium channel blocker + diuretic</td>
<td>• Studies that start with a calcium antagonist do not always show a benefit of adding a diuretic*</td>
</tr>
<tr>
<td>Beta blockers + alpha₂ stimulants</td>
<td>• Not additive</td>
</tr>
<tr>
<td></td>
<td>• Potential for paradoxical increase in BP</td>
</tr>
<tr>
<td></td>
<td>• Rebound hypertension</td>
</tr>
<tr>
<td>Beta blocker + nondihydropyridine calcium channel blocker</td>
<td>• Can cause extreme bradycardia, advanced heart block, systolic heart failure</td>
</tr>
<tr>
<td></td>
<td>• May be useful in patients with hyperkinetic heart syndrome or hypertrophic cardiomyopathy</td>
</tr>
<tr>
<td>Beta blocker + ACE inhibitor</td>
<td>• Not additive for hypertension, but should be used in heart failure and MI</td>
</tr>
<tr>
<td>Alpha₂ stimulant + alpha₁ blocker</td>
<td>• Not additive for hypertension</td>
</tr>
<tr>
<td>Loop diuretic + thiazide diuretic</td>
<td>• Potential volume depletion and electrolyte disturbance</td>
</tr>
</tbody>
</table>

* Data are inconclusive.

SOURCE: PRISANT 1989

**FIGURE 3** Concomitant use of antihypertensive drugs

Diuretic → Ca-Blocker

α₁-Blocker → β-Blocker

ACE Inhibitor → AT1-Blocker

AT1-blocker = angiotensin receptor blocker; ACE = angiotensin converting enzyme inhibitor

SOURCE: MOSER AND PRISANT 1997
• Remain effective over 24 hours with once-daily dosing
• Achieve a high response rate
• Cause minimal number of adverse events (comparable to placebo)
• Reduce negative metabolic side effects
• Remain affordable, especially for those on fixed incomes

Regardless of whether the labeling advises it, physicians will continue to use combinations of antihypertensives for first-line therapy, especially in patients with comorbidities, to prevent potentially fatal or debilitating cardiovascular events.

REFERENCES
Hypertension & angina
Betablockers ± dihydropyridine calcium antagonist ± nitrates
ACE inhibitors or ARB + beta blockers ± spironolactone
ACE inhibitors or ARB + diuretic
Diuretic ± calcium antagonist

SOURCE: CHALMERS 1993

Hypertension, the most treatable cardiovascular disease, remains widely undertreated. Moreover, blood pressure (BP) is controlled to <140/90 mm Hg in only one third of hypertensive individuals, according to data from the National Health and Nutrition Examination Survey (JNC-7 2003). The public health toll of inadequate treatment is considerable. Without aggressive efforts to treat and control hypertension, its socioeconomic burdens can only rise.

Why is hypertension not controlled, despite the availability of many effective therapies to treat it? Many have suggested that access to care is a problem, yet the majority of individuals with hypertension are seen in clinical practice settings on an annual basis. Studies suggest that lack of control is not attributable solely to lack of access to care, but to a broad spectrum of patient, provider, and health care delivery-related factors (Miller 1997).

**Patient issues.** Because hypertension is usually asymptomatic, patients frequently do not comply with therapy. Some studies suggest that less than half of patients remain on their antihypertensive medications at 1 year (McCombs 1994). The factors associated with patient nonadherence are numerous and complex, and are covered in detail by Elliott elsewhere in this publication.

**Provider issues.** Lack of BP control can be related to many factors, including physicians’ lack of adherence to a therapy program (Moser 2001), failure to prescribe a more aggressive treatment regimen when indicated (Berlowitz 1998), or disregarding the importance of systolic blood pressure (SBP). Failure to recognize the role of SBP is largely derived from old teachings that diastolic blood pressure (DBP) is a stronger predictor of cardiovascular risk and that elderly patients do not tolerate reductions in systolic blood pressure; however, the Framingham Heart Study (Kannel 1971) and the Multiple Risk Factor Intervention Trial (Neaton 1992) provide evidence that SBP is highly predictive of coronary heart disease death.

**Health care delivery issues.** Studies suggest that when health plans provide physicians with feedback and reminders about their patients’ BP status (based on laboratory values and other clinical records), control rates improve (JNC-7 2003). Health plan audits of medical records to determine whether patients are being managed according to standards based on national guidelines also have led to improved rates of control.

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**SUMMARY**

Using tools developed by NCQA, Rand, and other institutions, health plans and providers can take an aggressive stance toward managing hypertension. This effort has led to gains in blood pressure control in some populations, greater recognition of the importance of controlling hypertension, and increased attention to processes that promote higher-quality health care.

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1 Nancy Houston Miller, RN, is Associate Director of the Stanford Cardiac Rehabilitation Program and adjunct clinical assistant professor at the University of California–San Francisco (UCSF) School of Nursing. Her responsibilities include directing major clinical research trials in prevention and cardiac rehabilitation. Miller is a past chairman of the California affiliate of the American Heart Association. She represents the American Nurses Association on the Coordinating Committee of the National High Blood Pressure Education Program. She has written more than 100 articles and book chapters in the areas of risk factor management, case management, and recovery of post-MI patients. Miller received her bachelor of science degree from the University of Washington School of Nursing.
**QUALITY MEASUREMENT**

**NCQA’S ROLE**

The opportunity to raise standards of care for the hypertensive population has been recognized and addressed by the National Committee for Quality Assurance (NCQA), a not-for-profit organization dedicated to improving health care quality through its evaluation and accreditation of health plans and physicians. NCQA’s Health Plan Employer Data and Information Set (HEDIS) is a tool used by more than 90 percent of health plans to measure performance on processes and outcomes of care within managed care plans. Most HEDIS measures estimate the percentage of eligible plan members who receive appropriate health care services; eligibility and appropriateness is determined by accepted standards of health care practice. Health care purchasers use HEDIS data to choose plans that provide high-quality care. Thus, the measures stimulate both competition and performance among health plans. The result is increased attention to processes that promote higher-quality health care.

**HEDIS hypertension measure**

In 1999, NCQA introduced a measure to assess the degree to which commercial managed care plans succeed at caring for members with high blood pressure. Initially, the measure’s definition of control of treated hypertension was identical to that identified in the sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-6). The HEDIS measure *Controlling High Blood Pressure* determined the extent to which blood pressure was controlled to \(<140/90 \text{ mm Hg}\) in members age 46–85 who have diagnosed hypertension. Both SBP and DBP had to be below these thresholds for the member’s blood pressure to be considered controlled.

In 1999, the figure indicating a health plan’s performance on this measure was the percentage of members who take medications for hypertension and whose BP was controlled to \(<140/90 \text{ mm Hg}\) (this has since been altered; discussion to follow). This estimate of performance is derived from a sample of 411 eligible members, selected at random. The BP reading recorded during the member’s last three clinic visits in the measuring year are averaged; if fewer than three readings are available, then a single measurement or two averaged measurements, depending on what is available, is reported to NCQA.

The hypertension measure has two goals:

• To provide a means of objectively quantifying the performance of different HMOs in controlling blood pressure among diagnosed hypertensive members; and

• To provide an incentive to health plans to control members’ blood pressure, in the hope that the result will be actual improvement (Steinberg 2000).

**Health plan performance**

In 1999, when the HEDIS measure was implemented, the mean control rate among participating HMOs was 39.0 percent, meaning that fewer than 4 of 10 hypertensive members’ blood pressure was controlled. The average rate rose to 51.5 percent in 2000 (Figure 1), although some of this increase may be attributable to a change in how data were collected. The rate of increase was slightly lower in plans whose performance on this measure was below average, while above-average plans had larger increases — 14 percentage points at the 75th percentile and 15 percentage points at the 90th percentile.

The near-13-point increase in the average score from 1999 to 2000 translated to roughly 250,000 additional people whose blood pressure was controlled in 2000, reducing their risk of heart disease, heart attack, and stroke (NCQA 2001).

This increase is impressive, but some analysts — and NCQA itself — suggest that it may provide a somewhat inflated picture of how well hypertension is being controlled within the overall managed care population. In 2000, the HEDIS definition of hypertension control was changed to SBP \(\leq 140 \text{ mm Hg}\) and DBP \(\leq 90 \text{ mm Hg}\). The change was made to accommodate practitioners who round their results up.

Researchers from Group Health Cooperative’s Center for Health Promotion, in Seattle, undertook an investigation to determine the extent to which this change may have led to increases in HEDIS scores (Green 2003). Their analysis indicates that when the target for BP was changed, the difference between patients in their health plan with uncontrolled versus controlled BP trended upward; they found a 4-percent difference below age 40 and an 8- to 9-percent difference at age 60 and older. Forty-one percent had a SBP of \(\leq 140 \text{ mm Hg}\), but only 33 percent were \(<140 \text{ mm Hg}\). A decline of even 1 mm Hg might result in a substantial reduction in cardiovascular events, so any upward change in the measure’s definition of control could have significant ramifications in terms of actual clinical outcomes.

The authors rightly conclude that while defined targets for achieved BP have some utility in comparing health plans, they do not necessarily adequately measure the more complex issue of how well hypertension is actually being controlled in clinical practice. Bias rounding, variations in blood pressure readings due to examiner skill, and the imprecision of measuring instruments can contribute to falsely optimistic findings about how well our nation is managing hypertension (Green 2003).

In 2001, with no further changes in the definition, the average control rate increased 4 percentage points, to 55.4 percent (Figure 1). While the rate of increase was smaller, it nonetheless indicates new attention and ad-
herence to evidence-based treatment recommendations.

In 2000, NCQA extended its reporting to people enrolled in managed Medicaid and Medicare plans (Figure 2). The average Medicaid rate of compliance with the HEDIS hypertension measure was 45.4 percent, 6 percentage points lower than the commercial rate, while the average Medicare plan scored 46.7. The lower rates of control are significant, and are due to the difficulty of managing hypertension in disadvantaged populations and the elderly.

**BEYOND HEDIS**

While the HEDIS measure helps to promote positive change in clinical practice, it exists within the context of numerous logistical and practical considerations. Of particular note is the fact that the unit of analysis for this measure is the health plan, not the physician. Although the HEDIS measure reflects the health plan’s performance, it does not provide any information about the performance of an individual physician. Whereas better health plan performance may draw more employers to the plan and result in business benefits, physicians do not have such gains — and actually participate in measurement of services at a financial loss. They are required to perform time- and labor-intensive data extraction from medical files to report their performance to the health plan, frequently without compensation (Steinberg 2000).

Further, the HEDIS measure can help a plan to determine when improvement is needed, but it is up to individual health plans to determine best practices for achieving positive change. The objective here is not to belabor any shortcomings of the HEDIS measure, but to emphasize that even though a number of groups have produced quality-assessment tools, they typically suffer from a variety of limitations: Information is obtained on only a few dimensions of quality; the tools rely exclusively on administrative data; they examine quality only for users of services rather than populations; or they fail to provide a scientific basis for the quality indicators (Rand 2000).

**Outcomes vs. process measures**

The HEDIS standard is an outcomes measure. The Rand Corp., alternatively, developed a process hypertension measure, the QA Tool. Process measures include the ways in which clinicians and patients interact and the appropriateness of medical treatment for a specific pa-
QUALITY MEASUREMENT

tient. Outcomes measures, on the other hand, include changes in patients’ health status.

Cary Sennett, MD, PhD, NCQA’s former executive vice president, describes the relationship between process and outcomes as a pyramid. The peak is the outcome of interest. The base contains all the knowledge necessary to maximize the likelihood of achieving that outcome. Some relevant questions designed to gather that knowledge are presented in Table 1 (Sennett 2000).

The Rand QA Tool screening measure is based on published guidelines from the Canadian Task Force on the Periodic Health Examination, the United States Preventive Services Task Force, and the American College of Physicians. For indicators of treatment and follow-up care, Rand relied on JNC-5 recommendations (now considerably out of date in light of the release of JNC-7).

In developing the QA Tool, Rand selected areas for clinical measurement based on scientific literature. The hypertension module of the QA Tool includes several measures of treatment intensity known to affect BP control. This type of information can help health plans to focus their interventions; when the HEDIS measure points to a problem with hypertension control, the QA Tool can help identify specific processes that need to be improved. But can health plans afford to implement both outcomes and process measures, particularly when incentives reside solely within the outcomes-based tool?

In many instances, as well as in the management of hypertension, process may not be as important as outcome. For example, completeness may suggest procedures that do not affect outcome; most hypertensive patients do not require extensive or expensive procedures either before or during therapy (Moser 1994).

Power to change behavior

The recent release of JNC-7 suggests that continued efforts to control high blood pressure are paramount. The report suggests that many millions of Americans with blood pressure levels previously labeled as normal are now prehypertensive— and may be at increased risk of stroke, heart failure, and kidney disease.

In the future, quality indicators like those of NCQA may change based on the release of new guidelines or a need to modify measures based on opinion from health plans. The National Committee for Quality Assurance recognizes the capability of MCOs to improve blood pressure control in members, especially in such subpopulations as the elderly. However, the JNC-7 report challenges medical directors, physicians, pharmacists, and other health care professionals to play an active role in responding to the need to improve control.

Medical directors are in a unique position to offer educational messages to the health care community about the need to achieve better control rates. Continuing education programs about the guidelines that plans share with physicians and other health care professionals offer a mechanism for achieving this goal. Providing feedback to physicians about their own patients’ control is another successful technique for influencing behavior. This is especially beneficial when incentives are provided to physicians who work successfully with patients to achieve improved control.

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Disassembling key patient and physician management processes</th>
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</thead>
<tbody>
<tr>
<td><strong>Patient treatment and compliance</strong></td>
<td><strong>Physician understanding and management</strong></td>
</tr>
<tr>
<td>• Are patients with hypertension identified?</td>
<td>• Does the physician understand the importance of BP control?</td>
</tr>
<tr>
<td>• Once they are identified, do they see a physician regularly? How often?</td>
<td>• Does the physician understand the importance of isolated systolic hypertension?</td>
</tr>
<tr>
<td>• Are patients sent reminders to schedule or keep key appointments?</td>
<td>• In the exam room, does the physician counsel the patient about nonadherence?</td>
</tr>
<tr>
<td>• When patients see a physician, are they properly medicated?</td>
<td>• Are lifestyle issues addressed regularly?</td>
</tr>
<tr>
<td>• If patients are properly medicated, do they adhere to their therapeutic regimen?</td>
<td>• What is done between appointments to ensure that patients adhere to therapy or lead healthy lifestyles? Phone intervention? E-mail?</td>
</tr>
<tr>
<td>• If patients do not adhere to therapy, do they understand the importance of BP control?</td>
<td>• Is there appropriate managerial intervention if the physician does not follow proper clinical guidelines for hypertension?</td>
</tr>
<tr>
<td>• If patients do not adhere to therapy, have they been offered educational materials to help them understand the importance of BP control?</td>
<td></td>
</tr>
</tbody>
</table>

SOURCE: SENNETT 2000
However, data must be analyzed to determine whether the problem is failing to achieve a blood pressure goal due to inadequate therapy or patient nonadherence to a prescribed regimen. Poor adherence resulting from adverse drug reactions cannot be ignored. Thus, data must be accurately recorded to determine specific problems associated with lack of control. In a study published in the *New England Journal of Medicine*, 18 percent of patients reported adverse effects from medications prescribed for them, yet only 3 percent of medical records indicated these events (Ghandi 2000).

Physicians also can have a positive influence through their own initiatives. While the NCQA hypertension measure will not be changed in the near future, NCQA has initiated a program with the American Heart Association to recognize physicians who achieve blood pressure control, as well as other important quality indicators, such as LDL cholesterol goals in patients with cardiovascular disease. In this program, physicians (or MCOs that wish to recognize their physicians) can voluntarily submit data related to the treatment of their cardiovascular patients. Such reward- and recognition programs improve physicians’ awareness of processes that result in improved clinical outcomes, as evidenced by a previous NCQA partnership with the American Diabetes Association; here, physicians far exceeded national averages on NCQA diabetes measures (NCQA 2002). Pharmacists can support efforts to achieve better hypertension control. They are often familiar with methods used to obtain HEDIS data and can assist with efforts to acquire claims data and drug costs. Pharmacy systems may allow for access to information about patients’ acquisition of drugs, missed refills, and support for physicians to monitor side effects that may result from medications. In addition, drug-utilization tracking systems support pharmacists who work with physicians on drug simplification or help to identify patients who may need assistance in following a therapeutic regimen. By educating and counseling patients when dispensing drugs, community pharmacists can play an important role. Their capability to offer information about blood pressure, along with more widespread recognition of the importance of control.

Adequate control of blood pressure through achievement of goals is not easy. JNC-7 challenges health plans and professionals to improve treatment of a complex condition. The challenge is now.

REFERENCES


CONCLUSION

Significant barriers exist to improving hypertension control in the United States. Yet it is also clear that thousands of people — providers, people working in health care delivery systems, and accreditation groups — are committed to managing the problem aggressively. Many others have dedicated enormous time and resources to analyzing current management theories and best practices to determine the best way of doing so. Health plans and many providers continue to play a leadership role in this effort, guided by tools developed by NCQA and other institutions. The result has been significant gains in controlling blood pressure, along with more widespread recognition of the importance of control.

These people may not require specific treatment but should be followed and hygienic measures should be introduced (see article by Moser, beginning on page 12).
Compliance with hypertension therapy is key to achieving target blood pressure control rates. Compliance and persistence rates vary by drug class, but clinicians can take practical steps to improve patient adherence to any prescribed regimen. JNC-7 recognizes barriers to physician compliance with treatment recommendations.

Compliance in hypertension has many meanings. This discussion will focus on the ability of patients with hypertension to carry out a recommended therapeutic regimen — and a correlate, the ability of physicians to follow national guidelines regarding drug treatment and blood pressure (BP) goals.

The use of “compliance” in this sense (people following orders) is politically incorrect today, because it is paternalistic. In today’s world, patients are seen as autonomous, and their relationship with their physician is one of partnership in therapeutic decision making. For this reason, the term compliance increasingly is superseded by the more politically correct term, adherence. Hereinafter, the terms compliance and adherence are used interchangeably.

Compliance with hypertension therapy is key to achieving target blood pressure control rates. Compliance and persistence rates vary by drug class, but clinicians can take practical steps to improve patient adherence to any prescribed regimen. JNC-7 recognizes barriers to physician compliance with treatment recommendations.

PATIENT COMPLIANCE WITH DRUG THERAPY

The reasons for nonadherence are complex; its implications have important public health consequences. Overall, less than 50 percent of patients continue to take their initially prescribed class of antihypertensive drug for 4 years (Conlin 2001). The portion of those who properly adhere to therapy improves modestly when the drugs and medical care are provided free of charge, as in clinical trials.

Information about compliance with chronic drug therapy in clinical trials is limited. To achieve valid study results, investigators in clinical trials are highly motivated to ensure that participants comply with their regimens. In fact, most clinical trials have a run-in period, during which patients are given placebos to see if they take the medications as instructed. If they do not, they are disqualified from the study. Consequently, there is a substantial bias in clinical trials against people who are noncompliant.

Widespread noncompliance with medications may occasionally lead to different results and conclusions than the original intention-to-treat analysis. One famous example is the Beta Blocker Heart Attack Trial (BHAT), which was conducted from 1978 to 1980.
Horwitz (1990) obtained BHAT study data from the National Institutes of Health and published an analysis of the relationship between adherence and mortality. Surprisingly, BHAT participants who did not adhere well to their treatment regimen were 2.6 times more likely than good adherers to die within 1 year, whether they were on propranolol or placebo. The severity of their myocardial infarction (MI) did not account for their increased risk of death, nor did sociodemographic features, smoking status, or psychological characteristics. Good adherers on placebo also did better than poor adherers on placebo, and almost as well as good adherers on propranolol.

One explanation for these findings is that good adherers not only take their medicine correctly, but they also are likely to practice other health-promoting behaviors, such as seeing their doctors as recommended, maintaining appropriate body weight, eating a healthful diet, and exercising. This “healthy-cohort effect” means that adherence may be a marker for other behaviors that positively affect treatment outcomes.

Adherence in general practice

Unfortunately, patients in general medical practice tend to be less interested in and less educated about the disease process, its treatment, and the treatment options than participants in clinical trials. They tend to have more cognitive impairments; for example, they would not always be able to sign an informed consent form, a requirement for participating in a clinical study. Nor do many patients receive the degree of attention from their physicians that they would get in clinical trials from physicians, study coordinators, and other allied health personnel.

Approximately 10 percent of the overall expenditures on hypertension in the United States are wasted, due to noncompliance with medical advice and antihypertensive drug therapy (Levine 1996). Patients who do not follow the advice of their physicians and who do not take their medications correctly have an infinite cost/benefit ratio, because they incur all the costs associated with the therapy but do not derive any of the benefits of treatment.

Precisely assessing compliance with antihypertensive medications is generally difficult, but several simple measures are often recommended (JNC-6 1997). Some medications induce physical signs that are absent in those who have not recently taken them, e.g., bradycardia with beta blockers, orthostatic BP change with alpha blockers, and an increase in serum urate with diuretics. A telephone call to the patient’s pharmacy generally will reveal how many times the prescribed medications have been refilled during the last year.

Several interventions have been advocated to improve compliance with therapy (Table). Not all authorities would agree with every one of these points, but each can be helpful for some patients. For example, some studies show that a greater number of pills increases adherence (Sharkness 1992, Billips 2000), but these studies generally do not account for the fact that a greater severity of illness confounds these analyses. Sicker patients take more medications and are also more compliant.

Differential persistence with refills, by class of antihypertensive drug

There are significant differences in persistence (the proportion of patients who remain on initially prescribed therapy) with different classes of antihypertensive drug therapies in some clinical trials and in many pharmacy databases. One of the earliest experiences was in the United Kingdom, from 1992–1994, when 10,222 newly diagnosed hypertensive patients were studied. Continuation of therapy among four classes of hypertension drugs (diuretics, beta blockers, calcium channel blockers [CCBs], and angiotensin-converting enzyme [ACE] inhibitors) decreased progressively, with continuation of therapy at less than 50 percent for each class after 6 months of observation (Jones 1995).

Analysis of medical claims data from the Pennsylvania Medicaid Management Information System found that compliance is better among patients receiving newer classes of antihypertensive agents (i.e., ACE inhibitors or CCBs) than with older classes (i.e., diuretics and beta blockers), and that poor compliance is associated with higher health care costs (Rizzo 1997). Rizzo suggested that drugs’ adverse effect/tolerability profiles inversely affected compliance. It also is possible that, to some degree, lack of persistence may relate to the marketing of newer drugs.

More recent data, from comparative trials submitted to the U.S. Food and Drug Administration as part of new drug applications and from pharmacy benefit managers (PBMs), show even better persistence with angiotensin II receptor blockers (ARBs) than ACE inhibitors. A retrospective analysis of the Merck-Medco disease management database covering 1.3 to 1.6 million enrollees indicated that 64 percent of patients continued initial ARB therapy, with lower rates of persistence among those receiving ACE inhibitor, CCB, beta blocker, and thiazide diuretic therapy after 12 months of follow-up (Figure, Bloom 1998). Bloom theorized that tolerability may be a factor in the higher rates of persistence associated with ARB therapy, but emphasized that more studies are needed to explain the differences. A subsequent study of a subset of the same database over a 4-year follow-up period also showed that a higher percentage of patients remained on ARB therapy compared to other
antihypertensive drug classes (Figure, Conlin 2001).

In the largest published experience, two analyses of Saskatchewan Health databases also focused on persistence with hypertension therapy in actual practice. In the first analysis, patients with a prior diagnosis of hypertension were more persistent (97 percent at 1 year, 82 percent at 4.5 years) than those with newly diagnosed hypertension (78 percent at 1 year and 46 percent at 4.5 years). Among the newly diagnosed, older patients were more likely to persist with therapy than younger ones, and women more than men (Caro 1999a).

In a second analysis of these data, there was significantly higher persistence with ACE inhibitors after 6 months (89 percent) than with CCBs, beta blockers, and diuretics (86, 85, and 80 percent, respectively). ARBs were not included in this study because they were new. This ordering was also seen at 1 year and achieved statistical significance for all three comparisons against diuretics. These findings contrast with recommendations based on clinical trial evidence that diuretics be prescribed as the preferred initial therapy and changed if poorly tolerated. While the reasons for poor persistence and for differences in persistence between drug classes are unclear, higher persistence with ACE inhibitors may be due to better tolerability (Caro 1999b).

Consequences of nonpersistence
Discontinuing some antihypertensive medications (including beta blockers and clonidine) can increase BP and MI risk in succeeding hours and days. There is some evidence that lack of persistence with drug therapy increases the risk of cardiovascular events. The best data on outcomes are from BHAT, in which decreased persistence with therapy was associated with a higher risk of second MI.

Nonpersistence also carries a large economic cost, which represents a balance between the following:

- The cost of office visits and wasted pills, as well as opportunity costs of future events that could have been prevented if the patient had taken medications as prescribed
- The short-term savings of not having to fill prescriptions that a patient stops taking on his/her own.

Even nonpersistence that results in a change in therapy carries a large economic cost. For example:

- Hospital/ER services may increase if serious adverse events occur with the old drug.
- Pharmacy charges increase, due to additional drugs needed.
- Health care provider services increase, due to increased visits to assess efficacy.
- Laboratory charges may increase due to need for increased surveillance.
- Costs are associated with lost productivity.
- Transportation costs are incurred for visits to the pharmacy and the physician’s office.

**Adherence to scheduled clinic appointments**

In an effort to identify factors that might affect whether a patient will “drop out” of clinic, we found a correlation between nonadherence to scheduled clinic appointments and not refilling prescriptions (Elliott 1993). The simplest explanation is that obtaining a prescription is most commonly done during office visits, and conversely, that patients who abandon their office visits are likely to abandon their prescribed therapy also.

In 1985, our clinic adopted an unusual standard operating procedure, to invite all patients who missed an appointment to return. This effort began within 1 hour of the missed appointment. Patients were defined as dropouts if they did not return to clinic after three consecutive telephone calls or letters. After excluding patients who had a “good” reason not to return to clinic (e.g., death, referral to another physician, moving out of state

**TABLE Interventions that promote patient adherence**

- Educate the patient regarding the proper use of medications
- Improve patient’s social support network (e.g., spouse, caretaker)
- Increase patient’s autonomy and involvement in decision making
- Be perceived as having a more caring relationship with patients
- Remove barriers to compliance with pill taking
- Integrate into activities of daily living (e.g., brushing or other daily care for teeth)
- Avoid large (“horse”) pills
- Avoid bad-tasting formulations (e.g., lactulose, quinine)
- Simplify the therapeutic regimen
  - Minimize the number of pills
  - Minimize the frequency of pill taking
  - Minimize the inconvenience of pill taking
- Provide positive reinforcement about achieving therapeutic goals
- Maintain continuity of care with the same practitioner
- Use well-tolerated antihypertensive drug therapy, individualized for each patient
or more than 100 miles away), we compared the characteristics of the 1,204 dropouts with the 997 who continued in care.

Those who continued in care had significantly higher age and systolic blood pressure (SBP) at the initial visit. We compared drug therapies at the last visit between those who dropped out and those who continued in care, to see if specific types of therapy affected the patients’ willingness to continue with their care in our clinic. All drug classes were used (in order of frequency: diuretics, CCBs, ACE inhibitors, beta blockers, centrally acting drugs, alpha blockers, and vasodilators).

In detailed analyses, there were also correlations between drug class and the proportion of patients who continue to adhere to scheduled clinic appointments (Elliott 1994). The lowest adherers were significantly more likely to take diuretics or beta blockers, and higher adherers were more likely to be on CCBs or ACE inhibitors. Low adherers tended to be at higher risk for hospitalization and emergency room visits.

We also have studied the association of initial drug therapy on the propensity for dropping out of clinic among the 1,114 patients who were initially untreated at presentation. After adjustment (as before), an initial diuretic was associated with a significant 42-percent higher risk of dropping out of clinic in the future. An initial prescription for a diuretic or beta blocker (“preferred therapy” in the fifth report of the Joint National Committee on the Detection, Evaluation, and Treatment of High Blood Pressure [JNC-5]) was similarly associated with a 39-percent increased risk of dropping out of clinic in the future. If the first two prescriptions followed stepped-care principles (diuretic, then a beta blocker or centrally acting drug), there was a significant, 52-percent higher risk of dropping out.

Our preliminary data indicate that people who quit taking medications (as assessed by pharmacy records) have a significant, 58-percent higher risk of dropping out of clinic. Similarly, people who drop out of clinic have a significant, 86-percent higher risk of death or cardiovascular hospitalization after adjustment for all baseline differences across groups.

These data have some important inherent limitations, including that they are generated from a retrospective analysis of one clinic’s data, there was no randomization of drug treatment, and, though we attempted to adjust statistically for socioeconomic and other confounders, we may not have been able to include them all.

**PHYSICIAN COMPLIANCE WITH TREATMENT RECOMMENDATIONS**

In the 1960s and 1970s, high BP (defined as ≥160/95 mm Hg) was controlled in only 16 percent of patients in the United States. Today, 65 percent of these patients are reducing their BP with medication, and 34 percent are controlling their BP to <140/90 mm Hg with medication (JNC-7 2003). While controlled hypertension in the United States is higher than in other countries, the current proportion of 34 percent is substantially below the goal of 50 percent that was set in Healthy People 2010 (HHS 2000). Several studies suggest that physician noncompliance with national guidelines may be a factor.

In a study of 800 hypertensive men at five Department of Veterans Affairs sites during a 2-year period, BP declined 6.3 mm Hg among patients with the most intensive treatment, but increased 4.8 mm Hg among patients with the least intensive treatment (Berlowitz 1998). The authors concluded that many physicians are not sufficiently aggressive in their approach to hypertension treatment.
IMPROVING OUTCOMES

An analysis of data from the Third National Health and Nutrition Examination Survey (1988–1994) showed that only 23 percent of those with hypertension were taking medications that controlled their condition, despite the fact that the great majority had health insurance. Being 65 years or older was the biggest single predictor for both lack of awareness of hypertension and for the lack of control among those who were aware of their condition (Hyman 2001). This analysis challenges widely held beliefs that poor control is due to access problems, noncompliance with treatment, or a disproportionate prevalence of hypertension in ethnic and racial minorities, and suggests that physician practice patterns may contribute to lack of awareness of hypertension in their patients and/or lack of control among those receiving treatment (Moser 2001).

In the early 1990s, there was strong evidence that physician prescribing patterns did not correspond to national guidelines. In 1993, JNC-5 recommended diuretics and beta blockers as preferred drugs, as they had been shown in clinical trials to prevent cardiovascular events. Nevertheless, between 1992 and 1995, the proportion of dispensed CCB and ACE inhibitors increased (CCBs, from 33 to 38 percent of all antihypertensive prescriptions; ACE inhibitors, from 25 to 33 percent), while prescriptions for beta blockers and diuretics declined (from 18 to 11 percent and from 16 to 8 percent, respectively) (Siegel 1997). The prescribing of newer and more expensive drugs was at least partially attributed to pharmaceutical promotional efforts (Moser 1998).

More recent data from the U.S. Department of Veterans Affairs (where promotional practices may have less effect) are more aligned with national guidelines. From 1997 to 1999, the share of dispensed diuretics and beta blockers increased (11.3 and 10.5 percent, respectively), while prescriptions for CCBs decreased 11.2 percent (Siegel 2001).

Intensified treatment in high-risk patients

JNC-6 (1997) recommended lower target BP for individuals with diabetes, renal impairment, heart failure, and other high-risk conditions. Since JNC-7 (2003), a target BP of <140/90 mm Hg is recommended for patients with uncomplicated hypertension, while <130/80 mm Hg is recommended for diabetic patients and the renally impaired.

Evidence from clinical trials strongly supports the association between control and increased quality of life/decreased morbidity and mortality. Economic data demonstrate that intensified treatment of high-risk individuals also results in substantial savings in overall health costs. While most physicians are aware of these recommended targets, however, many are not attempting to meet or exceed them. Polypharmacy is a major barrier; patient compliance declines with increasing complexity (e.g., a larger number of pills per day or those that must be taken more than once daily).

Physician compliance with guidelines

Although there are no proven methods to improve physician compliance with guidelines, many are being studied. Surveillance of a physician's prescribing habits, to assess compliance with guidelines, has become an important function of PBMs and some managed care organizations. One option for health plans is to deselect a noncompliant physician from their provider panels and replace that physician with one who is relatively more compliant. Another is to tie financial incentives, such as withholdings, to outcomes goals (e.g., controlling hypertension in a specified portion of a panel of diagnosed hypertensive patients).

Many health plans employ a related strategy: profiling a physician's prescribing patterns to ensure that the proportions of diuretics, beta blockers, ACE inhibitors, and ARBs prescribed are appropriate. If, for example, one's pattern falls outside of a health plan's prescribing guidelines, that physician can be targeted for "academic detailing." If inappropriate prescribing patterns continue, or if a physician is in the bottom 5 percent of a provider panel in terms of compliance, he or she may experience such consequences as financial disincentives or deselection.

Eliminating physicians who prescribe inappropriately, while rewarding physicians who do comply, should substantially improve physician compliance with national guidelines. Several studies in progress will increase understanding of factors that contribute to physician compliance and will suggest innovative ways to improve it. With the advent of JNC-7, which unequivocally emphasizes the need for improved physician attention to its recommendations (JNC-7 2003), public and private payers, in concert with governmental agencies, professional societies, and not-for-profit advocacy organizations, are expected to make an unprecedented effort to increase physician compliance and awareness by disseminating the new guidelines through multiple communications media.

CONCLUSION

Effective management of hypertension depends on patient compliance with lifestyle recommendations, with drug therapy regimens, and with scheduled clinic appointments, as well as on physician compliance with treatment recommendations and national guidelines. While a variety of initiatives are contemplated to increase physician compliance, a correspondingly large ef-
fort to increase patient compliance may now be in order. A team-based approach that includes nurses and pharmacists collaborating with physicians may provide the support and education that patients need to comply not only with their antihypertensive drug therapy and scheduled office visits, but also with recommended lifestyle changes.

REFERENCES


CONTINUING EDUCATION POST-TEST

P&T Digest
Hypertension

Please tear out the combined answer sheet/evaluation form on page 63 (physicians) or page 64 (pharmacists). On the answer sheet, place an X through the box of the letter corresponding with the correct response for each question. There is only one correct answer to each question.

1. What are the chances that a normotensive 55-year-old will develop hypertension during the course of his or her lifetime?
   a. 50 percent.
   b. 60 percent.
   c. 70 percent.
   d. 80 percent.
   e. 90 percent.

2. If a person were older than 40 with a blood pressure (BP) up to 185/115 mm, how would a 20/10 mm Hg increase in BP affect that person’s risk for cardiovascular disease?
   a. It would have no effect on risk.
   b. It would double the risk.
   c. It would increase risk by 10 percent.
   d. It would increase risk by 25 percent.

3. In an individual older than 65 with a blood pressure >140/90 mm Hg, what is 2 or 3 times more likely to happen in that person than in a normotensive counterpart?
   a. Angina.
   b. Myocardial infarction.
   c. Sudden death.
   d. All the above.

4. Is the “J-curve phenomenon” (implying that lowering systolic blood pressure in the elderly is hazardous) still considered valid?
   a. Yes.
   b. No.

5. How many hypertensive individuals over age 60 have isolated systolic hypertension?
   a. 20 percent.
   b. One third.
   c. Two thirds.
   d. 80 percent.

6. In Framingham Heart Study patients whose systolic blood pressure was >160 mm Hg, how did cardiovascular events, such as CHD or stroke, correlate with their diastolic blood pressure?
   a. Cardiovascular risk was closely correlated with diastolic blood pressure.
   b. Cardiovascular risk was directly correlated with diastolic blood pressure.
   c. There was a trend toward a correlation.
   d. They were weakly or inversely correlated.

7. Which type of diuretic is recommended when treating patients with CHF or renal disease?
   a. Thiazide.
   b. Loop.
   c. Potassium-sparing.
   d. Type is inconsequential; all the above are appropriate.

8. What is the approximate yearly cost of hypertension in the United States, including both direct and indirect costs?
   a. $20 billion.
   b. $30 billion.
   c. $40 billion.
   d. $50 billion.

9. The aggregate cost estimate for hypertension and its complications was $108.8 billion in 1998, which was ______ of the total national health care expenditure.
   a. One fourteenth
   b. One twelfth
   c. One eighth
   d. One quarter

10. AT-II receptor blockers, or ARBs:
    a. Prevent AT-II–mediated vasoconstriction and aldosterone release, thereby reducing blood pressure.
    b. Cause cough and angioedema less frequently than ACE inhibitors.
    c. Do not alter the metabolism of bradykinin, norepinephrine, or substance P.
    d. Often are used as second-line alternatives for patients, such as those with heart failure or diabetes, who would benefit from an ACE inhibitor but who suffer from intolerable coughing.
    e. All the above.

11. Combination therapy chemically alters two or more body systems involved in hypertension, thus allowing lower doses.
    a. True.
    b. False.

12. In the United States thus far (up to JNC-7), combination antihypertensives approved for first-line therapy included all except:
    a. Bisoprolol/HCTZ.
    b. Captopril/HCTZ.
    c. Double diuretics (e.g., amiloride with HCTZ).
    d. Propranolol/HCTZ.

continued on page 65
CONTINUING EDUCATION ANSWER SHEET/CERTIFICATE REQUEST

P&T Digest

Hypertension

CME CREDIT FOR PHYSICIANS
Sponsored by The Chatham Institute

See page 64 for answer sheet for pharmacists

I certify that I have completed this educational activity and post-test and claim ______ credits.

Signature: _______________________________________

First name, M.I. ___________________________________

Last name, degree ________________________________

Title ___________________________________________

Affiliation _______________________________________

Specialty ________________________________________

Address ________________________________________

City _____________________ State  _____  ZIP ________

Daytime telephone (_______) _______________________

Fax (________) ___________________________________

E-mail __________________________________________

Physician — Maximum of 4 category 1 credits toward AMA Physician's Recognition Award.

Complete answer sheet/evaluation form and mail to:

Office of Continuing Education
The Chatham Institute
26 Main Street, 3rd Floor
Chatham, NJ 07928

Alternatively, this completed form may be faxed to (973) 701-2515.

Credit will be awarded on successful completion of assessment questions (80 percent or better) and completion of program evaluation. If a score of 80 percent or better is not achieved, no credit will be awarded and the registrant will be notified.

Please allow up to 6 weeks for processing.

The cost of this activity is provided at no charge to the participant through an educational grant by AstraZeneca.

EXAMINATION: Place an X through the box of the letter that represents the best answer to each question on pages 62 and 65. There is only ONE answer per question. Place all answers on this answer form:

1. A B C D E
2. A B C D E
3. A B C D E
4. A B C D E
5. A B C D E
6. A B C D E
7. A B C D E
8. A B C D E
9. A B C D E
10. A B C D E
11. A B C D E
12. A B C D E

PROGRAM EVALUATION
So that we may assess the value of this self-study program, we ask that you please fill out this evaluation form.

Have the activity's objectives been met?
(See page 4 for objectives)

<table>
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<th>Objective no.</th>
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Was this publication fair, balanced, and free of commercial bias? Yes _____ No _____
If no, please explain: _______________________________________________________

This educational activity has contributed to my personal effectiveness and should improve my ability to:

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Effectiveness of this method of presentation:

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Time spent reading this publication: H _____ M _______

What other topics would you like to see addressed?

_________________________________________________________________________

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Comments: ________________________________________________________________

_________________________________________________________________________
CONTINUING EDUCATION ANSWER SHEET/REQUEST FOR STATEMENT OF CREDIT

P&T Digest
Hypertension

CPE CREDIT FOR PHARMACISTS
Sponsored by The Chatham Institute

See page 63 for answer sheet for physicians

I certify that I have completed this educational activity and post-test and claim ______ credits.

Signature: _______________________________________
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Complete answer sheet/evaluation form and mail to:
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26 Main Street, 3rd Floor
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Alternatively, this completed form may be faxed to (973) 701-2515.

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EXAMINATION: Place an X through the box of the letter that represents the best answer to each question on pages 62 and 65. There is only ONE answer per question. Place all answers on this answer form:

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PROGRAM EVALUATION
To receive continuing education credit, please provide all information requested below. This assures prompt and accurate issuance of your continuing education certificate.

Please rate this program as follows:

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<td>Value to me in my daily responsibilities</td>
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How long did it take you to complete this continuing education activity?
Hours _____ Minutes _____

Requested topics/skills to address in future programs:

__________________________________________________

Did you detect any bias in this presentation?
Yes _____ No _____
If yes, please explain:

__________________________________________________

Comments :

__________________________________________________
13. All the following are true about the mechanisms of action of beta blockers except:
a. They decrease renin release.
b. They diminish sympathetic reflex (in combination with exercise).
c. They reduce central release of adrenergic substances.
d. They increase cardiac contractility and output.
e. They inhibit peripheral epinephrine release.

14. Overall, how many patients continue to take their initially prescribed class of antihypertensive drug for 4 years?
a. An unknown number.
b. Less than half.
c. The vast majority.
d. Slightly more than half.

15. What was a surprise finding of the Beta Blocker Heart Attack Study (BHAT), which studied 1-year mortality outcomes for treatment adherers versus nonadherers?
a. Placebo was not as preventive as propranolol in reducing mortality.
b. Nonadherers had 2.6 times the 1-year risk of death, whether on placebo or propranolol.
c. Adherers had 5.2 times the risk of death, regardless of treatment group status.
d. Adherence was not an influence on outcomes.

16. About 10 percent of the overall expenditure on hypertension in the United States is wasted because of noncompliance with medical advice and antihypertensive drug therapy.
a. True.
b. False.

17. How many patients can be expected to respond to initial monotherapy that is carefully evaluated and selected?
a. One third.
b. One half.
c. One fourth.
d. One eighth.

18. In a hypertensive patient with diabetic nephropathy, _____ is the medication of choice, though it is often necessary in such a patient to add a diuretic to the treatment regimen to achieve goal blood pressure.
a. A beta blocker
b. An ACE inhibitor or ARB
c. A calcium channel blocker
d. An aldosterone receptor blocker

19. What is likely to happen when adding a diuretic to the regimen of a patient with resistant hypertension?
a. The patient will achieve blood pressure control.
b. The patient will drop out of the treatment program.
c. Adherence to therapy will suffer dramatically.
d. The patient will develop headaches.

20. What would a black patient likely achieve when using a diuretic with either an ACE inhibitor or an ARB?
a. If doses were chosen carefully, no change in blood pressure would occur.
b. Blood pressure response would be smaller.
c. Blood pressure response would be greater.
d. Diuretics are not recommended in blacks.

21. The majority of uncontrolled hypertension occurs in patients with systolic rather than diastolic blood pressure elevations.
a. True.
b. False.

22. A major message of JNC-7 is that more attention must be paid to treating minimal elevations in blood pressure, particularly in systolic blood pressure.
a. True.
b. False.

23. What has happened to the blood pressure goals for diabetics and the renally impaired (<130/80 mm Hg) with the JNC-7 report?
a. The goal has remained the same.
b. The JNC is awaiting further evidence to make a determination.
c. The goal blood pressure is lower than previous recommendations.
d. Goals for difficult-to-treat groups were not addressed by JNC-7.

24. One significant change in the JNC-7 guidelines is the establishment of a classification known as _____, which is defined as systolic blood pressure of 120–139 mm Hg and/or diastolic blood pressure of 80–89 mm Hg.
a. Malignant hypertension
b. Stage 1 hypertension
c. Level 1 hypertension
d. Prehypertension

25. In 2001, according to HEDIS statistics, the average control rate among commercial managed care enrollees with diagnosed hypertension was:
a. 55.4%.
b. 51.5%.
c. 46.7%.
d. 39.0%.
The data reported in this section reflect aggregate national formulary statuses of prescription hypertension agents, separated by classes. The data are current as of June 2003. This information is supplied by Yardley, Pa.-based MediMedia Information Technologies, which collects it from managed care plans and pharmacy benefit managers (PBMs).

Formulary status is reported several ways. First- and second-tier status, also known as “approved” products, are self-explanatory. Drugs labeled third tier are those that are explicitly listed on formularies’ third tiers. The health plan will pay for these so-called nonformulary drugs, but the member is usually responsible for a higher out-of-pocket copayment or coinsurance fee than for first- and second-tier prescription products.

Where a drug is categorized as nonformulary/reimbursed, it is not assigned to a specific formulary tier, although the health plan will bear at least some financial responsibility for the product if a physician writes a prescription for it.

Two categories can be considered having negative formulary status: nonformulary/not reimbursed and prior authorization. Products categorized as not reimbursed are, simply, products that a health plan or PBM’s pharmacy and therapeutics committee has chosen not to cover. Prior authorization is somewhat less restrictive; in this case, it refers to prescription drugs that are not covered unless medical necessity is established on a case-by-case basis.

1 MediMedia Information Technologies, a division of MediMedia USA Inc., collects, standardizes, aggregates, and disseminates pharmaceutical information about managed care drug formularies (through such resources as Formulary Compass, Infoscan Formulary Database, and FormTrak Cards), as well as hospital-based diagnosis-and-treatment information (Hospital Diagnosis and Therapy Audit, or HDTA). MediMedia Information Technologies also conducts primary market research on behalf of clients through its proprietary web-based information service, PTCommunity.com. Formulary Compass is a registered trademark of MediMedia Information Technologies.
FORMULARY ACCEPTANCE OF ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

In general, newer drugs gradually displace older medications as preferred products, as their safety, efficacy, and financial outcomes become established over time. Year-to-year comparisons of angiotensin-converting enzyme (ACE) inhibitor formulary acceptance would seem to reinforce this concept.

Figure 1 compares aggregate HMO formulary status of ACE inhibitors from 1998 to 2003. By 2001, ACE inhibitors as a class were available as a first-, second-, or third-tier product to more than 7 of every 10 HMO members. This year, ACE inhibitors fall into the most restrictive categories — prior authorization and not reimbursed — for less than 7 percent of members.

The sharp increase in 2001 of HMOs’ placement of ACE inhibitors on the third tier may be, in part, a reflection of the growth in popularity of three-tier formularies among employers at the time.

FORMULARY ACCEPTANCE OF BETA BLOCKERS/CALCIUM CHANNEL BLOCKERS

Figure 2 indicates current and previous HMO formulary status of beta blockers and calcium channel blockers (CCBs). Access to beta blockers has become more restrictive since 2001, which may seem counterintuitive given the National Committee for Quality Assurance’s HEDIS measure urging their use after a heart attack. Yet, while hypertension is the most common reason for prescribing a beta blocker, these drugs have numerous indications; formulary trends, then, may reflect some apprehension on the part of P&T committees that these drugs may be being prescribed for other uses.

Formulary acceptance of CCBs has remained steady for 3 years, perhaps due to the lack of market entries in recent years and the fact that most are available as generics.

**FIGURE 1** 1998–2003 formulary-status comparisons, ACE inhibitors

*Share of covered lives with degree of access*

**FIGURE 2** 2001–2003 formulary-status comparisons, beta blockers and calcium channel blockers

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2 MediMedia Information Technologies captures formulary data from 98 percent of HMOs in the United States, and counts the number of covered lives for approximately 90 percent of them. These HMOs’ admittance of pharmacy benefits for approximately 90 million commercial beneficiaries.

3 NCQA’s Health Plan Employer Data and Information Set is explained in the article by Miller elsewhere in this publication.
ANALYSIS OF ARBs

Angiotensin II receptor blockers (ARBs) comprise a relatively new class of antihypertensive agents, and their place in therapy received formal recognition from the medical establishment in JNC-7 (2003).

Manufacturers seeking formulary acceptance for newer products initially face considerable hurdles, such as cost-and-rebate considerations and the need to demonstrate to P&T committees that these medications are more clinically effective than older products. Acknowledgement of ARBs’ potential from established medical societies and, ultimately, from JNC-7, may have helped ARBs gain relatively quick formulary acceptance among both HMOs and pharmacy benefit managers (PBMs) (Figure 3).

FIGURE 3  Current formulary acceptance of ARBs

Examples: As of mid-2003, ARBs are listed on the first or second tier for 44 percent of health plan members with a pharmacy benefit. They also are listed as first- or second-tier products on 37 percent of PBM formularies. Five top PBMs are used in this analysis: AdvancePCS, Caremark, Express Scripts, Medco Health Solutions, and National Prescription Administrators (NPA).

COMBINATION THERAPY GAINS ADHERENTS

Largely shunned in medical and pharmacy teaching for decades, combination therapy — particularly for hypertension — has enjoyed a renaissance in recent years. JNC-7 unequivocally takes the position that when a single agent is unable to control hypertension, practitioners should consider the use of two or more drugs concurrently. The JNC-7 report lists many fixed-dose combination agents that are suitable as second-line therapy or, in certain circumstances, for use in initiating therapy (see articles by Moser and Carter elsewhere in this publication).

Increased P&T committee recognition of the role of combination therapy is illustrated in Figure 4, which depicts formulary acceptance of fixed-dose combination agents for hypertension.

REFERENCE


SOURCE: INFOSCAN FORMULARY DATABASE, MEDIMEDIA INFORMATION TECHNOLOGIES, YARDLEY, PA., JUNE 2003