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Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure

Aram V. Chobanian, George L. Bakris, Henry R. Black, William C.ushman, Lee A. Green, Joseph L. Izzo, Jr, Daniel W. Jones, Barry J. Materson, Suzanne Oparil, Jackson T. Wright, Jr, Edward J. Roccella and the National High Blood Pressure Education Program Coordinating Committee

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SEVENTH REPORT OF THE JOINT NATIONAL COMMITTEE ON PREVENTION, DETECTION, EVALUATION, AND TREATMENT OF HIGH BLOOD PRESSURE

Aram V. Chobanian, George L. Bakris, Henry R. Black, William C. Cushman, Lee A. Green, Joseph L. Izzo, Jr, Daniel W. Jones, Barry J. Materson, Suzanne Oparil, Jackson T. Wright, Jr, Edward J. Roccella, and the National High Blood Pressure Education Program Coordinating Committee

Abstract—The National High Blood Pressure Education Program presents the complete Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Like its predecessors, the purpose is to provide an evidence-based approach to the prevention and management of hypertension. The key messages of this report are these: in those older than age 50, systolic blood pressure (BP) of greater than 140 mm Hg is a more important cardiovascular disease (CVD) risk factor than diastolic BP; beginning at 115/75 mm Hg, CVD risk doubles for each increment of 20/10 mm Hg; those who are normotensive at 55 years of age will have a 90% lifetime risk of developing hypertension; prehypertensive individuals (systolic BP 120–139 mm Hg or diastolic BP 80–89 mm Hg) require health-promoting lifestyle modifications to prevent the progressive rise in blood pressure and CVD; for uncomplicated hypertension, thiazide diuretic should be used in drug treatment for most, either alone or combined with drugs from other classes; this report delineates specific high-risk conditions that are compelling indications for the use of other antihypertensive drug classes (angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, beta-blockers, calcium channel blockers); two or more antihypertensive medications will be required to achieve goal BP (<140/90 mm Hg, or <130/80 mm Hg) for patients with diabetes and chronic kidney disease; for patients whose BP is more than 20 mm Hg above the systolic BP goal or more than 10 mm Hg above the diastolic BP goal, initiation of therapy using two agents, one of which usually will be a thiazide diuretic, should be considered; regardless of therapy or care, hypertension will be controlled only if patients are motivated to stay on their treatment plan. Positive experiences, trust in the clinician, and empathy improve patient motivation and satisfaction. This report serves as a guide, and the committee continues to recognize that the responsible physician's judgment remains paramount. (*Hypertension*. 2003;42:1206–1252.)

For more than 3 decades, the National Heart, Lung, and Blood Institute (NHLBI) has administered the National High Blood Pressure Education Program (NHBPEP) Coordinating Committee, a coalition of 39 major professional, public, and voluntary organizations and 7 federal agencies. One important function is to issue guidelines and advisories designed to increase awareness, prevention, treatment, and control of hypertension (high blood pressure).

Data from the National Health and Nutrition Examination Survey (NHANES) have indicated that 50 million or more Americans have high blood pressure (BP) warranting some form of treatment.^{1,2} Worldwide prevalence estimates for

hypertension may be as much as 1 billion individuals, and approximately 7.1 million deaths per year may be attributable to hypertension.³ The World Health Organization reports that suboptimal BP (>115 mm Hg SBP) is responsible for 62% of cerebrovascular disease and 49% of ischemic heart disease, with little variation by sex. In addition, suboptimal blood pressure is the number one attributable risk for death throughout the world.³

Considerable success has been achieved in the past in meeting the goals of the program. The awareness of hypertension has improved from a level of 51% of Americans in the period 1976 to 1980 to 70% in 1999 to 2000 (Table 1). The

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The executive committee, writing teams, and reviewers served as volunteers without remuneration.

Members of the National High Blood Pressure Education Program Coordinating Committee are listed in the Appendix.

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TABLE 1. Trends in Awareness, Treatment, and Control of High Blood Pressure 1976–2000

	National Health and Nutrition Examination Survey, %			
	1976–80 ²⁵⁷	1988–91 ²⁵⁷	1991–94 ⁴	1999–2000 ⁵
Awareness	51	73	68	70
Treatment	31	55	54	59
Control*	10	29	27	34

Percentage of adults aged 18 to 74 years with systolic blood pressure (SBP) of 140 mm Hg or greater, diastolic blood pressure (DBP) of 90 mm Hg or greater, or taking antihypertensive medication.

*SBP below 140 mm Hg and DBP below 90 mm Hg and on antihypertensive medication.

percentage of patients with hypertension receiving treatment has increased from 31% to 59% in the same period, and the percentage of persons with high BP controlled to below 140/90 mm Hg has increased from 10% to 34%. Between 1960 and 1991, median systolic BP (SBP) for individuals 60 to 74 years old declined by approximately 16 mm Hg (Figure 1). These changes have been associated with highly favorable trends in the morbidity and mortality attributed to hypertension. Since 1972, age-adjusted death rates from stroke and coronary heart disease (CHD) have declined by approximately 60% and 50%, respectively (Figures 2 and 3). These benefits have occurred independent of gender, age, race, or socioeconomic status. Within the last 2 decades, better treatment of hypertension has been associated with a considerable reduction in the hospital case-fatality rate for heart failure (HF) (Figure 4). This information suggests that there have been substantial improvements.

However, these improvements have not been extended to the total population. Current control rates for hypertension in the United States are clearly unacceptable. Approximately 30% of adults are still unaware of their hypertension, more than 40% of individuals with hypertension are not on treatment, and two thirds of hypertensive patients are not being controlled to BP levels less than 140/90 mm Hg (Table 1).

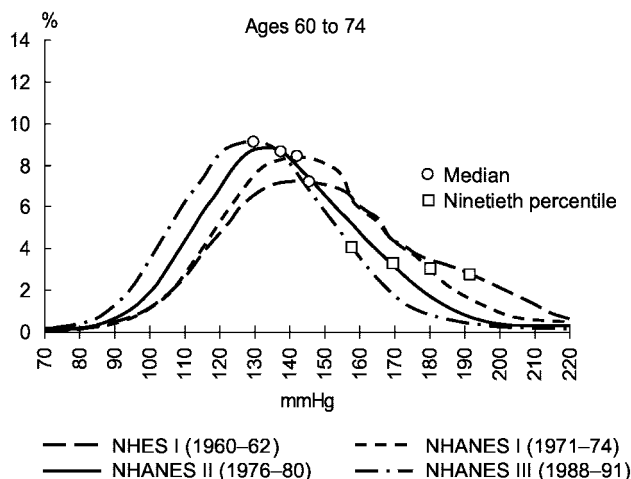


Figure 1. Smoothed weighted frequency distribution, median, and 90th percentile of SBP for ages 60 to 74 years, United States, 1960 to 1991. Source: Burt et al. *Hypertension* 1995;26:60–69. Erratum in: *Hypertension* 1996;27:1192.

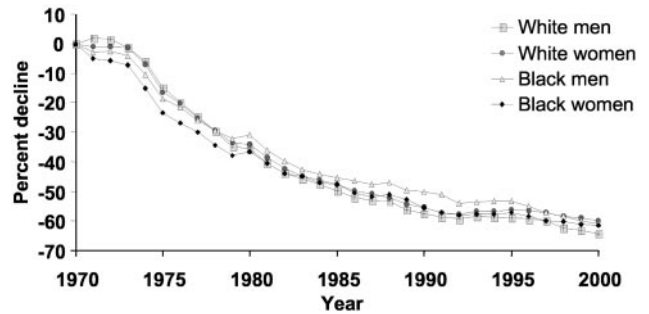


Figure 2. Percentage decline in age-adjusted mortality rates for stroke by gender and race: United States, 1970 to 2000. Source: Prepared by T. Thom, National Heart, Lung, and Blood Institute from Vital Statistics of the United States, National Center for Health Statistics. Death rates are age-adjusted to the 2000 US census population.

Furthermore, the rates of decline of deaths from CHD and stroke have slowed in the past decade. In addition, the prevalence and hospitalization rates of HF, wherein the majority of patients have hypertension before developing heart failure, have continued to increase (Figures 5 and 6). Moreover, there is an increasing trend in end-stage renal disease (ESRD) by primary diagnosis. Hypertension is second only to diabetes as the most common antecedent for this condition (Figure 7). Undiagnosed, untreated, and uncontrolled hypertension clearly places a substantial strain on the health care delivery system.

Methods

The decision to appoint a committee for *The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7)* was based on 4 factors: the publication of many new hypertension observational studies and clinical trials since the last report was published in 1997⁴; the need for a new clear and concise guideline that would be useful to clinicians; the need to simplify the classification of BP; and a clear recognition that the JNC reports did not result in maximum benefit to the public. This JNC report is presented in 2 separate publications. The initial “Express” version, a succinct practical guide, was published in the May 21, 2003, issue of the *Journal of the American Medical Association*.⁵ The current, more comprehensive report provides a broader discussion and justification for the recommendations made by the committee. As with prior JNC reports, the

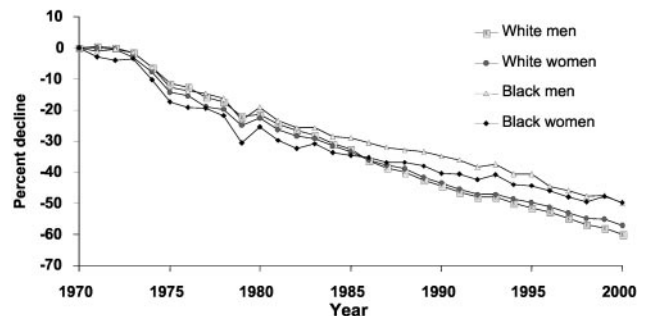


Figure 3. Percentage decline in age-adjusted mortality rates for CHD by gender and race: United States, 1970 to 2000. Source: Prepared by T. Thom, National Heart, Lung, and Blood Institute from Vital Statistics of the United States, National Center for Health Statistics. Death rates are age-adjusted to the 2000 US census population.

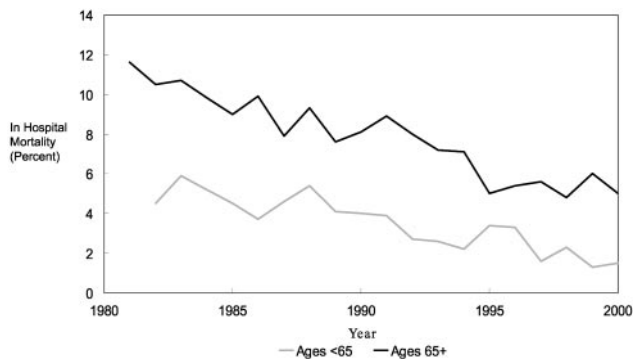


Figure 4. Hospital case-fatality rates for congestive heart failure, ages <65 and 65+: United States, 1981 to 2000. Source: National Heart, Lung, and Blood Institute. *Morbidity and Mortality: 2002 Chart Book on Cardiovascular, Lung, and Blood Disease*. Chart 3–36. Accessed September 2003. <http://www.nhlbi.nih.gov/resources/docs/cht-book.htm>.

committee recognizes that the responsible physician’s judgment is paramount in managing his or her patients.

Since the publication of the JNC 6 report, the NHBPEP Coordinating Committee, chaired by the director of the NHLBI, has regularly reviewed and discussed studies on hypertension. To conduct this task, the Coordinating Committee is divided into 4 subcommittees: Science Base; Long Range Planning; Professional, Patient, and Public Education; and Program Organization. The subcommittees work together to review the hypertension scientific literature from clinical trials, epidemiology, and behavioral science. In many instances, the principal investigator of the larger studies has presented the information directly to the Coordinating Committee. The committee reviews are summarized and posted on the NHLBI web site.⁶ This ongoing review process keeps the committee apprised of the current state of the science, and the information is also used to develop program plans for future activities, such as continuing education.

During fall 2002, the NHBPEP Coordinating Committee chair solicited opinions regarding the need to update the JNC 6 report. The entire Coordinating Committee membership provided, in writing, a detailed rationale explaining the necessity for updating JNC 6, outlined critical issues, and provided concepts to be addressed in the new report. Thereafter, the NHBPEP Coordinating Committee chair

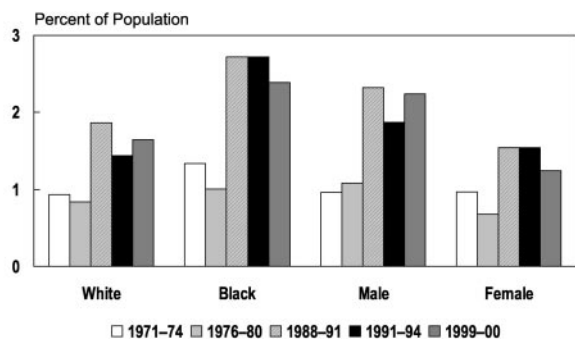


Figure 5. Prevalence of CHF by race and gender, ages 25 to 74: United States, 1971 to 1974 to 1999 to 2000. Age-adjusted to 2000 US census population. White and African American in 1999 to 2000 excludes Hispanics. Source: National Heart, Lung, and Blood Institute. *Morbidity and Mortality: 2002 Chart Book on Cardiovascular, Lung, and Blood Disease*. Accessed September 2003. <http://www.nhlbi.nih.gov/resources/docs/cht-book.htm> and 1999 to 2000 unpublished data computed by M. Wolz and T. Thom, National Heart, Lung, and Blood Institute. June 2003.

appointed the JNC 7 chair and an Executive Committee derived from the Coordinating Committee membership. The Coordinating Committee members served on 1 of 5 JNC 7 writing teams, which contributed to the writing and review of the document.

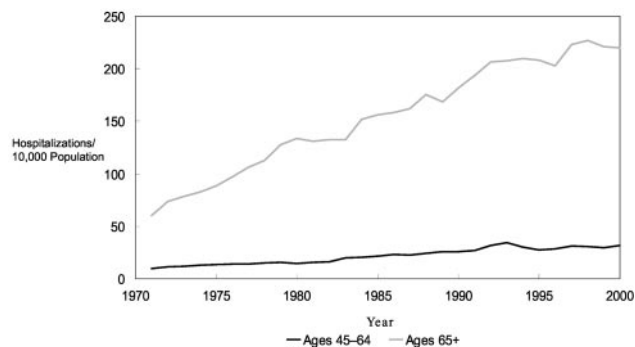
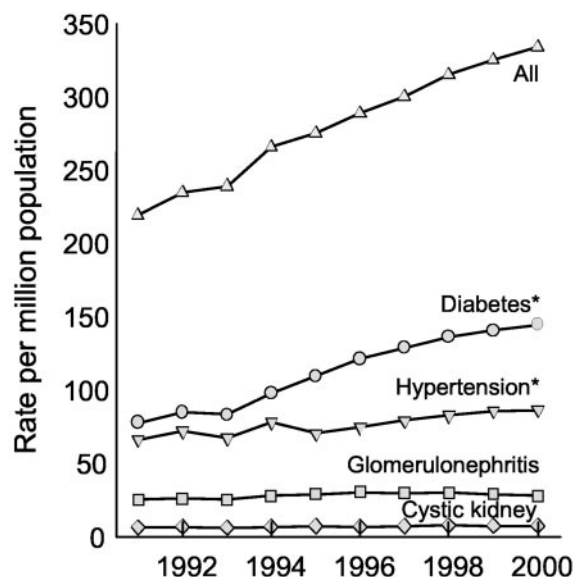


Figure 6. Hospitalization rates for congestive heart failure, ages 45 to 64 and 65+: United States, 1971 to 2000. Source: National Heart, Lung, and Blood Institute. *Morbidity and Mortality: 2002 Chart Book on Cardiovascular, Lung, and Blood Disease*. Chart 3–35. Accessed September 2003. <http://www.nhlbi.nih.gov/resources/docs/cht-book.htm>.

The concepts for the new report identified by the NHBPEP Coordinating Committee membership were used to create the report outline. On the basis of these critical issues and concepts, the Executive Committee developed relevant medical subject headings (MeSH) terms and keywords to further review the scientific literature. These MeSH terms were used to generate MEDLINE searches that focused on English-language, peer-reviewed scientific literature from January 1997 through April 2003. Various systems of grading the evidence were considered, and the classification scheme used in JNC 6 and other NHBPEP clinical guidelines was selected.^{4,7–10} This scheme classifies studies according to a process adapted from Last and Abramson (see the section Scheme Used for Classification of the Evidence).¹¹

In reviewing the exceptionally large body of research literature in hypertension, the Executive Committee focused its deliberations on

Rate per million population



*These disease categories were treated as being mutually exclusive.

Figure 7. Trends in incident rates of ESRD, by primary diagnosis (adjusted for age, gender, race). Disease categories were treated as being mutually exclusive. Source: United States Renal Data System. 2002. Figure 1.14. Accessed September, 2003. <http://www.usrds.org/slides.htm>.

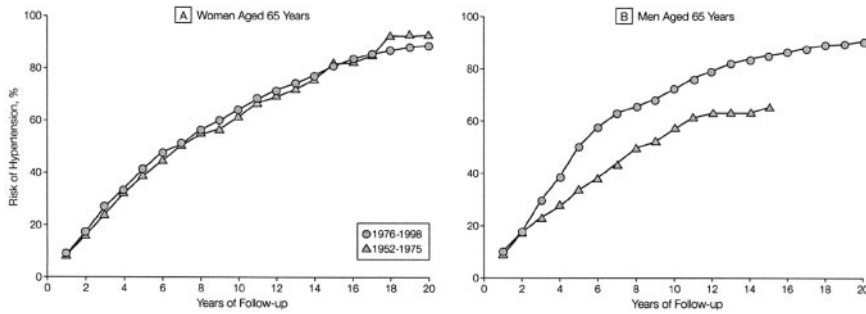


Figure 8. Residual lifetime risk of hypertension in women and men aged 65 years. Cumulative incidence of hypertension in 65-year-old women and men. Data for 65-year-old men in the 1952 to 1975 period are truncated at 15 years since there were few participants in this age category who were followed up beyond this time interval. Source: *JAMA* 2002;287:1003–1010. Copyright 2002, American Medical Association. All rights reserved.

evidence pertaining to outcomes of importance to patients and with effects of sufficient magnitude to warrant changes in medical practice (“patient oriented evidence that matters” [POEMs]).^{12,13} Patient-oriented outcomes include not only mortality but also other outcomes that affect patients’ lives and well-being, such as sexual function, ability to maintain family and social roles, ability to work, and ability to carry out activities of daily living. These outcomes are strongly affected by nonfatal stroke, HF, coronary heart disease, and renal disease; hence, these outcomes were considered along with mortality in the committee’s evidence-based deliberations. Studies of physiological end points (disease-oriented evidence [DOEs]) were used to address questions where POEMs were not available.

The Coordinating Committee began the process of developing the JNC 7 Express report in December 2002, and the report was submitted to the *Journal of the American Medical Association* in April 2003. It was published in an electronic format on May 14, 2003, and in print on May 21, 2003. During this time, the Executive Committee met on 6 occasions, 2 of which included meetings with the entire Coordinating Committee. The writing teams also met by teleconference and used electronic communications to develop the report. Twenty-four drafts were created and reviewed repeatedly. At its meetings, the Executive Committee used a modified nominal group process¹⁴ to identify and resolve issues. The NHBPEP Coordinating Committee reviewed the penultimate draft and provided written comments to the Executive Committee. In addition, 33 national hypertension leaders reviewed and commented on the document. The NHBPEP Coordinating Committee approved the JNC 7 Express report. To complete the longer JNC 7 version, the Executive Committee members met via teleconferences and in person and circulated sections of the larger document via e-mail. The sections were assembled and edited by the JNC 7 chair and were

circulated among the Coordinating Committee members for review and comment. The JNC 7 chair synthesized the comments, and the longer version was submitted to the journal *Hypertension* in November, 2003.

Lifetime Risk of Hypertension

Hypertension is an increasingly important medical and public health issue. The prevalence of hypertension increases with advancing age to the point where more than half of people aged 60 to 69 years old and approximately three-fourths of those aged 70 years and older are affected.¹ The age-related rise in SBP is primarily responsible for an increase in both incidence and prevalence of hypertension with increasing age.¹⁵

Whereas the short-term absolute risk for hypertension is conveyed effectively by incidence rates, the long-term risk is best summarized by the lifetime risk statistic, which is the probability of developing hypertension during the remaining years of life (either adjusted or unadjusted for competing causes of death). Framingham Heart Study investigators recently reported the lifetime risk of hypertension to be approximately 90% for men and women who were nonhypertensive at 55 or 65 years old and survived to age 80 to 85 (Figure 8).¹⁶ Even after adjusting for competing mortality, the remaining lifetime risks of hypertension were 86 to 90% in women and 81 to 83% in men.

The impressive increase of BP to hypertensive levels with age is also illustrated by data indicating that the 4-year rates

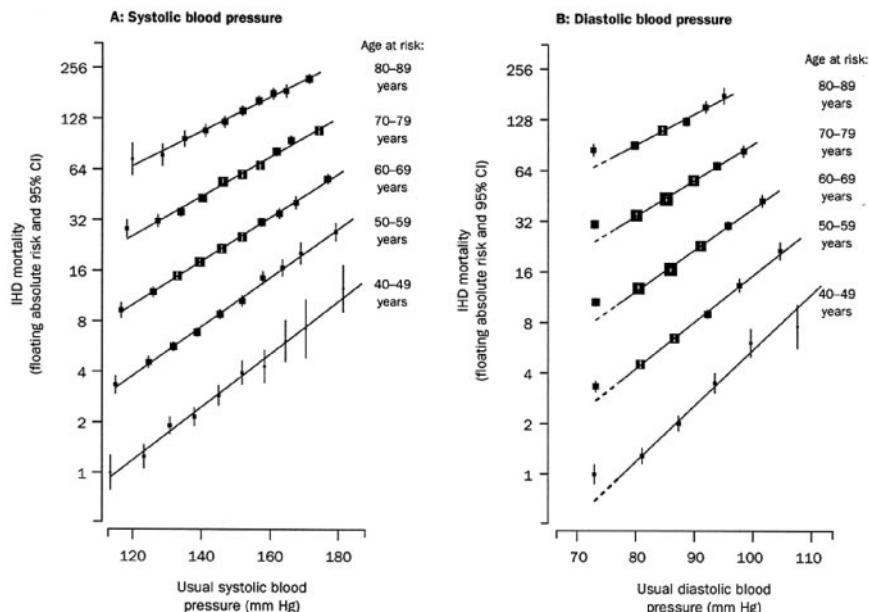


Figure 9. Ischemic heart disease (IHD) mortality rate in each decade of age versus usual blood pressure at the start of that decade. Source: Reprinted with permission from Elsevier (*The Lancet*, 2002;360:1903–1913).

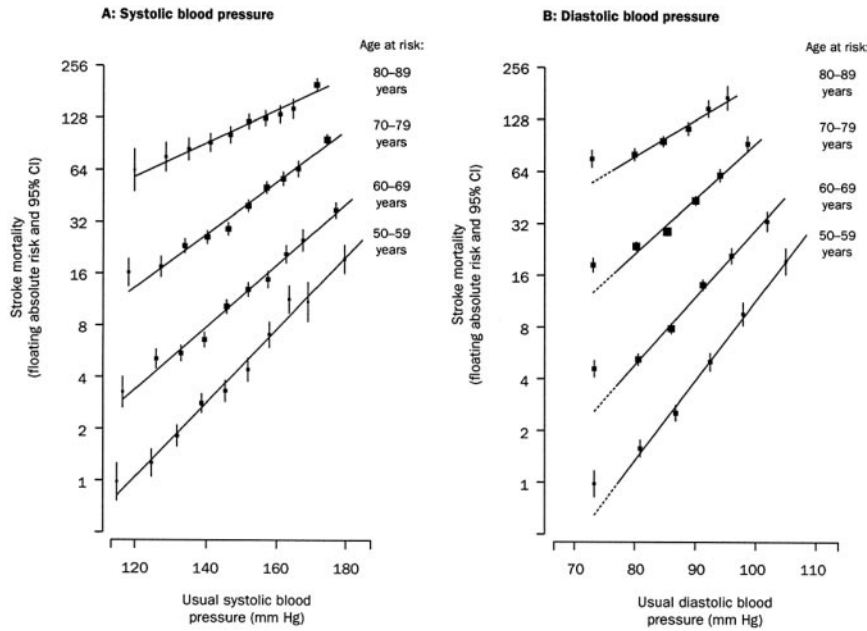


Figure 10. Stroke mortality rate in each decade of age versus usual blood pressure at the start of that decade. Source: Reprinted with permission from Elsevier (*The Lancet*, 2002;360:1903–1913).

of progression to hypertension are 50% for those 65 years and older with BP in the 130 to 139/85 to 89 mm Hg range and 26% for those with BP in the 120 to 129/80 to 84 mm Hg range.¹⁷

Blood Pressure and Cardiovascular Risk

Data from observational studies involving more than 1 million individuals have indicated that death from both ischemic heart disease and stroke increases progressively and linearly from BP levels as low as 115 mm Hg systolic and 75 mm Hg diastolic upward (Figures 9 and 10).¹⁸ The increased risks are present in all age groups ranging from 40 to 89 years old. For every 20 mm Hg systolic or 10 mm Hg diastolic increase in BP, there is a doubling of mortality from both ischemic heart disease and stroke.

In addition, longitudinal data obtained from the Framingham Heart Study have indicated that BP values in the 130 to 139/85 to 89 mm Hg range are associated with a more than 2-fold increase in relative risk from cardiovascular disease (CVD) compared with those with BP levels below 120/80 mm Hg (Figure 11).¹⁹

Basis for Reclassification of Blood Pressure

Because of the new data on lifetime risk of hypertension and the impressive increase in the risk of cardiovascular complications associated with levels of BP previously considered to be normal, the JNC 7 report has introduced a new classification that includes the term “prehypertension” for those with BPs ranging from 120 to 139 mm Hg systolic and/or 80 to

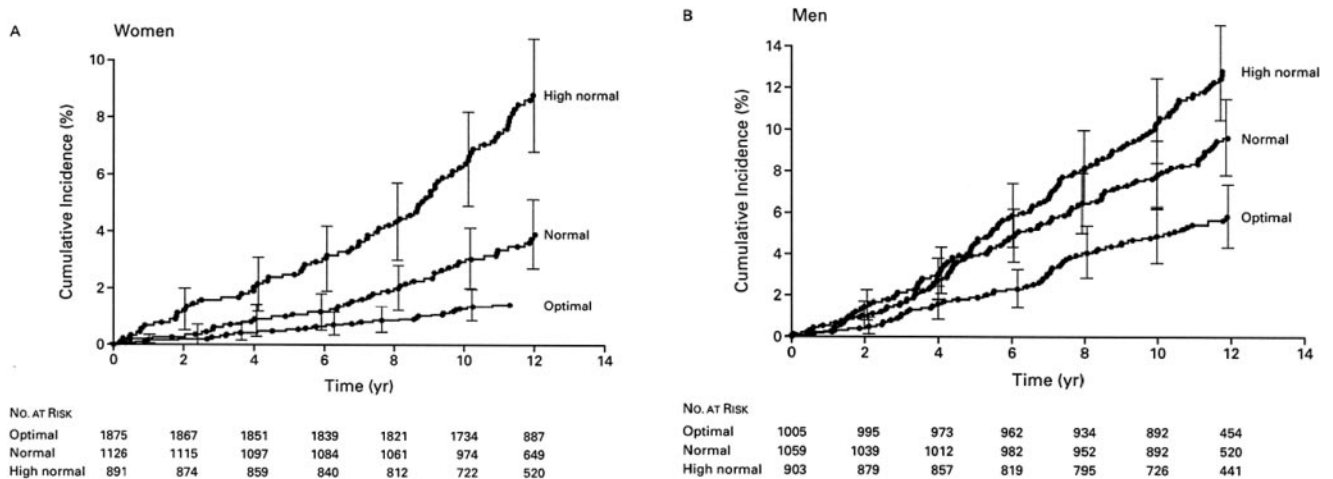


Figure 11. Impact of high normal blood pressure on the risk of cardiovascular disease. Cumulative incidence of cardiovascular events in women (A) and men (B) without hypertension, according to blood-pressure category at the baseline examination. Vertical bars indicate 95% confidence intervals. Optimal BP is defined here as a systolic pressure of less than 120 mm Hg and a diastolic pressure of less than 80 mm Hg. Normal BP is a systolic pressure of 120 to 129 mm Hg or a diastolic pressure of 80 to 84 mm Hg. High-normal BP is a systolic pressure of 130 to 139 mm Hg or a diastolic pressure of 85 to 89 mm Hg. If the systolic and diastolic pressure readings for a subject were in different categories, the higher of the two categories was used. Source: *N Engl J Med* 2001;345:1291–1297. Copyright © 2001, Massachusetts Medical Society. All rights reserved.

TABLE 2. Changes in Blood Pressure Classification

JNC 6 Category	SBP/DBP	JNC 7 Category
Optimal	< 120/80	Normal
Normal	120–129/80–84	Prehypertension
Borderline	130–139/85–89	
Hypertension	≥ 140/90	Hypertension
Stage 1	140–159/90–99	Stage 2
Stage 2	160–179/100–109	
Stage 3	≥ 180/110	

Sources: The sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Arch Intern Med* 1997;157:2413–46.
The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *JAMA* 2003;289:2560–2571.

89 mm Hg diastolic blood pressure (DBP). This new designation is intended to identify those individuals in whom early intervention by adoption of healthy lifestyles could reduce BP, decrease the rate of progression of BP to hypertensive levels with age, or prevent hypertension entirely.

Another change in classification from JNC 6 is the combining of stage 2 and stage 3 hypertension into a single stage 2 category. This revision reflects the fact that the approach to the management of the former two groups is similar (Table 2).

Classification of Blood Pressure

Table 3 provides a classification of BP for adults aged 18 and older. The classification is based on the average of 2 or more properly measured, seated BP readings on each of 2 or more office visits.

Prehypertension is not a disease category. Rather it is a designation chosen to identify individuals at high risk of developing hypertension, so that both patients and clinicians are alerted to this risk and encouraged to intervene and prevent or delay the disease from developing. Individuals who are prehypertensive are not candidates for drug therapy on the basis of their level of BP and should be firmly and unambiguously advised to practice lifestyle modification in order to reduce their risk of developing hypertension in the future (see the section Lifestyle Modifications). Moreover, individuals with prehypertension who also have diabetes or kidney disease should be considered candidates for appropriate drug therapy if a trial of lifestyle modification fails to reduce their BP to 130/80 mm Hg or less.

This classification does not stratify hypertensives by the presence or absence of risk factors or target organ damage in order to make different treatment recommendations, if either or both are present. JNC 7 suggests that all people with hypertension (Stages 1 and 2) be treated. The treatment goal

TABLE 3. Classification of Blood Pressure for Adults

BP Classification	SBP mm Hg	DBP mm Hg
Normal	<120	and <80
Prehypertension	120–139	or 80–89
Stage 1 hypertension	140–159	or 90–99
Stage 2 hypertension	≥160	or ≥100

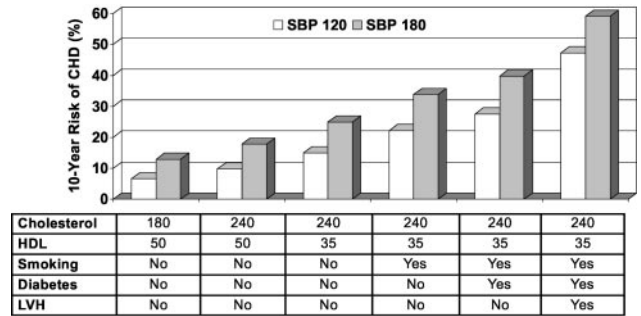


Figure 12. Ten-year risk for CHD by SBP and presence of other risk factors. Source: Derived from K.M. Anderson, P.W.F. Wilson, P.M. Odell, W.B. Kannel. An updated coronary risk profile. A statement for health professionals. *Circulation* 1991;83:356–362.

for individuals with hypertension and no other compelling conditions is <140/90 mm Hg (see the section Compelling Indications). The goal for individuals with prehypertension and no compelling indications is to lower BP to normal with lifestyle changes and prevent the progressive rise in BP using the recommended lifestyle modifications (See the section Lifestyle Modification).

Cardiovascular Disease Risk

The relationship between BP and risk of CVD events is continuous, consistent, and independent of other risk factors. The higher the BP, the greater is the chance of heart attack, HF, stroke, and kidney diseases. The presence of each additional risk factor compounds the risk from hypertension, as illustrated in Figure 12.²⁰ The easy and rapid calculation of a Framingham CHD risk score using published tables²¹ may assist the clinician and patient in demonstrating the benefits of treatment. Management of these other risk factors is essential and should follow the established guidelines for controlling these coexisting problems that contribute to overall cardiovascular risk.

Importance of Systolic Blood Pressure

Impressive evidence has accumulated to warrant greater attention to the importance of SBP as a major risk factor for

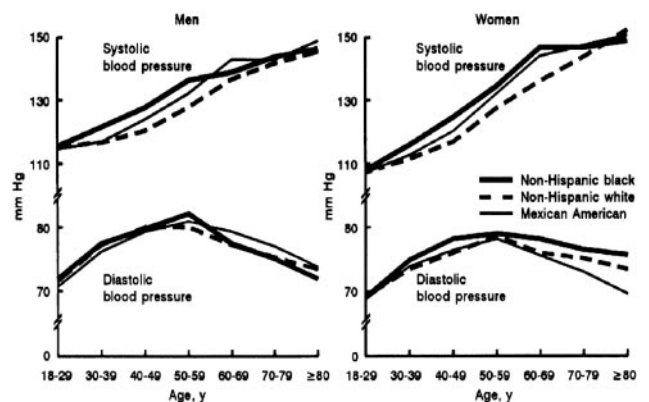


Figure 13. Changes in systolic and diastolic blood pressure with age. SBP and DBP by age and race or ethnicity for men and women over 18 years of age in the US population. Data from NHANES III, 1988 to 1991. Source: Burt VL et al. *Hypertension* 1995;23:305–313.

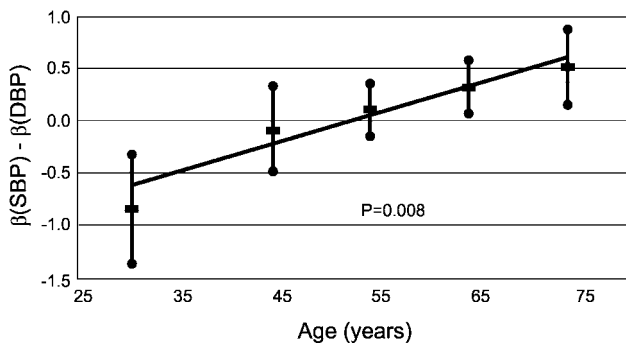


Figure 14. Difference in CHD prediction between systolic and diastolic blood pressure as a function of age. The strength of the relationship as a function of age is indicated by an increase in the β coefficient. Difference in β coefficients (from Cox proportional-hazards regression) between SBP and DBP is plotted as function of age, obtaining this regression line: $\beta(\text{SBP}) - \beta(\text{DBP}) = 1.4948 + 0.0290 \times \text{age}$ ($P=0.008$). A β coefficient level <0.0 indicates a stronger effect of DBP on CHD risk, while levels >0.0 suggest a greater importance of systolic pressure. Source: *Circulation* 2001;103:1247.

CVDs. Changing patterns of BP occur with increasing age. The rise in SBP continues throughout life, in contrast to DBP, which rises until approximately 50 years old, tends to level off over the next decade, and may remain the same or fall later in life (Figure 13).^{1,15} Diastolic hypertension predominates before 50 years of age, either alone or in combination with SBP elevation. The prevalence of systolic hypertension increases with age, and above the age of 50 years, systolic hypertension represents the most common form of hypertension. DBP is a more potent cardiovascular risk factor than SBP until age 50; thereafter, SBP is more important (Figure 14).²²

Clinical trials have demonstrated that control of isolated systolic hypertension reduces total mortality, cardiovascular mortality, stroke, and HF events.^{23–25} Both observational studies and clinical trial data suggest that poor SBP control is largely responsible for the unacceptably low rates of overall BP control.^{26,27} In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) and Controlled Onset Verapamil Investigation of Cardiovascular End Points (CONVINCE) trial, DBP control rates exceeded 90%, but SBP control rates were considerably less (60 to 70%).^{28,29} Poor SBP control is at least in part related to physician attitudes. A survey of primary care physicians indicated that three-fourths of them failed to initiate antihypertensive therapy in older individuals with SBP of 140 to 159 mm Hg, and most primary care physicians did not pursue control to less than 140 mm Hg.^{30,31} Most physicians have been taught that the diastolic pressure is more important than SBP and thus treat accordingly. Greater emphasis must clearly be placed on managing systolic hypertension. Otherwise, as the US population becomes older, the toll of uncontrolled SBP will cause increased rates of cardiovascular and renal diseases.

Prevention of Hypertension: Public Health Challenges

The prevention and management of hypertension are major public health challenges for the United States. If the rise in

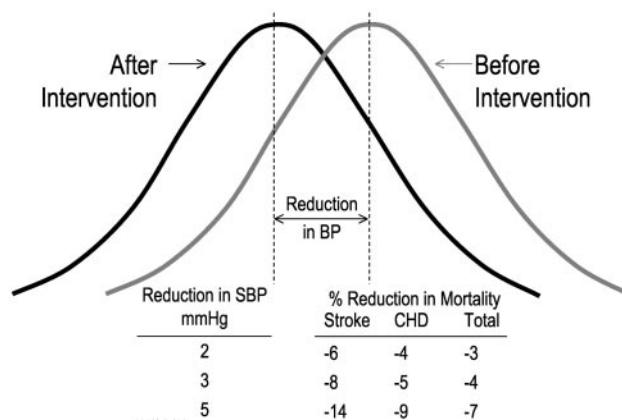


Figure 15. Systolic blood pressure distributions. Source: Whelton PK et al. *JAMA* 2002;288:1884.

BP with age could be prevented or diminished, much of hypertension, cardiovascular and renal disease, and stroke might be prevented. A number of important causal factors for hypertension have been identified, including excess body weight; excess dietary sodium intake; reduced physical activity; inadequate intake of fruits, vegetables, and potassium; and excess alcohol intake.^{10,32} The prevalence of these characteristics is high. One hundred twenty-two million Americans are overweight or obese.³³ Mean sodium intake is approximately 4100 mg per day for men and 2750 mg per day for women, 75% of which comes from processed foods.^{34,35} Fewer than 20% of Americans engage in regular physical activity,³⁶ and fewer than 25% consume 5 or more servings of fruits and vegetables daily.³⁷

Because the lifetime risk of developing hypertension is very high (Figure 8), a public health strategy that complements the hypertension treatment strategy is warranted. In order to prevent BP levels from rising, primary prevention measures should be introduced to reduce or minimize these causal factors in the population, particularly in individuals with prehypertension. A population approach that decreases the BP level in the general population by even modest amounts has the potential to substantially reduce morbidity and mortality or at least delay the onset of hypertension. For example, it has been estimated that a 5 mm Hg reduction of SBP in the population would result in a 14% overall reduction in mortality due to stroke, a 9% reduction in mortality due to CHD, and a 7% decrease in all-cause mortality (Figure 15).^{10,38}

Barriers to prevention include cultural norms; insufficient attention to health education by health care practitioners; lack of reimbursement for health education services; lack of access to places to engage in physical activity; larger servings of food in restaurants; lack of availability of healthy food choices in many schools, worksites, and restaurants; lack of exercise programs in schools; large amounts of sodium added to foods by the food industry and restaurants; and the higher cost of food products that are lower in sodium and calories.¹⁰ Overcoming the barriers will require a multipronged approach directed not only to high-risk populations but also to communities, schools, worksites, and the food industry. The recent recommendations by the American Public Health

Association and the NHBPEP Coordinating Committee that the food industry, including manufacturers and restaurants, reduce sodium in the food supply by 50% over the next decade is the type of approach that, if implemented, would reduce BP in the population.^{39,40}

Community Programs

Healthy People 2010 has identified the community as a significant partner and vital point of intervention for attaining healthy goals and outcomes.⁴¹ Partnerships with community groups such as civic, philanthropic, religious, and senior citizen organizations provide locally focused orientation to the health needs of diverse populations. The probability of success increases as interventional strategies more aptly address the diversity of racial, ethnic, cultural, linguistic, religious, and social factors in the delivery of medical services. Community service organizations can promote the prevention of hypertension by providing culturally sensitive educational messages and lifestyle support services and by establishing cardiovascular risk factor screening and referral programs. Community-based strategies and programs have been addressed in prior NHLBI publications and other documents (*Facts About the DASH Eating Plan*,⁴² *Your Guide to Lowering High Blood Pressure*,⁴³ *National High Blood Pressure Education Month*,⁴⁴ *The Heart Truth: A National Awareness Campaign for Women About Heart Disease*,⁴⁵ *Mobilizing African American Communities To Address Disparities in Cardiovascular Health: The Baltimore City Health Partnership Strategy Development Workshop Summary Report*,⁴⁶ *NHLBI Healthy People 2010 Gateway*,⁴⁷ *Cardiovascular Disease Enhanced Dissemination and Utilization Centers [EDUCs] Awardees*,⁴⁸ *Hearts N' Parks*,⁴⁹ *Healthbeat Radio Network*,⁵⁰ *Salud para su Corazón [For the Health of Your Heart]*).⁵¹

Calibration, Maintenance, and Use of Blood Pressure Devices

The potential of mercury spillage contaminating the environment has led to the decreased use or elimination of mercury in sphygmomanometers as well as in thermometers.⁵² However, concerns regarding the accuracy of nonmercury sphygmomanometers have created new challenges for accurate BP determination.^{53,54} When mercury sphygmomanometers are replaced, the new equipment, including all home BP measurement devices, must be appropriately validated and checked regularly for accuracy.⁵⁵

Accurate Blood Pressure Measurement in the Office

The accurate measurement of BP is the sine qua non for successful management. The equipment, whether aneroid, mercury, or electronic, should be regularly inspected and validated. The operator should be trained and regularly retrained in the standardized technique, and the patient must be properly prepared and positioned.^{4,56,57} The auscultatory method of BP measurement should be used.⁵⁸ Persons should be seated quietly for at least 5 minutes in a chair (rather than on an examination table), with feet on the floor, and arm supported at heart level. Caffeine, exercise, and smoking

TABLE 4. Recommendations for Follow-Up Based on Initial Blood Pressure Measurements for Adults Without Acute End Organ Damage

Initial Blood Pressure, mm Hg*	Follow-Up Recommended†
Normal	Recheck in 2 years
Prehypertension	Recheck in 1 year‡
Stage 1 hypertension	Confirm within 2 months‡
Stage 2 hypertension	Evaluate or refer to source of care within 1 month. For those with higher pressures (eg, >180/110 mm Hg), evaluate and treat immediately or within 1 week depending on clinical situation and complications.

*If systolic and diastolic categories are different, follow recommendations for shorter time follow-up (e.g., 160/86 mm Hg should be evaluated or referred to source of care within 1 month).

†Modify the scheduling of follow-up according to reliable information about past BP measurements, other cardiovascular risk factors, or target organ disease.

‡Provide advice about lifestyle modifications (see Lifestyle Modifications section).

should be avoided for at least 30 minutes prior to measurement. Measurement of BP in the standing position is indicated periodically, especially in those at risk for postural hypotension, prior to necessary drug dose or adding a drug, and in those who report symptoms consistent with reduced BP on standing. An appropriately sized cuff (cuff bladder encircling at least 80% of the arm) should be used to ensure accuracy. At least two measurements should be made and the average recorded. For manual determinations, palpated radial pulse obliteration pressure should be used to estimate SBP; the cuff should then be inflated 20 to 30 mm Hg above this level for the auscultatory determinations; the cuff deflation rate for auscultatory readings should be 2 mm Hg per second. SBP is the point at which the first of two or more Korotkoff sounds is heard (onset of phase 1), and the disappearance of Korotkoff sound (onset of phase 5) is used to define DBP. Clinicians should provide to patients, verbally and in writing, their specific BP numbers and the BP goal of their treatment.

Follow-up of patients with various stages of hypertension is recommended as shown in Table 4.

Ambulatory Blood Pressure Monitoring

Ambulatory blood pressure monitoring (ABPM) provides information about BP during daily activities and sleep.⁵⁹ BP has a reproducible circadian profile, with higher values while awake and mentally and physically active, much lower values during rest and sleep, and early morning increases for 3 or more hours during the transition of sleep to wakefulness.⁶⁰ These devices use either a microphone to measure Korotkoff sounds or a cuff that senses arterial waves using oscillometric techniques. Twenty-four-hour BP monitoring provides multiple readings during all of a patient's activities. While office BP values have been used in the numerous studies that have established the risks associated with an elevated BP and the benefits of lowering BP, office measurements have some shortcomings. For example, a white-coat effect (increase in BP primarily in the medical care environment) is noted in as many as 20 to 35% of patients diagnosed with hypertension.⁶¹

TABLE 5. Clinical Situations in Which Ambulatory Blood Pressure Monitoring May Be Helpful

Suspected white-coat hypertension in patients with hypertension and no target organ damage
Apparent drug resistance (office resistance)
Hypotensive symptoms with antihypertensive medication
Episodic hypertension
Autonomic dysfunction

Ambulatory BP values are usually lower than clinic readings. Awake hypertensive individuals have an average BP of >135/85 mm Hg and during sleep, >120/75 mm Hg. The level of BP measurement using ABPM correlates better than office measurements with target organ injury.¹⁵ ABPM also provides a measure of the percentage of BP readings that are elevated, the overall BP load, and the extent of BP fall during sleep. In most people, BP drops by 10 to 20% during the night; those in whom such reductions are not present appear to be at increased risk for cardiovascular events. In addition, it was reported recently that ABPM patients whose 24-hour BP exceeded 135/85 mm Hg were nearly twice as likely to have a cardiovascular event as those with 24-hour mean BPs less than 135/85 mm Hg, irrespective of the level of the office BP.^{62,63}

Indications for the use of ABPM are listed in Table 5. Medicare reimbursement for ABPM is now provided to assess patients with suspected white-coat hypertension.

Self-Measurement

Self-monitoring of BP at home and work is a practical approach to assess differences between office and out-of-office BP prior to consideration of ambulatory monitoring. For those whose out-of-office BPs are consistently <130/80 mm Hg despite an elevated office BP and who lack evidence of target organ disease, 24-hour monitoring or drug therapy can be avoided.

Self-measurement or ambulatory monitoring may be particularly helpful in assessing BP in smokers. Smoking raises BP acutely, and the level returns to baseline in about 15 minutes after stopping.

Patient Evaluation

Evaluation of hypertensive patients has three objectives: (1) to assess lifestyle and identify other cardiovascular risk factors or concomitant disorders that may affect prognosis and guide treatment (Table 6); (2) to reveal identifiable causes of high BP (Table 7); and (3) to assess the presence or absence of target organ damage and CVD.

Patient evaluation is made through medical history, physical examination, routine laboratory tests, and other diagnostic procedures. The physical examination should include an appropriate measurement of BP, with verification in the contralateral arm; examination of the optic fundi; calculation of body mass index (BMI) (measurement of waist circumference is also very useful); auscultation for carotid, abdominal, and femoral bruits; palpation of the thyroid gland; thorough examination of the heart and lungs; examination of the abdomen for enlarged kidneys, masses, distended urinary bladder, and abnormal aortic pulsation; palpation of the lower

TABLE 6. Cardiovascular Risk Factors

Major risk factors
Hypertension*
Age (older than 55 for men, 65 for women)†
Diabetes mellitus*
Elevated LDL (or total) cholesterol or low HDL cholesterol*
Estimated GFR <60 mL/min
Family history of premature cardiovascular disease (men aged <55 or women aged <65)
Microalbuminuria
Obesity* (body mass index ≥ 30 kg/m ²)
Physical inactivity
Tobacco usage, particularly cigarettes
Target organ damage
Heart
Left ventricular hypertrophy
Angina/prior myocardial infarction
Prior coronary revascularization
Heart failure
Brain
Stroke or transient ischemic attack
Dementia
Chronic kidney disease
Peripheral arterial disease
Retinopathy

GFR indicates glomerular filtration rate.

*Components of the metabolic syndrome. Reduced HDL and elevated triglycerides are components of the metabolic syndrome. Abdominal obesity is also a component of metabolic syndrome.

†Increased risk begins at approximately 55 and 65 for men and women, respectively. Adult Treatment Panel III used earlier age cutpoints to suggest the need for earlier action.

extremities for edema and pulses; and neurological assessment.

Data from epidemiological studies and clinical trials have demonstrated that elevations in resting heart rate and reduced heart rate variability are associated with higher cardiovascular risk. In the Framingham Heart Study, an average resting heart rate of 83 beats per minute was associated with a substantially higher risk of death from a CV event than those

TABLE 7. Identifiable Causes of Hypertension

Chronic kidney disease
Coarctation of the aorta
Cushing syndrome and other glucocorticoid excess states including chronic steroid therapy
Drug-induced or drug-related (see Table 18)
Obstructive uropathy
Pheochromocytoma
Primary aldosteronism and other mineralocorticoid excess states
Renovascular hypertension
Sleep apnea
Thyroid or parathyroid disease

TABLE 8. Screening Tests for Identifiable Hypertension

Diagnosis	Diagnostic Test
Chronic kidney disease	Estimated GFR
Coarctation of the aorta	CT angiography
Cushing syndrome and other glucocorticoid excess states including chronic steroid therapy	History/dexamethasone suppression test
Drug-induced/related (see Table 18)	History; drug screening
Pheochromocytoma	24-hour urinary metanephrine and normetanephrine
Primary aldosteronism and other mineralocorticoid excess states	24-hour urinary aldosterone level or specific measurements of other mineralocorticoids
Renovascular hypertension	Doppler flow study; magnetic resonance angiography
Sleep apnea	Sleep study with O ₂ saturation
Thyroid/parathyroid disease	TSH; serum PTH

GFR indicates glomerular filtration rate; CT, computed tomography; TSH, thyroid stimulating hormone; PTH, parathyroid hormone.

at lower heart rate levels.⁶⁴ Moreover, reduced heart rate variability was also associated with an increase in CV mortality.⁶⁵ No clinical trials have prospectively evaluated the impact of reducing heart rate on CV outcomes.

Laboratory Tests and Other Diagnostic Procedures

Routine laboratory tests recommended before initiating therapy include a 12-lead ECG; urinalysis; blood glucose and hematocrit; serum potassium, creatinine (or the corresponding estimated glomerular filtration rate [eGFR]), and calcium⁶⁶; and a lipoprotein profile (after 9- to 12-hour fast) that includes HDL and LDL cholesterol (HDL-C and LDL-C) and triglycerides (TGs). Optional tests include measurement of urinary albumin excretion or albumin/creatinine ratio (ACR), except for those with diabetes or kidney disease, for whom annual measurements should be made. More extensive testing for identifiable causes is not indicated generally unless BP control is not achieved or the clinical and routine laboratory evaluation strongly suggests an identifiable secondary cause (ie, vascular bruits, symptoms of catecholamine excess, unprovoked hypokalemia). See the section Identifiable Causes of Hypertension for a more thorough discussion.

The presence of decreased GFR or albuminuria has prognostic implications as well. Studies reveal a strong relationship between decreases in GFR and increases in cardiovascular morbidity and mortality.^{67,68} Even small decreases in GFR increase cardiovascular risk.⁶⁷ Serum creatinine may overestimate glomerular filtration. The optimal tests to determine GFR are debated, but calculating GFR from the recent modifications of the Cockcroft and Gault equations is useful.⁶⁹

The presence of albuminuria, including microalbuminuria, even in the setting of normal GFR, is also associated with an increase in cardiovascular risk.^{70–72} Urinary albumin excretion should be quantitated and monitored on an annual basis in high-risk groups, such as those with diabetes or renal disease.

Additionally, three emerging risk factors—(1) high-sensitivity C-reactive protein (HS-CRP), a marker of inflammation; (2) homocysteine; and (3) elevated heart rate—may

be considered in some individuals, particularly those with CVD but without other risk factor abnormalities. Results of an analysis of the Framingham Heart Study cohort demonstrated that those with an LDL value within the range associated with low CV risk, who also had an elevated HS-CRP value, had a higher CV event rate as compared with those with low CRP and high LDL-C.⁷³ Other studies also have shown that elevated CRP is associated with a higher CV event rate, especially in women.⁷⁴ Elevations in homocysteine have also been described as associated with higher CV risk; however, the results with this marker are not as robust as those with high HS-CRP.^{75,76}

Identifiable Causes of Hypertension

Additional diagnostic procedures may be indicated to identify causes of hypertension, particularly in patients whose (1) age, history, physical examination, severity of hypertension, or initial laboratory findings suggest such causes; (2) BP responds poorly to drug therapy; (3) BP begins to increase for uncertain reason after being well controlled; and (4) onset of hypertension is sudden. Screening tests for particular forms of identifiable hypertension are shown in Table 8.

Pheochromocytoma should be suspected in patients with labile hypertension or with paroxysms of hypertension accompanied by headache, palpitations, pallor, and perspiration.⁷⁷ Decreased pressure in the lower extremities or delayed or absent femoral arterial pulses may indicate aortic coarctation; truncal obesity, glucose intolerance, and purple striae suggest Cushing syndrome. Examples of clues from the laboratory tests include unprovoked hypokalemia (primary aldosteronism), hypercalcemia (hyperparathyroidism), and elevated creatinine or abnormal urinalysis (renal parenchymal disease). Appropriate investigations should be conducted when there is a high index of suspicion of an identifiable cause.^{78–81}

The most common parenchymal kidney diseases associated with hypertension are chronic glomerulonephritis, polycystic kidney disease, and hypertensive nephrosclerosis. These can generally be distinguished by the clinical setting and additional testing. For example, a renal ultrasound is useful in diagnosing polycystic kidney disease. Renal artery stenosis

and subsequent renovascular hypertension should be suspected in a number of circumstances, including (1) onset of hypertension before 30 years of age, especially in the absence of family history, or onset of significant hypertension after age 55; (2) an abdominal bruit, especially if a diastolic component is present; (3) accelerated hypertension; (4) hypertension that had been easy to control but is now resistant; (5) recurrent flash pulmonary edema; (6) renal failure of uncertain etiology, especially in the absence of proteinuria or an abnormal urine sediment; and (7) acute renal failure precipitated by therapy with an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) under conditions of occult bilateral renal artery stenosis or moderate to severe volume depletion.

In patients with suspected renovascular hypertension, non-invasive screening tests include the ACEI-enhanced renal scan, duplex Doppler flow studies, and magnetic resonance angiography. While renal artery angiography remains the gold standard for identifying the anatomy of the renal artery, it is not recommended for diagnosis alone because of the risk associated with the procedure. At the time of intervention, an arteriogram will be performed using limited contrast to confirm the stenosis and identify the anatomy of the renal artery.

Genetics of Hypertension

The investigation of rare genetic disorders affecting BP has led to the identification of genetic abnormalities associated with several rare forms of hypertension, including mineralocorticoid-remediable aldosteronism, 11- β -hydroxylase and 17 α -hydroxylase deficiencies, Liddle syndrome, the syndrome of apparent mineralocorticoid excess, and pseudohypoaldosteronism type II.⁸² The individual and joint contributions of these genetic mutations to BP levels in the general population, however, are very small. Genetic association studies have identified polymorphisms in several candidate genes (eg, angiotensinogen, α -adducin, β - and DA-adrenergic receptors, β -3 subunit of G proteins), and genetic linkage studies have focused attention on several genomic sites that may harbor other genes contributing to primary hypertension.^{83–85} However, none of these various genetic abnormalities has been shown, either alone or in joint combination, to be responsible for any applicable portion of hypertension in the general population.

Treatment

Blood Pressure Control Rates

Hypertension is the most common primary diagnosis in America (35 million office visits as the primary diagnosis).⁵ Current control rates (SBP <140 mm Hg and DBP <90 mm Hg), though improved, are still far below the Healthy People goal of 50% (originally set as the year 2000 goal and since extended to 2010; Table 1). In the majority of patients, reducing SBP has been considerably more difficult than lowering DBP. Although effective BP control can be achieved in most patients who are hypertensive, the majority will require 2 or more antihypertensive drugs.^{28,29,86} Failure to prescribe lifestyle modifications, adequate antihypertensive

drug doses, or appropriate drug combinations may result in inadequate BP control.

Goals of Therapy

The ultimate public health goal of antihypertensive therapy is to reduce cardiovascular and renal morbidity and mortality. Since most persons with hypertension, especially those >50 years old, will reach the DBP goal once the SBP goal is achieved, the primary focus should be on attaining the SBP goal. Treating SBP and DBP to targets that are <140/90 mm Hg is associated with a decrease in CVD complications.⁸⁷ In patients with hypertension and diabetes or renal disease, the BP goal is <130/80 mm Hg.^{88,89}

Benefits of Lowering Blood Pressure

In clinical trials, antihypertensive therapy has been associated with reductions in stroke incidence averaging 35% to 40%; myocardial infarction, 20% to 25%; and HF, >50%.⁹⁰ It is estimated that in patients with stage 1 hypertension (SBP 140 to 159 mm Hg and/or DBP 90 to 99 mm Hg) and additional cardiovascular risk factors, achieving a sustained 12 mm Hg reduction in SBP over 10 years will prevent 1 death for every 11 patients treated. In the added presence of CVD or target organ damage, only 9 patients would require such BP reduction to prevent 1 death.⁹¹

Lifestyle Modifications

Adoption of healthy lifestyles by all persons is critical for the prevention of high BP and is an indispensable part of the management of those with hypertension.¹⁰ Weight loss of as little as 10 lbs (4.5 kg) reduces BP and/or prevents hypertension in a large proportion of overweight persons, although the ideal is to maintain normal body weight.^{92,93} BP is also benefited by adoption of the Dietary Approaches to Stop Hypertension (DASH) eating plan,⁹⁴ which is a diet rich in fruits, vegetables, and lowfat dairy products with a reduced content of dietary cholesterol as well as saturated and total fat (modification of whole diet). It is rich in potassium and calcium content.⁹⁵ Dietary sodium should be reduced to no more than 100 mmol per day (2.4 g of sodium).^{94–96} Everyone who is able should engage in regular aerobic physical activity such as brisk walking at least 30 minutes per day most days of the week.^{97,98} Alcohol intake should be limited to no more than 1 oz (30 mL) of ethanol, the equivalent of two drinks, per day in most men and no more than 0.5 oz of ethanol (one drink) per day in women and lighter weight persons. A drink is 12 oz of beer, 5 oz of wine, and 1.5 oz of 80-proof liquor (Table 9).⁹⁹ Lifestyle modifications reduce BP, prevent or delay the incidence of hypertension, enhance antihypertensive drug efficacy, and decrease cardiovascular risk. For example, in some individuals, a 1600 mg sodium DASH eating plan has BP effects similar to single drug therapy.⁹⁴ Combinations of 2 (or more) lifestyle modifications can achieve even better results.¹⁰⁰ For overall cardiovascular risk reduction, patients should be strongly counseled to quit smoking.

Pharmacological Treatment

A large number of drugs are currently available for reducing BP. Tables 10 and 11 provide a list of the commonly used

TABLE 9. Lifestyle Modifications To Prevent and Manage Hypertension*

Modification	Recommendation	Approximate SBP Reduction (Range)†
Weight reduction	Maintain normal body weight (body mass index 18.5–24.9 kg/m ²).	5–20 mm Hg/10 kg ^{92,93}
Adopt DASH eating plan	Consume a diet rich in fruits, vegetables, and low-fat dairy products with a reduced content of saturated and total fat.	8–14 mm Hg ^{94,95}
Dietary sodium reduction	Reduce dietary sodium intake to no more than 100 mmol per day (2.4 g sodium or 6 g sodium chloride).	2–8 mm Hg ^{94–96}
Physical activity	Engage in regular aerobic physical activity such as brisk walking (at least 30 minutes per day, most days of the week).	4–9 mm Hg ^{97,98}
Moderation of alcohol consumption	Limit consumption to no more than 2 drinks (eg, 24 oz beer, 10 oz wine, or 3 oz 80-proof whiskey) per day in most men and to no more than 1 drink per day in women and lighter-weight persons.	2–4 mm Hg ⁹⁹

DASH indicates Dietary Approaches to Stop Hypertension.

*For overall cardiovascular risk reduction, stop smoking.

†The effects of implementing these modifications are dose- and time-dependent and could be greater for some individuals.

antihypertensive agents and their usual dose range and frequency of administration.

More than two-thirds of hypertensive individuals cannot be controlled on one drug and will require two or more antihypertensive agents selected from different drug classes.^{28,87,101–103} For example, in ALLHAT, 60% of those whose BP was controlled to <140/90 mm Hg received two or more agents, and only 30% overall were controlled on one drug.²⁸ In hypertensive patients with lower BP goals or with substantially elevated BP, 3 or more antihypertensive drugs may be required.

Since the first VA Cooperative trial published in 1967, thiazide-type diuretics have been the basis of antihypertensive therapy in the majority of placebo-controlled outcome trials in which CVD events, including strokes, CHD, and HF, have been reduced by BP lowering.^{104–108} However, there are also excellent clinical trial data proving that lowering BP with other classes of drugs, including ACEIs, ARBs, β -blockers (BBs), and calcium channel blockers (CCBs), also reduces the complications of hypertension.^{90,101,102,107,109–112} Several randomized controlled trials have demonstrated reduction in CVD with BBs, but the benefits are less consistent than with diuretics.^{107,108} The European Trial on Systolic Hypertension in the Elderly (Syst-EUR) study showed significant reductions in stroke and all CVD with the dihydropyridine CCB, nitrendipine, compared with placebo.¹¹³ The Heart Outcomes Prevention Evaluation (HOPE) trial, which was not restricted to hypertensive individuals but which included a sizable hypertensive subgroup, showed reductions in a variety of CVD events with the ACEI ramipril compared with placebo in individuals with prior CVD or diabetes mellitus combined with other risk factor(s).¹¹⁰ The European trial on reduction of cardiac events with perindopril in stable coronary artery

disease (EUROPA), in which the ACEI perindopril was added to existent therapy in patients with stable coronary disease and without HF, also demonstrated reduction in CVD events with ACEIs.¹¹⁴

Since 1998, several large trials comparing newer classes of agents, including CCBs, ACEIs, an α_1 receptor blocker, and an ARB, with the older diuretics and/or BBs have been completed.^{101,102,109,112,115–118} Most of these studies showed the newer classes were neither superior nor inferior to the older ones. One exception was the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study, in which CVD events were 13% lower (because of differences in stroke but not CHD rates) with the ARB losartan than with the BB atenolol.¹⁰² There has not been a large outcome trial completed as yet comparing an ARB with a diuretic. All of these trials taken together suggest broadly similar cardiovascular protection from BP-lowering with ACEIs, CCBs, and ARBs, as with thiazide-type diuretics and BBs, although some specific outcomes may differ between the classes. There do not appear to be systematic outcome differences between dihydropyridine and nondihydropyridine CCBs in hypertension morbidity trials. On the basis of other data, short-acting CCBs are not recommended in the management of hypertension.

Rationale for Recommendation of Thiazide-Type Diuretics as Preferred Initial Agent

In trials comparing diuretics with other classes of antihypertensive agents, diuretics have been virtually unsurpassed in preventing the cardiovascular complications of hypertension. In the ALLHAT study, which involved more than 40 000 hypertensive individuals,¹⁰⁹ there were no differences in the primary CHD outcome or mortality between the thiazide-type

TABLE 10. Oral Antihypertensive Drugs

Class	Drug (Trade Name)	Usual Dose Range, mg/d	Usual Daily Frequency*
Thiazide diuretics	Chlorothiazide (Diuril)	125–500	1–2
	Chlorthalidone (generic)	12.5–25	1
	Hydrochlorothiazide (Microzide, HydroDIURIL†)	12.5–50	1
	Polythiazide (Renese)	2–4	1
	Indapamide (Lozol†)	1.25–2.5	1
	Metolazone (Mykrox)	0.5–1.0	1
	Metolazone (Zaroxolyn)	2.5–5	1
Loop diuretics	Bumetanide (Bumex†)	0.5–2	2
	Furosemide (Lasix†)	20–80	2
	Torsemide (Demadex†)	2.5–10	1
Potassium-sparing diuretics	Amiloride (Midamor†)	5–10	1–2
	Triamterene (Dyrenium)	50–100	1–2
Aldosterone receptor blockers	Eplerenone (Inspra)	50–100	1
	Spirolactone (Aldactone†)	25–50	1
BBs	Atenolol (Tenormin†)	25–100	1
	Betaxolol (Kerlone†)	5–20	1
	Bisoprolol (Zebeta†)	2.5–10	1
	Metoprolol (Lopressor†)	50–100	1–2
	Metoprolol extended release (Toprol XL)	50–100	1
	Nadolol (Corgard†)	40–120	1
	Propranolol (Inderal†)	40–160	2
	Propranolol long-acting (Inderal LA†)	60–180	1
	Timolol (Blocadren†)	20–40	2
BBs with intrinsic sympathomimetic activity	Acebutolol (Sectral†)	200–800	2
	Penbutolol (Levitol)	10–40	1
	Pindolol (generic)	10–40	2
Combined α -blockers and BBs	Carvedilol (Coreg)	12.5–50	2
	Labetalol (Normodyne, Trandate†)	200–800	2
ACEIs	Benazepril (Lotensin†)	10–40	1
	Captopril (Capoten†)	25–100	2
	Enalapril (Vasotec†)	5–40	1–2
	Fosinopril (Monopril)	10–40	1
	Lisinopril (Prinivil, Zestril†)	10–40	1
	Moexipril (Univasc)	7.5–30	1
	Perindopril (Aceon)	4–8	1
	Quinapril (Accupril)	10–80	1
	Ramipril (Altace)	2.5–20	1
	Trandolapril (Mavik)	1–4	1
Angiotensin II antagonists	Candesartan (Atacand)	8–32	1
	Eprosartan (Teveten)	400–800	1–2
	Irbesartan (Avapro)	150–300	1
	Losartan (Cozaar)	25–100	1–2
	Olmesartan (Benicar)	20–40	1
	Telmisartan (Micardis)	20–80	1
	Valsartan (Diovan)	80–320	1–2

TABLE 10. Oral Antihypertensive Drugs (continued)

Class	Drug (Trade Name)	Usual Dose Range, mg/d	Usual Daily Frequency*
CCBs—Nondihydropyridines	Diltiazem extended release (Cardizem CD, Dilacor XR, Tiazact†)	180–420	1
	Diltiazem extended release (Cardizem LA)	120–540	1
	Verapamil immediate release (Calan, Isoptin†)	80–320	2
	Verapamil long acting (Calan SR, Isoptin SR†)	120–480	1–2
	Verapamil (Coer, Covera HS, Verelan PM)	120–360	1
CCBs—Dihydropyridines	Amlodipine (Norvasc)	2.5–10	1
	Felodipine (Plendil)	2.5–20	1
	Isradipine (Dynacirc CR)	2.5–10	2
	Nicardipine sustained release (Cardene SR)	60–120	2
	Nifedipine long-acting (Adalat CC, Procardia XL)	30–60	1
	Nisoldipine (Sular)	10–40	1
α_1 blockers	Doxazosin (Cardura)	1–16	1
	Prazosin (Minipress†)	2–20	2–3
	Terazosin (Hytrin)	1–20	1–2
Central α_2 agonists and other centrally acting drugs	Clonidine (Cataprest†)	0.1–0.8	2
	Clonidine patch (Catapres-TTS)	0.1–0.3	1 weekly
	Methyldopa (Aldomet†)	250–1 000	2
	Reserpine (generic)	0.1–0.25	1
	Guanfacine (Tenex†)	0.5–2	1
Direct vasodilators	Hydralazine (Apresolin†)	25–100	2
	Minoxidil (Loniten†)	2.5–80	1–2

Source: *Physicians' Desk Reference*. 57th ed. Montvale, NJ: Thomson PDR; 2003.

*In some patients treated once daily, the antihypertensive effect may diminish toward the end of the dosing interval (trough effect). BP should be measured just prior to dosing to determine if satisfactory BP control is obtained. Accordingly, an increase in dosage or frequency may need to be considered. These dosages may vary from those listed in the *Physician's Desk Reference*, 57th ed.

†Available now or soon to become available in generic preparations.

diuretic chlorthalidone, the ACEI lisinopril, or the CCB amlodipine. Stroke incidence was greater with lisinopril than chlorthalidone therapy, but these differences were present primarily in blacks, who also had less BP lowering with lisinopril than diuretics. The incidence of HF was greater in CCB-treated and ACEI-treated individuals compared with those receiving the diuretic in both blacks and whites. In the Second Australian National Blood Pressure (ANBP₂) study, which compared the effects of an ACEI-based regimen against diuretics-based therapy in 6000 white hypertensive individuals, cardiovascular outcomes were less in the ACEI group, with the favorable effect apparent only in men.¹¹² CVD outcome data comparing ARB with other agents are limited.

Clinical trial data indicate that diuretics are generally well tolerated.^{103,109} The doses of thiazide-type diuretics used in successful morbidity trials of low-dose diuretics

were generally the equivalent of 25 to 50 mg of hydrochlorothiazide or 12.5 to 25 mg of chlorthalidone, although therapy may be initiated at lower doses and titrated to these doses if tolerated. Higher doses have been shown to add little additional antihypertensive efficacy but are associated with more hypokalemia and other adverse effects.^{119–122}

Uric acid will increase in many patients receiving a diuretic, but the occurrence of gout is uncommon with dosages ≤ 50 mg/d of hydrochlorothiazide or ≤ 25 mg of chlorthalidone. Some reports have described an increased degree of sexual dysfunction when thiazide diuretics, particularly at high doses, are used. In the Treatment of Mild Hypertension Study (TOMHS), participants randomized to chlorthalidone reported a significantly higher incidence of erection problems through 24 months of the study; however, the incidence rate at 48 months was similar to placebo.¹²³ The

TABLE 11. Combination Drugs for Hypertension

Combination Type	Fixed-Dose Combination, mg*	Trade Name
ACEIs and CCBs	Amlodipine-benazepril hydrochloride (2.5/10, 5/10, 5/20, 10/20)	Lotrel
	Enalapril-felodipine (5/5)	Lexxel
	Trandolapril-verapamil (2/180, 1/240, 2/240, 4/240)	Tarka
ACEIs and diuretics	Benazepril-hydrochlorothiazide (5/6.25, 10/12.5, 20/12.5, 20/25)	Lotensin HCT
	Captopril-hydrochlorothiazide (25/15, 25/25, 50/15, 50/25)	Capozide
	Enalapril-hydrochlorothiazide (5/12.5, 10/25)	Vaseretic
	Fosinopril-hydrochlorothiazide (10/12.5, 20/12.5)	Monopril/HCT
	Lisinopril-hydrochlorothiazide (10/12.5, 20/12.5, 20/25)	Prinzide, Zestoretic
	Moexipril-hydrochlorothiazide (7.5/12.5, 15/25)	Uniretic
	Quinapril-hydrochlorothiazide (10/12.5, 20/12.5, 20/25)	Accuretic
ARBs and diuretics	Candesartan-hydrochlorothiazide (16/12.5, 32/12.5)	Atacand HCT
	Eprosartan-hydrochlorothiazide (600/12.5, 600/25)	Teveten-HCT
	Irbesartan-hydrochlorothiazide (150/12.5, 300/12.5)	Avalide
	Losartan-hydrochlorothiazide (50/12.5, 100/25)	Hyzaar
	Olmesartan medoxomil-hydrochlorothiazide (20/12.5, 40/12.5, 40/25)	Benicar HCT
	Telmisartan-hydrochlorothiazide (40/12.5, 80/12.5)	Micardis-HCT
	Valsartan-hydrochlorothiazide (80/12.5, 160/12.5, 160/25)	Diovan-HCT
BBs and diuretics	Atenolol-chlorthalidone (50/25, 100/25)	Tenoretic
	Bisoprolol-hydrochlorothiazide (2.5/6.25, 5/6.25, 10/6.25)	Ziac
	Metoprolol-hydrochlorothiazide (50/25, 100/25)	Lopressor HCT
	Nadolol-bendroflumethiazide (40/5, 80/5)	Corzide
	Propranolol LA-hydrochlorothiazide (40/25, 80/25)	Inderide LA
	Timolol-hydrochlorothiazide (10/25)	Timolide
Centrally acting drug and diuretic	Methyldopa-hydrochlorothiazide (250/15, 250/25, 500/30, 500/50)	Aldoril
	Reserpine-chlorthalidone (0.125/25, 0.25/50)	Demi-Regroton, Regroton
	Reserpine-chlorothiazide (0.125/250, 0.25/500)	Diupres
	Reserpine-hydrochlorothiazide (0.125/25, 0.125/50)	Hydropres
Diuretic and diuretic	Amiloride-hydrochlorothiazide (5/50)	Moduretic
	Spirolactone-hydrochlorothiazide (25/25, 50/50)	Aldactazide
	Triamterene-hydrochlorothiazide (37.5/25, 75/50)	Dyazide, Maxzide

BB indicates β -blocker; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker.

*Some drug combinations are available in multiple fixed doses. Each drug dose is reported in milligrams.

VA Cooperative study did not document a significant difference in the occurrence of sexual dysfunction using diuretics compared with other antihypertensive medications¹⁰³ (see the section Erectile Dysfunction). Adverse metabolic effects may occur with diuretics. In ALLHAT, diabetes incidence after 4 years of therapy was 11.8% with chlorthalidone therapy, 9.6% with amlodipine, and 8.1% with lisinopril. However, those differences did not translate to fewer CV events for the ACEI or CCB groups.¹⁰⁹ Those who were already diabetic had fewer CV events in the diuretic group than with ACEI treatment. Trials longer than 1 year duration using modest doses of diuretics generally have

not shown an increase in serum cholesterol in diuretic-treated patients.^{124,125} In ALLHAT, serum cholesterol did not increase from baseline in any group, but it was 1.6 mg/dL lower in the CCB group and 2.2 mg/dL lower in the ACEI group than in diuretic-treated patients.¹⁰⁹ Thiazide-induced hypokalemia could contribute to increased ventricular ectopy and possible sudden death, particularly with high doses of thiazides in the absence of a potassium-sparing agent.¹²¹ In the Systolic Hypertension in the Elderly Program (SHEP) trial, the positive benefits of diuretic therapy were not apparent when serum potassium levels were below 3.5 mmol/L.¹²⁶ However, other studies

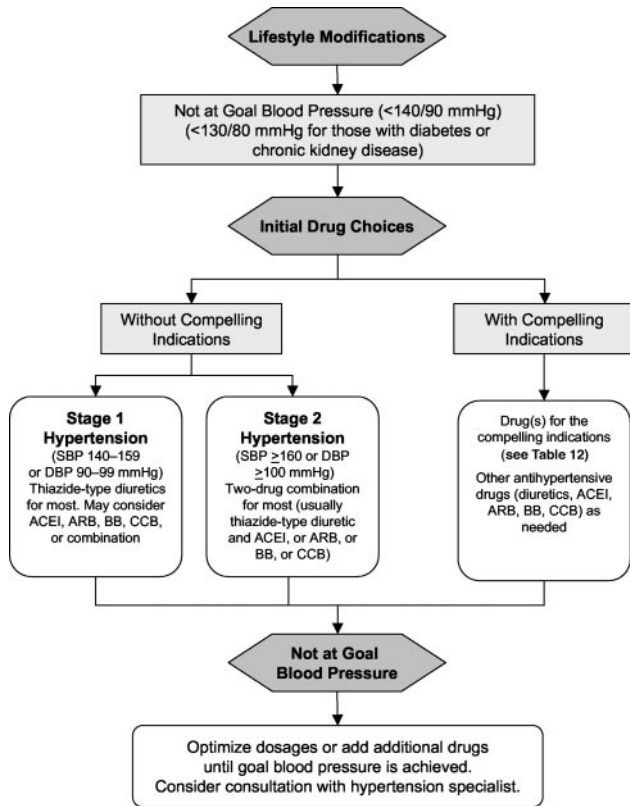


Figure 16. Algorithm for treatment of hypertension.

have not demonstrated increased ventricular ectopy as a result of diuretic therapy.¹²⁷ Despite potential adverse metabolic effects of diuretics, with laboratory monitoring, thiazide-type diuretics are effective and relatively safe for the management of hypertension.

Thiazide diuretics are less expensive than other antihypertensive drugs, although as members of other classes of drugs

have become available in generic form, their cost has been reduced. Despite the various benefits of diuretics, they remain underutilized.¹²⁸

Achieving Blood Pressure Control in Individual Patients

The algorithm for the treatment of hypertensive patients is shown in Figure 16. Therapy begins with lifestyle modification, and if the BP goal is not achieved, thiazide-type diuretics should be used as initial therapy for most patients, either alone or in combination with one of the other classes (ACEIs, ARBs, BBs, CCBs) that have also been shown to reduce one or more hypertensive complications in randomized controlled outcome trials. Selection of one of these other agents as initial therapy is recommended when a diuretic cannot be used or when a compelling indication is present that requires the use of a specific drug, as listed in Table 12. If the initial drug selected is not tolerated or is contraindicated, then a drug from one of the other classes proven to reduce cardiovascular events should be substituted.

Since most hypertensive patients will require 2 or more antihypertensive medications to achieve their BP goals, addition of a second drug from a different class should be initiated when use of a single agent in adequate doses fails to achieve the goal. When BP is more than 20 mm Hg above systolic goal or 10 mm Hg above diastolic goal, consideration should be given to initiate therapy with 2 drugs, either as separate prescriptions or in fixed-dose combinations (Figure 16).¹²⁹

The initiation of therapy with more than one drug increases the likelihood of achieving BP goal in a more timely fashion. The use of multidrug combinations often produces greater BP reduction at lower doses of the component agents, resulting in fewer side effects.^{129,130}

The use of fixed-dose combinations may be more convenient and simplify the treatment regimen and may cost less

TABLE 12. Clinical Trial and Guideline Basis for Compelling Indications for Individual Drug Classes

Compelling Indication*	Recommended Drugs						Clinical Trial Basis†
	Diuretic	BB	ACEI	ARB	CCB	Aldo ANT	
Heart failure	●	●	●	●		●	ACC/AHA Heart Failure Guideline, ¹³² MERIT-HF, ¹³³ COPERNICUS, ¹³⁴ CIBIS, ¹³⁵ SOLVD, ¹³⁶ AIRE, ¹³⁷ TRACE, ¹³⁸ ValHEFT, ¹³⁹ RALES, ¹⁴⁰ CHARM ¹⁴¹
Post-myocardial infarction		●	●			●	ACC/AHA Post-MI Guideline, ¹⁴² BHAT, ¹⁴³ SAVE, ¹⁴⁴ Capricorn, ¹⁴⁵ EPHEBUS ¹⁴⁶
High coronary disease risk	●	●	●		●		ALLHAT, ¹⁰⁹ HOPE, ¹¹⁰ ANBP2, ¹¹² LIFE, ¹⁰² CONVINCe, ¹⁰¹ EUROPA, ¹¹⁴ INVEST ¹⁴⁷
Diabetes	●	●	●	●	●		NKF-ADA Guideline, ^{88,89} UKPDS, ¹⁴⁸ ALLHAT ¹⁰⁹
Chronic kidney disease			●	●			NKF Guideline, ⁸⁹ Captopril Trial, ¹⁴⁹ RENAAL, ¹⁵⁰ IDNT, ¹⁵¹ REIN, ¹⁵² AASK ¹⁵³
Recurrent stroke prevention	●		●				PROGRESS ¹¹¹

BB indicates β-blocker; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; Aldo ANT, aldosterone antagonist.

*Compelling indications for antihypertensive drugs are based on benefits from outcome studies or existing clinical guidelines; the compelling indication is managed in parallel with the BP.

†Conditions for which clinical trials demonstrate benefit of specific classes of antihypertensive drugs used as part of an antihypertensive regimen to achieve BP goal to test outcomes.

than the individual components prescribed separately. Use of generic drugs should be considered to reduce prescription costs, and the cost of separate prescription of multiple drugs available generically may be less than nongeneric, fixed-dose combinations. The starting dose of most fixed-dose combinations is usually below the doses used in clinical outcome trials, and the doses of these agents should be titrated upward to achieve the BP goal before adding other drugs. However, caution is advised in initiating therapy with multiple agents, particularly in some older persons and in those at risk for orthostatic hypotension, such as diabetics with autonomic dysfunction.

Follow-Up and Monitoring

Once antihypertensive drug therapy is initiated, most patients should return for follow-up and adjustment of medications at monthly intervals or less until the BP goal is reached. More frequent visits will be necessary for patients with stage 2 hypertension or with complicating comorbid conditions. Serum potassium and creatinine should be monitored at least 1 to 2 times/year. After BP is at goal and stable, follow-up visits can usually be at 3- to 6-month intervals. Comorbidities such as HF, associated diseases such as diabetes, and the need for laboratory tests influence the frequency of visits. Other cardiovascular risk factors should be monitored and treated to their respective goals, and tobacco avoidance must be promoted vigorously. Low-dose aspirin therapy should be considered only when BP is controlled because of the increased risk of hemorrhagic stroke when the hypertension is not controlled.¹³¹

Special Situations in Hypertension Management

Compelling Indications

Hypertension may exist in association with other conditions in which there are compelling indications for use of a particular treatment based on clinical trial data demonstrating benefits of such therapy on the natural history of the associated condition (Table 12). Compelling indications for specific therapy involve high-risk conditions that can be direct sequelae of hypertension (HF, ischemic heart disease, chronic kidney disease, recurrent stroke) or commonly associated with hypertension (diabetes, high coronary disease risk). Therapeutic decisions in such individuals should be directed at both the compelling indication and BP lowering.

The absence of a positive indication can signify a lack of information for a particular drug class. For example, in recurrent stroke, there is no study employing CCBs or ARBs. Different stages of the conditions may dictate different strategies. In HF management, thiazide-type diuretics are recommended for reducing the incidence of HF but not in lengthening survival in individuals who already have the condition. Furthermore, widespread use of combination therapy in clinical trials confounds interpretation of the effects of single drugs. In the Perindopril Protection Against Recurrent Stroke Study (PROGRESS) trial, recurrent stroke rate was reduced only when a thiazide-type diuretic was added to ACEI background therapy.

Ischemic Heart Disease

Hypertensive patients are at increased risk for myocardial infarction (MI) or other major coronary event and may be at higher risk of death following an acute MI. Myocardial oxygen supply in hypertensives may be limited by coronary artery disease (CAD) while myocardial oxygen demand is often greater because of the increased impedance to left ventricular ejection and the frequent presence of left ventricular hypertrophy (LVH).¹⁵⁴ Lowering both SBP and DBP reduces ischemia and prevents CVD events in patients with CAD, in part by reducing myocardial oxygen demand. One caveat with respect to antihypertensive treatment in patients with CAD is the finding in some studies of an apparent increase in coronary risk at low levels of DBP. For example, in the SHEP study, lowering DBP to <55 or 60 mm Hg was associated with an increase in cardiovascular events, including MI.¹⁵⁵ No similar increase in coronary events (a J-shaped curve) has been observed with SBP. Patients with occlusive CAD and/or LVH are put at risk of coronary events if DBP is low. Overall, however, many more events are prevented than caused if BP is aggressively treated.

Stable Angina and Silent Ischemia

Therapy is directed toward preventing MI and death and reducing symptoms of angina and the occurrence of ischemia. Unless contraindicated, pharmacological therapy should be initiated with a BB.^{142,156} BBs will lower BP, reduce symptoms of angina, improve mortality, and reduce cardiac output, heart rate, and AV conduction. The reduced inotropy and heart rate decrease myocardial oxygen demand. Treatment should also include smoking cessation, management of diabetes, lipid lowering, antiplatelet agents, exercise training, and weight reduction in obese patients.

If angina and BP are not controlled by BB therapy alone, or if BBs are contraindicated, as in the presence of severe reactive airway disease, severe peripheral arterial disease, high-degree AV block, or the sick sinus syndrome, either long-acting, dihydropyridine or nondihydropyridine-type CCBs may be used. CCBs decrease total peripheral resistance, which leads to reduction in BP and in wall tension. CCBs also decrease coronary resistance and enhance poststenotic coronary perfusion. Nondihydropyridine CCBs also can decrease heart rate, but when in combination with a BB, they may cause severe bradycardia or high degrees of heart block. Therefore, long-acting dihydropyridine CCBs are preferred for combination therapy with BBs. If angina or BP is still not controlled on this two-drug regimen, nitrates can be added, but these should be used with caution in patients taking phosphodiesterase-5 inhibitors such as sildenafil. Short-acting dihydropyridine CCBs should not be used because of their potential to increase mortality, particularly in the setting of acute MI.

Heart Failure

The HF syndrome occurs when the heart is incapable of maintaining sufficient flow to accommodate tissue perfusion and metabolic requirements. Forty to 50% of patients with symptoms of HF may have preserved systolic function. These patients are more likely to have hypertension, LVH, and isolated diastolic dysfunction and are more likely to be

women.^{141,157} A variety of neurohormonal systems, especially the renin-angiotensin-aldosterone and sympathetic nervous systems may be activated in response to the LV dysfunction, but such activation may lead to abnormal ventricular remodeling, further LV enlargement, and reduced cardiac contractility. The inexorable progression to more severe stages of LV dysfunction can be significantly reduced by effective therapy with ACEIs, BBs, and diuretics.

Hypertension precedes the development of HF in approximately 90% of patients and increases risk for HF by 2- to 3-fold. Hypertension is especially important in HF affecting African Americans and the elderly. CAD is the cause of HF in approximately two-thirds of HF patients in the United States. The true incidence of HF has been unchanged in men and has declined among women during the past 50 years.¹⁵⁸ However, HF hospitalization rates have more than doubled in the past 20 years¹⁵⁹ because of the improved therapy resulting in increased life expectancy. HF will probably become even more prevalent in the future as our population ages.

Optimal therapy for HF may require the use of specialized HF disease management programs and utilization of a variety of health professionals to reinforce treatment recommendations. American College of Cardiology/American Heart Association (ACC/AHA) guidelines are available to manage HF.¹³² In the stage A group (New York Heart Association [NYHA] class I), those at high risk for HF but no demonstrable clinical symptoms or LV dysfunction, treatment should include fastidious risk factor management to control BP, hypercholesterolemia, and hyperglycemia. ACEIs may be appropriate because of their beneficial effects on mortality in patients at high risk for CVD.^{110,114} The ALLHAT study also has suggested that thiazide-diuretic therapy is useful in preventing disease progression.¹⁰⁹ In stage B HF (NYHA class I) as defined by the presence of reduced LV function (ejection fraction [EF] $\leq 40\%$) in otherwise asymptomatic individuals, ACEIs and BBs are recommended. Stage C patients (NYHA class II–III) manifest LV dysfunction and overt symptoms, and in these individuals, ACEIs and BBs are again indicated. Aldosterone antagonists also may be of value in this situation.¹⁴⁰ Loop diuretics are often necessary to control volume retention. However, there is no evidence that diuretics prevent progression of disease, and diuretics can also increase serum creatinine levels when used in excess. Patients with stage D (NYHA class IV) HF may require advanced care, such as inotropic drugs, implantable defibrillators, biventricular pacemakers, mechanical-assist devices, or transplantation, in addition to the treatment described above for stage C patients.

HF is a “compelling indication” for the use of ACEIs. Abundant evidence exists to justify their use with all stages of HF (Table 12). In patients intolerant of ACEIs, ARBs may be used. BBs are also recommended in HF because of clinical studies demonstrating decreased morbidity and mortality and improvement in HF symptoms (Table 12).

Aldosterone antagonists may provide additional benefit in patients with severe LV dysfunction, usually late stage C (NYHA class III–IV). In the Randomized Aldactone Evaluation Study (RALES), low-dose spironolactone (12.5 to 25 mg daily), when added to standard therapy, decreased mor-

tality by 34%.¹⁴⁰ In the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHE-SUS), eplerenone reduced mortality by 15% in patients following a recent MI with LVEF $\leq 40\%$, 90% of whom had HF symptoms.¹⁴⁰ Hyperkalemia is a risk with aldosterone antagonists, even at low doses (especially since most patients also are taking ACEIs or ARBs), but its incidence can be reduced by limiting therapy to patients with serum creatinine < 2.5 mg/dL and monitoring serum potassium carefully.

BP targets in HF have not been firmly established, but lowering SBP is almost uniformly beneficial. In most successful trials, systolic blood pressures were lowered to the range of 110 to 130 mm Hg. One trial demonstrated benefits of β -blockade in patients with SBP > 85 mm Hg,¹³⁴ suggesting that very low BPs (eg, SBP < 100 mm Hg) may be desirable in some HF patients.

Digoxin continues to be used in HF despite inconsistent clinical results. In the Digitalis Investigation Group (DIG) trial, it did not reduce mortality in NYHA class II–III patients taking ACEIs and diuretics but did reduce HF symptoms and hospitalizations.¹⁶⁰

Diabetes and Hypertension

The combined unadjusted prevalence of total diabetes and impaired fasting glucose in those over 20 years old is 14.4% and is the leading cause of blindness, ESRD, and nontraumatic amputations.^{161–165} Type 2 diabetes constitutes over 90% of diabetes in the United States and is associated with a 70% to 80% chance of premature death from CVD and stroke.^{166–170} The concordance of hypertension and diabetes is increased in the population; hypertension is disproportionately higher in diabetics,¹⁷¹ while persons with elevated BP are 2.5 times more likely to develop diabetes within 5 years.^{172,173} The common absence of normal nocturnal “dipping” of BP in diabetics is linked to other CVD surrogates such as LVH and microalbuminuria.¹⁷¹

The coexistence of hypertension in diabetes is particularly pernicious because of the strong linkage of the 2 conditions with all CVD,^{168,169} stroke,^{87,109,110,168,169,174–176} progression of renal disease,^{165,175,177,178} and diabetic retinopathy.¹⁷⁹ The United Kingdom Prospective Diabetes Study (UKPDS)¹⁷⁴ demonstrated that each 10 mm Hg decrease in SBP was associated with average reductions in rates of diabetes-related mortality of 15%; myocardial infarction, 11%; and the microvascular complications of retinopathy or nephropathy, 13%. Randomized controlled trials that have included large diabetic populations, including UKPDS, Hypertension Optimal Treatment (HOT) Trial, SHEP, Syst-EUR,⁶⁷ HOPE Study,¹¹⁰ Losartan Intervention For Endpoint Reduction in Hypertension Study (LIFE), and ALLHAT, have demonstrated that adequate BP control improves CVD outcomes, especially stroke, when aggressive BP targets are achieved.^{87,88,109,164,175,180}

Microalbuminuria (30 to 300 mg/d) is associated with increased CVD risk in diabetics and other high-risk patients.^{67,181} Overt albuminuria (> 300 mg/d or > 200 mg/g creatinine on spot urine) or renal insufficiency (estimated GFR < 60 mL/min, corresponding to serum creatinine > 1.5 in men or > 1.3 mg/dL in women) defines the presence of

chronic kidney disease (CKD) in diabetic patients. SBP correlates better than DBP with renal disease progression in diabetics.^{171,177,178,182,183} The rate of decline in renal function among patients with diabetic nephropathy has been reported to be a continuous function of arterial pressure down to approximately 125 to 130 mm Hg SBP and 70 to 75 mm Hg DBP.^{177,178,182,183}

The JNC 7 recommendations are consistent with guidelines from the American Diabetes Association (ADA),^{88,164} which has also recommended that BP in diabetics be controlled to levels of 130/80 mm Hg or lower (although available data are somewhat sparse to justify the low target level of 130/80 mm Hg). Whatever the goal level, rigorous control of BP is paramount for reducing the progression of diabetic nephropathy to ESRD.^{88,164,177,178,181–183}

Regarding the selection of medications, clinical trials with diuretics, ACEIs, BBs, ARBs, and calcium antagonists have demonstrated benefit in the treatment of hypertension in both type 1 and type 2 diabetics.^{87,88,109,164,175,180} The question of which agent class is superior for lowering BP is somewhat moot because the majority of diabetic patients will require 2 or more drugs to achieve BP control.^{164,171,184}

Thiazide-type diuretics are beneficial in diabetics, either alone or as part of a combined regimen. In the prespecified diabetic subgroup of ALLHAT, therapy that began with chlorthalidone reduced the primary end point of fatal CHD and MI to the same degree as therapy based on lisinopril or amlodipine. Of potential concern is the tendency for thiazide-type diuretics to worsen hyperglycemia, but this effect tended to be small and did not produce more CV events compared with the other drug classes.¹⁸⁵

Therapy with an ACEI also is an important component of most regimens to control BP in diabetic patients.^{67,172,173,178,179} ACEIs may be used alone for BP lowering but are much more effective when combined with a thiazide-type diuretic or other antihypertensive drugs. The ADA has recommended ACEIs for diabetic patients over 55 years old at high risk for CVD and BBs for those with known CAD.⁸⁸ In the Micro-Hope subanalysis of the HOPE Study, which included both hypertensive and normotensive individuals,¹⁸⁶ high-risk diabetic patients treated with ACEI added to conventional therapy showed a reduction in combined MI, stroke, and CVD death of about 25% and reduction in stroke by about 33% compared with placebo plus conventional therapy. With respect to microvascular complications, the ADA has recommended both ACEIs and ARBs for use in Type 2 diabetic patients with CKD because these agents delay the deterioration in GFR and the worsening of albuminuria.^{88,164,171,181}

BBs, especially β_1 -selective agents, are beneficial in diabetics as part of multidrug therapy, but their value as monotherapy is less clear. A BB is indicated in a diabetic with ischemic heart disease but may be less effective in preventing stroke than an ARB, as was found in the LIFE study.¹⁸⁷ Although BBs can cause adverse effects on glucose homeostasis in diabetics, including worsening of insulin sensitivity and potential masking of the epinephrine-mediated symptoms of hypoglycemia, these problems are usually easily managed and are not absolute contraindications for BB use.

Calcium channel blockers may be useful in diabetics, particularly as part of combination therapy to control BP. They were shown to reduce CVD events in diabetics compared with placebo in several clinical outcome trials.^{87,101,113,118} In the diabetic cohort of ALLHAT, amlodipine was as effective as chlorthalidone in all categories except HF, where it was significantly inferior.¹⁰⁹ The Appropriate Blood Pressure Control in Diabetes (ABCD) study in diabetics was stopped prematurely when it was found that the dihydropyridine nitrendipine was inferior to lisinopril in reducing the incidence of ischemic cardiac events.¹⁸⁸ However, in normotensive diabetics in the Second ABCD (ABCD₂) study, nitrendipine was equivalent to lisinopril in stroke prevention and in retardation of the development of albuminuria.¹⁸⁹

Chronic Kidney Disease

Age and Kidney Function

Renal excretory function, as represented by GFR, deteriorates with age beginning in the third or fourth decade of life. By the sixth decade, GFR commonly declines by 1 to 2 mL/min per year. This age-related loss of renal function is proportional to BP level, and the rate of GFR deterioration can accelerate to 4 to 8 mL/min per year if SBP remains uncontrolled.¹⁶⁵ Such rates of deterioration may lead to the development of ESRD and the need for dialysis or transplantation, especially in those with other coexistent renal disease.

CKD is defined as either (1) reduced excretory function with an eGFR <60 mL/min/1.73 m² (approximately corresponding to a creatinine of >1.5 mg/dL in men or >1.3 mg/dL in women) or (2) the presence of albuminuria (>300 mg/d or 200 mg/g creatinine). In a number of laboratories, serum creatinine is being replaced as an index of renal function by eGFR, the values of which are derived from newer algorithms that include adjustments for gender, race, and age. These algorithms are available on web sites.⁶⁶ The measurements appear to be of greater value than 24-hour urine collections for creatinine clearance.

Urinary albumin excretion has diagnostic and prognostic value equivalent to reduced eGFR. To avoid inaccuracies associated with 24-hour urine collections, spot urine samples may be used and the ACR determined. Microalbuminuria is present when the spot urine ACR is between 30 and 200 mg albumin/g creatinine. ACR values >200 mg albumin/g creatinine signify the presence of CKD.

CVD Risk in CKD

CVD is the most common cause of death in individuals with CKD, and CKD is itself an independent risk factor for CVD. Individuals with eGFR <60 mL/min have an approximate 16% increase in CVD mortality, and individuals with eGFR <30 mL/min, a 30% increase.¹⁹⁰ CVD risk also exhibits a continuous relationship with albuminuria; the presence of microalbuminuria confers a 50% increase in risk and the presence of macroalbuminuria, a 350% increase.¹⁹¹

Therapy

NHANES III data indicated that about 3% (5.6 million people) of adults in the United States had elevated serum creatinine values and 70% of these had hypertension.¹⁹² While 75% of individuals received treatment, only 11% with

hypertension and elevated serum creatinine had BP <130/85 mm Hg and only 27% had BP <140/90 mm Hg.¹⁹³ In the prevention of CKD, the value of vigorous antihypertensive therapy is most pronounced in those individuals with the greatest degrees of albuminuria. In the Modification of Diet and Renal Disease (MDRD) study, individuals with proteinuria had slower rates of progression to ESRD if their SBP values were <130 mm Hg. A meta-analysis of individuals with CKD and albuminuria found that positive predictors of outcome were lower SBP levels (110 to 129 mm Hg), lower albumin excretion ratio (AER) (<1.0 g/d), and the presence of ACEI therapy.^{194,195} However, in the African American Study of Kidney Disease and Hypertension (AASK) study of African American individuals with hypertensive CKD, those achieving a mean BP of 128/78 mm Hg experienced renal deterioration at the same rate as those achieving a mean of 141/85 mm Hg.¹⁹⁶ Many studies demonstrate that antihypertensive regimens that include an ACEI or ARB are more effective in slowing progression of CKD than other antihypertensive regimens.^{149–152,196}

The joint recommendations of the American Society of Nephrology and the National Kidney Foundation (NKF) provide useful guidelines for management of hypertensive patients with CKD. They recommend a goal BP for all CKD patients of <130/80 mm Hg and a need for more than 1 antihypertensive drug to achieve this goal. The guidelines indicate that most patients with CKD should receive an ACEI or an ARB in combination with a diuretic and that many will require a loop diuretic rather than a thiazide. In addition, if there is a conflict between the goals of slowing progression of CKD and CVD risk reduction, individual decision-making is recommended, based on risk stratification.

Patients with Cerebrovascular Disease

The risk of clinical complications of cerebrovascular disease including ischemic stroke, hemorrhagic stroke, and dementia increases as a function of BP levels. Given the population distribution of BP, most ischemic strokes occur in individuals with prehypertension or stage 1 hypertension. The incidence of ischemic or hemorrhagic stroke is reduced substantially by treatment of hypertension. No specific agent has proven to be clearly superior to all others for stroke protection. In the LIFE study, there were fewer strokes in the losartan-treated group than in the group treated with atenolol.¹⁰² In the ALLHAT study, the stroke incidence was 15% greater with ACEI than with thiazide-type diuretic or dihydropyridine CCB, but the BP reduction in the lisinopril group was also less than with chlorthalidone or amlodipine.¹⁰⁹

With respect to the prevention of recurrent stroke, PROGRESS demonstrated that addition of the diuretic indapamide to the ACEI perindopril caused a 43% reduction in stroke occurrence.¹¹¹ The reduced incidence of stroke appeared related to the BP reduction obtained by the combination therapy even though many patients on entry into the study were not hypertensive.¹⁹⁷ No significant reduction was present in those on perindopril alone whose BP was only 5/3 mm Hg lower than in the control group.

The management of BP during an acute stroke remains controversial. BP is often elevated in the immediate post-

stroke period and is thought by some to be a compensatory physiological response to improve cerebral perfusion to ischemic brain tissue. As a result, it has been common practice after acute cerebral infarction to reduce or withhold BP treatment until the clinical condition has stabilized. There still are no large clinical studies on which to base definitive recommendations. Nevertheless, the American Stroke Association has provided the following guidelines: In patients with recent ischemic stroke whose SBP is >220 mm Hg or DBP 120 to 140 mm Hg, cautious reduction of BP by about 10% to 15% is suggested, while carefully monitoring the patient for neurological deterioration related to the lower pressure. If the DBP is >140 mm Hg, carefully monitored infusion of sodium nitroprusside should be used to reduce the BP by 10 to 15%.¹⁹⁸

BP control affects the use of thrombolytic agents in ischemic stroke. SBP >185 mm Hg or diastolic pressures >110 mm Hg are contraindications to the use of tissue plasminogen activator (t-PA) within the first 3 hours of an ischemic stroke. Once a thrombolytic agent has been initiated, BP should be monitored closely, especially in the first 24 hours after initiation of treatment. SBP \geq 180 mm Hg or DBP \geq 105 mm Hg usually necessitates therapy with intravenous agents to prevent intracerebral bleeding.¹⁹⁹

Other Special Situations

Minorities

The prevalence, impact, and control of hypertension differ across racial and ethnic subgroups of the US population. In African Americans, hypertension is more common, more severe, develops at an earlier age, and leads to more clinical sequelae than in age-matched non-Hispanic whites.²⁰⁰ Mexican Americans and Native Americans have lower control rates than non-Hispanic whites and African Americans.^{201,202} The pathogenesis of hypertension in different racial subgroups may differ with respect to the contributions of such factors as salt, potassium, stress, cardiovascular reactivity, body weight, nephron number, sodium handling, or hormonal systems, but in all subgroups, the pathogenesis is multifactorial.^{200,203} African Americans have a greater prevalence of other cardiovascular risk factors, especially obesity.^{200,203} Much of the variance in hypertension-related sequelae across racial or ethnic groups may be attributable to differences in socioeconomic conditions, access to healthcare services, or attitudes, beliefs, and deficits in accurate health-related information.^{200,203} For example, when medications and provider services were provided free of charge as in the Hypertension Detection and Follow-up Program, African American men treated with the intensive “Stepped-Care Approach” actually benefited more than whites.²⁰⁴

Weight reduction and sodium reduction are recommended for all prehypertensive and hypertensive patients but may be particularly effective in minorities. The salt content of some traditional diets in minorities may be very high.²⁰⁵ The low-sodium DASH eating plan was associated with greater reductions in BP in African Americans than other demographic subgroups.⁹⁴ In clinical trials, lowering BP prevents sequelae of hypertension in all racial or ethnic groups.^{200,203} Nonetheless, monotherapy with BBs, ACEIs, or ARBs lowers

BP to a somewhat lesser degree in African Americans than whites.^{109,206–208} In the ALLHAT trial with more than 15 000 blacks, the ACEIs were less effective in lowering blood pressure than either the thiazide-type diuretic or the CCBs. This was associated with a 40% greater risk of stroke, 32% greater risk of HF, and 19% greater risk of CVD in those randomized to the ACEI versus the diuretic.¹⁰⁹ The interracial differences in BP-lowering observed with these drugs are abolished when they are combined with a diuretic.^{109,203,208}

Racial differences in incidence of antihypertensive drug side effects may occur; African Americans and Asians have a 3- to 4-fold higher risk of angioedema^{109,209,210} and have more cough attributed to ACEIs than whites.²¹¹

Several other benefits of treatment have been demonstrated in minority populations. A 28% reduction in mortality was observed in African Americans who received BB therapy after acute myocardial infarction compared with those not receiving a BB.²¹² A greater degree of preservation of renal function occurred in African Americans with hypertensive nephrosclerosis treated with a regimen containing an ACEI compared with BB or a calcium antagonist.¹⁹⁶ No large outcome studies have been carried out with ARBs in African American and other minority patients. Unfortunately, sufficient numbers of Mexican Americans, other Hispanic Americans, Native Americans, or Asian/Pacific Islanders have not been included in most of the major clinical trials to allow reaching strong conclusions about their responses to individual antihypertensive therapies.

Irrespective of whether race or ethnicity should be a significant consideration in the choice of individual antihypertensive drugs, the use of combination or multiple antihypertensive drug therapy, which usually includes a thiazide-type diuretic, in minority groups will lower BP and reduce the burden of hypertension-related cardiovascular and renal disease.

Metabolic Syndrome

Definition and Associations

The term “metabolic syndrome” describes a constellation of cardiovascular risk factors related to hypertension, abdominal obesity, dyslipidemia, and insulin resistance. The definition adopted by the National Cholesterol Education Program (Adult Treatment Panel [ATP] III) guidelines in 2001²¹ is the presence of 3 or more of the 5 risk factors (Table 13). The World Health Organization has a somewhat different definition of the metabolic syndrome, but for consistency JNC 7 has adopted the ATP III definition.

Several other associated features have been reported, including hyperinsulinemia, insulin resistance, and higher density of LDL-C particles.²¹³ The metabolic syndrome has also been associated with high levels of inflammatory risk markers,²¹⁴ reduced fibrinolysis (including elevated plasminogen activator inhibitor-1),²¹⁵ heightened magnitude of oxidative stress,^{216,217} microalbuminuria,²¹⁸ abnormalities in autonomic regulation,²¹⁹ and activation of the renin-angiotensin-aldosterone axis.²²⁰

Prevalence

When the ATP III criteria were applied to the data from the NHANES III survey (1988–1994), the prevalence of the

TABLE 13. Clinical Criteria Defining the Metabolic Syndrome in ATP III

Waist circumference	>102 cm (>40 inches) for men >88 cm (>35 inches) for women
Blood pressure	≥130 mm Hg systolic and/or ≥85 mm Hg diastolic
Fasting glucose	≥110 mg/dL or 6.1 mmol/L
Triglycerides	≥150 mg/dL or 1.69 mmol/L
HDL cholesterol	<40 mg/dL (1.04 mmol/L) in men <50 mg/dL (1.29 mmol/L) in women

Source: Executive Summary of the Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 2001;285:2486–2497.

metabolic syndrome in adults in the United States was estimated at 23.7% or about 47 million individuals.²²¹ BMI (kg/m²) is related to the metabolic syndrome in both men and women (Table 14).²²² In addition, because abdominal obesity is also correlated with the metabolic syndrome, ATP III uses it rather than BMI. This becomes important in overweight individuals with a BMI 25 to 29.9 kg/m² and large waist circumference (>40 inches in men, >35 inches in women) who may have metabolic syndrome despite not being obese.

The metabolic syndrome will likely increase further in the next several years, primarily because of the rapid increase in obesity. The health problems related to the metabolic syndrome will likely escalate dramatically.

Age Trends

The prevalence of the metabolic syndrome is highly age-dependent. A prevalence of 7% among adults aged 20 to 29 years rises to 40% or more among Americans over 60 years old.

Clinical Impact

The metabolic syndrome is associated in men with a 4-fold increase in risk for fatal CHD and a 2-fold greater risk of CVD and all-cause mortality, even after adjustment for age, LDL-C, smoking, and family history of CHD.²²³ The metabolic syndrome is associated with increased CHD risk in women.²²⁴ Patients with the metabolic syndrome have a 5- to 9-fold increased risk of developing diabetes.^{225,226}

TABLE 14. Estimated Prevalence of the Metabolic Syndrome Using the ATP III Definition Among Normal Weight, Overweight, and Obese Men and Women in NHANES III²²²

Category	BMI, kg/m ²	Metabolic Syndrome Prevalence, %	
		Men	Women
Normal weight	<25.0	4.6%	6.2%
Overweight	25.0–29.9	22.4%	28.1%
Obese	>30	59.6%	50.0%

TABLE 15. Relative 10-Year Risk for Diabetes, Hypertension, Heart Disease, and Stroke Over the Next Decade Among Men Initially Free of Disease Stratified by Baseline BMI²³¹

BMI	Diabetes	Hypertension	Heart Disease	CVA
18.5–21.9	1.0	1.0	1.0	1.0
22.0–24.9	1.8	1.5	1.1	1.1
25.0–29.9	5.6	2.4	1.7	1.3
30.0–34.9	18.2	3.8	2.2	2.1
>35.0	41.2	4.2	2.4	2.5

Clinical Management of the Metabolic Syndrome

The cornerstone for clinical management in adults is appropriate lifestyle changes.

Overweight and Obesity. Treatment of overweight and obesity is summarized in the next section using key principles in the Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults.²²⁷

Physical Activity. The metabolic syndrome can improve with increased physical activity.²²⁸ (See the section Prevention and Lifestyle Modifications for Overweight and Obesity.)

Prehypertension and Hypertension. The vast majority of individuals with the metabolic syndrome will fall into the categories of prehypertension or stage 1 hypertension. Lifestyle modification is the cornerstone of management in all patients with prehypertension or with the metabolic syndrome, but if BP exceeds 140/90 mm Hg, pharmacological therapy is indicated as described in the hypertension treatment algorithm (Figure 16).

Lipids. Elevated TG and reduced HDL are typical lipid abnormalities in metabolic syndrome. Elevated LDL is not a prime feature of metabolic syndrome but is important in clinical management.²¹

Impaired Glucose Tolerance and Diabetes. Modest lifestyle change including healthful nutrition and increased physical activity can reduce the development of diabetes by nearly 60% in high-risk individuals.²²⁹ Management guidelines published by the American Diabetes Association are appropriate for individuals with impaired fasting glucose and diabetes.²³⁰

Lipids

All patients with lipid abnormalities for LDL, HDL, or TG should be treated according to the ATP III recommendations.²¹

Overweight and Obesity

Prevalence and Epidemiology

Using the NHANES databases for the periods 1988 to 1994 versus 1999 to 2000, the age-adjusted prevalence of obesity (BMI ≥ 30 kg/m²) among US adults increased from 22.9% to 30.5%,³³ while the prevalence of overweight (BMI ≥ 25 kg/m²) increased from 55.9% to 64.5%. Obese subjects, especially men, with no other risk factors have increased relative risk for CVD (Table 15).²³¹

Obesity occurs more often among Hispanics, Native Americans, and African Americans than whites in the United States. These demographic differences extend to children, in

TABLE 16. Lifestyle Changes Beneficial in Reducing Weight*

Decrease time in sedentary behaviors such as television watching, video game play, or spending time online
Increase physical activity such as walking, biking, aerobic dancing, tennis, soccer, basketball, etc.
Decrease portion sizes for meals, snacks
Reduce portion sizes or frequency of consumption of calorie-containing beverages

*For more detailed information refer to the *Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults. Obes Res.* 1998;6(suppl):51S–209S.

whom obesity and related health problems are increasing at nearly double the rate in ethnic minorities compared with whites.^{232,233} The rapid increase in the population of ethnic minorities in the United States is another factor that will lead to a rise in the prevalence of obesity and its complications unless effective, culturally diverse, population-based health promotion strategies are promoted.

Prevention and Lifestyle Modifications for Overweight and Obesity

The major goal of management of both the metabolic syndrome and overweight and obesity is to reduce the age-related rate of weight gain. This challenging task will require a complex combination of healthy behaviors, including decrease in sedentary activities, increase in physical activity, and reduction in calorie intake (Table 16). Simple yet practical suggestions include reducing time spent watching television or being online and increasing time spent walking or in activities that raise heart rate. The emphasis for weight management should be on avoidance of excess total energy intake and a regular pattern of physical activity. Reducing food portion sizes and limiting fat intake can assist in reducing overall calorie intake. High-sodium diets may be especially deleterious in obese subjects.²³⁴

Specific nutrient intakes for individuals should be based on lipoprotein levels, BP, and the presence of coexisting heart disease, diabetes, and other risk factors. For example, adoption of the well-studied low-sodium DASH eating plan⁹⁴ provides heart-healthy foods that can be used to promote weight loss, reduce BP in both hypertensive and prehypertensive individuals, and reduce LDL. The benefits of modest lifestyle changes on cardiovascular risk factors are well documented. In the Framingham Heart Study, weight loss of 5 pounds or greater was associated with reductions in cardiovascular risk of about 40%.²³⁵ A 10% reduction in body weight can reduce disease risk factors.²²⁷

Physical activity is a key feature of treatment. Increased physical activity, when combined with a reduction in calories, is essential to weight loss success. Based on the available evidence, the recommendation is to engage in regular physical activity at least 30 minutes per day, most days of the week (see Table 9). In addition, physical activity is critical to the maintenance of weight loss and is important for overall reduction in cardiovascular risk; 60 to 90 minutes per week of walking can reduce CHD mortality by about 50%.²³⁶ The CVD benefits of slow walking appear to be comparable to those of walking more quickly, suggesting that the most

important predictor of benefit was walking time, not speed. Exercise programs appear beneficial at any age and are associated with overall reductions in CVD outcomes by about 50%.²³⁷ Although aerobic fitness may negate much of the cardiovascular risk associated with obesity,²³⁸ studies report that individuals with obesity have much lower levels of physical activity and poorer aerobic fitness than leaner individuals.²³⁹

Left Ventricular Hypertrophy

The common feature of all forms of LVH is increased left ventricular mass, although there are many different presentations and subtypes, each with different prognosis and therapy.²⁴⁰ LVH subclasses can be characterized generally by the relative wall thickness, the presence or absence of reduced contractility, and the end-diastolic chamber size. LVH can occur in endurance athletes with normal or supranormal systolic function, large end-diastolic volumes, and elongation of myofibrils (eccentric hypertrophy). LVH due to hypertension is usually characterized by concentric hypertrophy with circumferential hypertrophy of myofibrils, normal or increased contractility, increased relative wall thickness, normal or low end-diastolic volumes, and at times impaired relaxation (diastolic dysfunction). In population-based samples, 30% to 50% of individuals with stage 1 and 2 hypertension have impaired LV relaxation, and in more severe forms of hypertension, about two-thirds have abnormal LV relaxation. In untreated or poorly treated individuals, LVH becomes a major risk factor for dilated cardiomyopathy and HF.²⁴¹

Detection and Risk

Echocardiography is much more sensitive than electrocardiography (ECG) for detection of LVH, although ECG-LVH is a highly specific indicator for the condition. Individuals with LVH are more than twice as likely to suffer premature cardiovascular events or death. Current ECG algorithms defining LVH produce a high false-positive rate in African Americans and overestimate the prevalence of LVH in this population.^{242,243} The attributable risk of LVH for all-cause mortality is greater than that of single or multivessel coronary artery disease or low EF.

Therapy

Several studies suggest that LVH regression is associated with a lower overall CVD risk. Weight loss, salt restriction, and BP lowering with most antihypertensive agents produce LVH regression. Selection of individual drugs appears to be less important, but certain trends have emerged. Fifty studies of LVH regression conducted before 1996 were subjected to meta-analysis.²⁴⁴ In these studies, predictors of LV mass reduction during treatment were higher pretreatment LV mass, greater fall in SBP or DBP, and longer duration of treatment. The most consistent reduction in LV mass was achieved with ACEIs, the least reduction occurred with BBs, and intermediate benefits occurred for diuretics and calcium antagonists. However, in both the Treatment of Mild Hypertension Study and the VA Cooperative Monotherapy trial, diuretic therapy achieved the greatest benefit in LV mass reduction.^{245,246} The LIFE study found that LVH, defined by

electrocardiography, was reduced significantly more by a losartan-based than atenolol-based regimen despite equivalent BP lowering.¹⁰²

Peripheral Arterial Disease

Major risk factors for peripheral arterial disease (PAD) are hypertension, diabetes, and smoking. Symptomatic peripheral arterial disease is associated with a greatly increased risk of death from CVD, in part because diffuse atherosclerosis, CAD, and renovascular disease frequently coexist in these patients. Therefore, more intensive screening for these related cardiovascular disorders is appropriate in persons with PAD. Renovascular hypertension should be strongly considered in this population if BP is uncontrolled and if ACEI or ARB treatment is being considered.

Antihypertensive drug treatment is ineffective in relieving the symptoms of PAD, and vasodilator agents such as ACEIs, CCBs, α -adrenergic blockers, and direct vasodilators do not improve walking distance or symptoms of claudication.²⁴⁷⁻²⁴⁹ This lack of efficacy may be due to inability of maximally dilated diseased vessels to dilate further during exercise, redistribution of flow caused by the creation of a "steal" phenomenon where blood flow increases in nondiseased vascular beds at the expense of diseased beds, or alteration of pressure-flow relationships distal to the occluded areas by BP reduction. BBs may cause peripheral vasoconstriction and have the potential to increase the frequency of intermittent claudication in individuals with PAD. However, recent studies have shown that BBs have little effect on walking distance or calf blood flow in patients with intermittent claudication.²⁵⁰ Thus, BBs can be used in PAD patients, especially if needed for treatment of CAD or HF.

No selective outcome benefit has been demonstrated for any individual class of antihypertensive medication in patients with PAD.¹⁰⁹ Therefore, antihypertensive drug choices should be made on the basis of the presence or absence of compelling indications. If Raynaud's phenomenon is present, CCBs can be used.²⁵¹ LDL lowering will reduce the risk for CVD events in people with PAD.²⁵²

Therapy

Treating hypertension in PAD patients reduces the risk of MI, stroke, HF, and death.²⁵³ A structured walking program has been shown to increase the pain-free and maximum walking distances in patients with intermittent claudication.²⁵⁴ Smoking cessation may be the most important factor in whether PAD progresses. Patients should be encouraged and assisted to stop smoking. Lipid abnormalities should be controlled using lifestyle modification or drugs as appropriate. Coexisting glucose intolerance or insulin resistance calls for increased exercise and weight reduction, and aggressive management of diabetes is indicated. Table 17 outlines medical therapies of PAD.

Hypertension in Older People

The number of Americans aged 65 years or older has increased from 24.2 million to 32.6 million from 1980 to 2000 and is expected to continue to rise.²⁵⁵ SBP increases almost linearly with age in industrialized societies (Figure 12), as does the overall prevalence of hypertension and the

TABLE 17. Medical Therapy of Peripheral Arterial Disease

Stop smoking
Achieve ideal body weight
Structure exercise program
Achieve goal blood pressure
Control lipids (goal LDL <100 mg/dL)
Prevent or control diabetes
Administer antiplatelet therapy (aspirin, clopidogrel, or both)
Consider use of Cilostazol for symptoms of claudication if exercise alone is ineffective

proportion of hypertensives with isolated SBP elevation (ISH) (Figure 17).¹⁹² In contrast, DBP increases in parallel with SBP until about age 55, after which it declines as a manifestation of age-related increases in central arterial stiffness. By age 60, about two-thirds of those with hypertension have ISH, and by age 75, almost all hypertensives have systolic hypertension and about three-fourths of hypertensives have ISH.

Individuals over age 60 represent the most rapidly growing segment of the US population, and even in those who remain normotensive between 55 and 65 years old, there remains a lifetime risk of developing hypertension that exceeds 90%.¹⁶ At the same time, there is a 3- to 4-fold increase in CVD risk in older compared with younger individuals. These facts prompted the NHBPEP to issue a Clinical Advisory statement in May, 2000, stating that SBP should be the primary target for the diagnosis and management of older people with hypertension.²⁵⁶ Currently, BP control rates (systolic <140 mm Hg and diastolic <90 mm Hg) are only about 20% in older hypertensives, largely due to poor control of SBP.²⁵⁷

Treatment Benefits

In the SHEP study involving hypertensives over 60 years old with pretreatment SBP >160 and DBP <90 mm Hg, individuals treated with chlorthalidone (with or without BB) had reductions in the primary end point of stroke (36%), as well

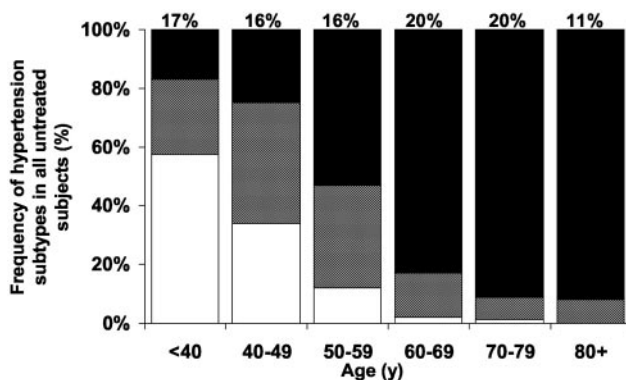


Figure 17. Frequency distribution of untreated hypertensive individuals by age and hypertension subtype. Frequency distribution of untreated hypertensive individuals by age and hypertension subtype. Numbers at the tops of bars represent the overall percentage distribution of untreated hypertension in that age group. ■, ISH (SBP ≥140 mm Hg and DBP <90 mm Hg); ▒, SDH (SBP ≥140 mm Hg and DBP ≥90 mm Hg); □, IDH (SBP <140 mm Hg and DBP ≥90 mm Hg). Source: Franklin SS et al. *Hypertension* 2001;37:869–874.

as HF events (54%), myocardial infarctions (27%), and overall CVD (32%)²⁴ as compared with the placebo group. Using a similar design and sample size, the Syst-EUR study compared a regimen based on nitrendipine to placebo and found a significant reduction in stroke (41%) as well as overall CVD events (31%).¹¹³ A meta-analysis of 8 placebo-controlled trials in 15 693 elderly patients followed for 4 years found that active antihypertensive treatment reduced coronary events (23%), strokes (30%), cardiovascular deaths (18%), and total deaths (13%), with the benefit particularly great in those older than 70 years.²⁵⁸ Benefits of therapy have been demonstrated even in individuals over 80 years old.^{116,259} Analyses of treatment trials in the elderly by the Hypertension Trialists group have suggested that the choice of initial agent is less important than the degree of BP reduction achieved.⁹⁰

Accurate and representative BP measurement can pose special problems in some older individuals (see the section Accurate Blood Pressure Measurement in the Office). BP is more variable in the older patient, often due to stiff large arteries and age-related decreases in baroreflex buffering. Exaggerated BP drops may occur in the elderly during postural change (see the section Orthostatic Hypotension), after meals,²⁶⁰ and after exercise.⁹⁷ Pseudohypertension, where cuff BP overestimates the actual intra-arterial pressure due to relative inability of the BP cuff to compress a thickened, stiff, or calcified brachial artery, is an uncommon condition in older persons. But this condition should be strongly considered if usual treatment does not reduce BP, especially in those patients who complain of symptoms consistent with postural hypotension.²⁶¹ A relatively small percentage of elderly patients have a reversible form of hypertension, most commonly due to renovascular disease, which is seen most often in smokers.²⁶²

SBP provides more appropriate classification and risk stratification than DBP in the elderly. In the Framingham Heart Study, SBP alone correctly classified the BP stage in 94% of adults over 60 years old, while DBP alone correctly classified 66%.¹⁹² Pulse pressure (PP) (SBP – DBP) is only marginally stronger than SBP for risk stratification in individuals over age 60, but under age 60, PP is not useful as a CVD risk predictor.¹⁸ PP generally decreases as a result of SBP lowering,^{24,263} but no prospective clinical trial has used PP as the primary clinical end point. Thus, on balance, SBP is superior to PP and DBP as a way to stratify patients and as a target for treatment in older persons.

Although there is no randomized prospective clinical trial that has conclusively proven the benefits of treatment in individuals with Stage 1 systolic hypertension (140 to 159 mm Hg), hypertension therapy should not be withheld in these patients, and therapy should not be withheld on the basis of age. There is no definitive evidence of an increase in risk of aggressive treatment (a J-curve) unless DBP is lowered to <55 or 60 mm Hg by treatment.¹⁵⁵

Treatment

Weight loss and reduced sodium intake are particularly beneficial in older people. In Trial of nonpharmacologic Interventions in the Elderly (TONE), reducing sodium to

80 mmol (2 g) per day reduced BP over 30 months, and about 40% of those on the low-salt diet were able to discontinue their antihypertensive medications.²⁶⁴ When weight loss was combined with salt reduction, an additional BP decrease was seen. Older persons should also be encouraged to avoid excessive alcohol intake and remain as physically active as feasible.

Use of specific drug classes in older people is largely similar to that recommended in the general algorithm and for individual compelling indications. Combination therapy with two or more drugs is generally needed to achieve optimal BP control. In routine practice, if the systolic goal is achieved, the diastolic goal will almost always be reached as well.

A significant number of elderly individuals have widely variable BP with exaggerated high and low extremes. Such individuals deserve consideration for a slow titration approach, as do individuals with a history of medication side effects and those with orthostatic hypotension. Unfortunately, the misperception that many elderly have "brittle hypertension" has contributed to widespread inadequacy of drug titration and to poor BP control.

Orthostatic Hypotension

BP measurements are typically recorded in the sitting position. This practice, while convenient for the practitioner, limits the ability to diagnose orthostatic hypotension (OH). Normally, standing is accompanied by a small increase in DBP and a small decrease in SBP when compared with supine values. OH is present when there is a supine-to-standing BP decrease >20 mm Hg systolic or >10 mm Hg diastolic. There is more OH in diabetics. OH occurred in about 7% of men over 70 years old in the Honolulu Heart Study, was highly age-dependent, and carried with it a 64% increase in age-adjusted mortality compared with a control population.²⁶⁵ There is a strong correlation between the severity of OH and premature death as well as increased numbers of falls and fractures.^{265–267} The causes of OH include severe volume depletion, baroreflex dysfunction, autonomic insufficiency, and certain venodilator antihypertensive drugs, especially α -blockers and α - β -blockers. Diuretics and nitrates may further aggravate OH.

In treating older hypertensive patients, clinicians should be alert to potential OH symptoms such as postural unsteadiness, dizziness, or even fainting. Lying and standing BPs should be obtained periodically in all hypertensive individuals over 50 years old. OH is a common barrier to intensive BP control that should be clearly documented; if present, drug therapy should be adjusted accordingly and appropriate warnings given to patients.

Resistant Hypertension

Resistant hypertension is defined as the failure to achieve goal BP in patients who are adhering to full doses of an appropriate 3-drug regimen that includes a diuretic. Several causes of resistant hypertension may be present.

Improper BP measurement can lead to overestimation of intra-arterial pressure. (See section on BP measurement.) Falsely high readings may also be observed in those whose brachial arteries are heavily calcified or arteriosclerotic and cannot be fully compressed.²⁶⁸ Clinic or white-coat hyperten-

sion may also lead to transient high readings that are not experienced throughout the day. This can be documented by home BP or ambulatory BP readings.

Inadequate diuretic therapy is common in resistant hypertension. Volume overload, once recognized, can be managed by use of appropriate diuretics. While a thiazide-type diuretic is recommended for the majority of hypertensive patients, a loop diuretic is often required for patients who have a decreased GFR or HF.

Failure to receive adequate medications can be the result of reluctance on the part of the patient or practitioner to use effective doses of medications. Causes and approaches to nonadherence are discussed in subsequent sections of this review.

Drug interactions that induce resistance may be difficult to detect unless the patient is asked open-ended questions regarding what they take when experiencing pain and what food supplements, health food preparations, and over-the-counter and Internet-purchased medications and supplements they use. Nonsteroidal anti-inflammatory drugs and pressor agents in cold remedies, nasal vasodilators, and some non-traditional remedies may counter the antihypertensive effects of prescribed medications.

If resistant hypertension persists after remediable causes are identified and corrected, then a concerted search for a cause of secondary hypertension should be conducted (Table 7). If resistance still persists, consultation with a hypertension specialist is a logical next step.

Specific causes of resistant hypertension are listed in Table 18. They usually can be identified by appropriate evaluation, and, once identified, can almost always be treated effectively. The prevalence of truly resistant hypertension is small.

Cognitive Function and Dementia

Dementia and cognitive impairment occur more commonly in people with hypertension. Reduced progression of cognitive impairment may occur with effective antihypertensive therapy.^{269,270} Narrowing and sclerosis of small penetrating arteries in the subcortical regions of the brain are common findings on autopsy in chronic hypertension.^{271–274} These changes are believed to contribute to hypoperfusion, loss of autoregulation, compromise of the blood-brain barrier, and ultimately to subcortical white matter demyelination, microinfarction, and cognitive decline. MRI studies in persons with chronic hypertension have revealed greater numbers of subcortical white matter lesions and microinfarcts, astrogliosis, ventricular enlargement, and extracellular fluid accumulation than in age-matched controls.^{275–285}

Mild cognitive impairment (MCI) is a diagnostic category that represents a transitional state between normal aging and mild dementia in which patients exhibit signs of poor recent memory but can still perform daily tasks such as managing finances, driving, shopping, and preparing meals.²⁸⁶ Hypertension and hypercholesterolemia are risk factors for MCI and for other signs of cognitive decline, such as impaired attention, reaction time, verbal fluency, or executive function.^{275,276,278,287–289}

TABLE 18. Causes of Resistant Hypertension

Improper BP measurement
Volume overload
Excess sodium intake
Volume retention from kidney disease
Inadequate diuretic therapy
Drug-induced or other causes
Nonadherence
Inadequate doses
Inappropriate combinations
Nonsteroidal anti-inflammatory drugs; cyclooxygenase 2 inhibitors
Cocaine, amphetamines, other illicit drugs
Sympathomimetics (decongestants, anorectics)
Oral contraceptive hormones
Adrenal steroid hormones
Cyclosporine and tacrolimus
Erythropoietin
Licorice (including some chewing tobacco)
Selected over-the-counter dietary supplements and medicines (eg, ephedra, ma haung, bitter orange)
Associated conditions
Obesity
Excess alcohol intake
Identifiable causes of hypertension (See Table 7.)

Effective antihypertensive therapy strongly reduces the risk of developing significant white matter changes on MRI.²⁹⁰ However, existing white matter changes, once established, do not appear to be reversible.^{291,292} The optimal SBP/DBP to prevent cognitive decline in older individuals is thought by some to be in the SBP 135 to 150 mm Hg and DBP 70 to 79 mm Hg range.^{287,288} In the SystEUR trial, CCB therapy was superior to placebo in slowing the decline in cognitive function,²⁹³ but no comparative data are available regarding whether certain classes of antihypertensive drugs are superior to others in preventing cognitive decline.

Hypertension in Women

Nonpregnant Women

Sexual Dimorphism of BP and Hypertension Prevalence in Women. There is a sexual dimorphism in BP, such that women have lower SBP levels than men during early adulthood, while the opposite is true after the sixth decade of life. DBP tends to be just marginally lower in women than men regardless of age.²⁹⁴ Similarly, in early adulthood, hypertension is less common among women than men. However, after the fifth decade of life, the incidence of hypertension increases more rapidly in women than men, and the prevalence of hypertension in women is equal to or exceeds that in men during the sixth decade of life. The highest prevalence rates of hypertension are observed in elderly black women, with hypertension occurring in more than 75% of women older than 75 years.²⁹⁵

Awareness, Treatment, and Control of High BP in Women. Women are more likely than men to know that they have hypertension, to have it treated, and to have it controlled.¹ In NHANES III, approximately 75% of hypertensive black and white women were aware of their high BP in contrast to just 65% of hypertensive men in these ethnic groups. Overall, 61% of hypertensive women, but only 44% of men, were being treated with antihypertensive medications. The higher treatment rates in women have been attributed to increased numbers of physician contacts.

Menopause and Blood Pressure. The effect of menopause on BP is controversial. Longitudinal studies have not documented a rise in BP with menopause, while cross-sectional studies have found significantly higher SBP and DBP in postmenopausal versus premenopausal women.²⁹⁴ In NHANES III, the rate of rise in SBP tended to be steeper in postmenopausal compared with premenopausal women until the sixth decade, when the rate of increase tended to slow. Staessen et al²⁹⁶ reported that even after adjustment for age and BMI, postmenopausal women are more than twice as likely to have hypertension as premenopausal women. In a prospective study of conventional and ambulatory BP levels, postmenopausal women had higher SBP (4 to 5 mm Hg) than pre- and perimenopausal controls.²⁹⁷ The increase in SBP per decade was 5 mm Hg greater in the peri- and postmenopausal women than in the premenopausal group. Thus, there is evidence that at least part of the rise in BP (particularly SBP) seen later in life in women is due to menopause. A menopause-related increase in BP has been attributed to a variety of factors, including estrogen withdrawal, overproduction of pituitary hormones, weight gain, or a combination of these and other yet undefined neurohumoral influences.²⁹⁸

Postmenopausal Hormone Therapy and BP. Results of studies evaluating the effects of hormone replacement therapy (HRT) on BP have been inconsistent. The Women's Health Initiative (WHI), the largest longitudinal study to address this question, found an average 1 mm Hg increase in SBP over 5.6 years of follow-up among 8506 postmenopausal women randomized to conjugated equine estrogen and medroxyprogesterone acetate as compared with a placebo group.²⁹⁹ There was no difference in DBP between the hormone treatment groups. Further, in the WHI cross-sectional analysis of almost 100 000 women aged 50 to 79 years, current hormone use was associated with a 25% greater likelihood of having hypertension compared with past use or no prior use.³⁰⁰

Smaller observational and interventional studies have found different results. In the Baltimore Longitudinal Study on Aging (BLSA), women receiving HRT had a significantly smaller increase in SBP over time than nonusers, but DBP was not affected. The Postmenopausal Estrogen/Progestin Intervention trial showed no effect of HRT on SBP or DBP.³⁰¹ In small studies that have used 24-hour ambulatory monitoring to evaluate the effects of HRT on BP, while overall results are inconsistent, several of the studies suggest that HRT improves or restores the normal nighttime reduction ("dipping") in BP that may be diminished in postmenopausal women. Such an effect would tend to reduce total BP load and thereby reduce target organ damage.²⁹⁸

Overall, HRT-related change in BP is likely to be modest and should not preclude hormone use in normotensive or hypertensive women. All hypertensive women treated with HRT should have their BP monitored closely at first and then at 6-month intervals.

TABLE 19. Classification of Hypertension in Pregnancy

Chronic hypertension	BP \geq 140 mm Hg systolic or 90 mm Hg diastolic prior to pregnancy or before 20 weeks gestation Persists >12 weeks postpartum
Preeclampsia	BP \geq 140 mm Hg systolic or 90 mm Hg diastolic with proteinuria (>300 mg/24 h) after 20 weeks gestation Can progress to eclampsia (seizures) More common in nulliparous women, multiple gestation, women with hypertension for \geq 4 years, family history of preeclampsia, hypertension in previous pregnancy, renal disease
Chronic hypertension with superimposed preeclampsia	New onset proteinuria after 20 weeks in a woman with hypertension In a woman with hypertension and proteinuria prior to 20 weeks gestation: Sudden 2- to 3-fold increase in proteinuria Sudden increase in BP Thrombocytopenia Elevated AST or ALT
Gestational hypertension	Hypertension without proteinuria occurring after 20 weeks gestation Temporary diagnosis May represent preproteinuric phase of preeclampsia or recurrence of chronic hypertension abated in midpregnancy May evolve to preeclampsia If severe, may result in higher rates of premature delivery and growth retardation than mild preeclampsia
Transient hypertension	Retrospective diagnosis BP normal by 12 weeks postpartum May recur in subsequent pregnancies Predictive of future primary hypertension

ALT indicates alanine aminotransferase; AST, aspartate aminotransaminase; BP, blood pressure.

Oral Contraceptives and BP. Many women taking oral contraceptives experience a small but detectable increase in BP; a small percentage experience the onset of frank hypertension. This is true even with modern preparations that contain only 30 μ g estrogen. The Nurses' Health Study found that current users of oral contraceptives had a significantly increased (relative risk [RR]=1.8; 95% confidence interval [CI]=1.5 to 2.3) risk of hypertension compared with never users.³⁰² Absolute risk was small: only 41.5 cases of hypertension per 10 000 person-years could be attributed to oral contraceptive use. Controlled prospective studies have demonstrated a return of BP to pretreatment levels within 3 months of discontinuing oral contraceptives, indicating that their BP effect is readily reversible.

Oral contraceptives occasionally may precipitate accelerated or malignant hypertension. Family history of hypertension, including preexisting pregnancy-induced hypertension, occult renal disease, obesity, middle age (>35 years), and duration of oral contraceptive use increase susceptibility to hypertension. Contraceptive-induced hypertension appears to be related to the progestogenic, not the estrogenic, potency of the preparation.

Regular monitoring of BP throughout contraceptive therapy is recommended, and it has been suggested that contraceptive prescriptions be limited to 6 months to ensure at least semiannual reevaluations. Withdrawal of the offending contraceptive agent is generally desirable in cases of contraceptive-induced hypertension, but such therapy may have to be continued in some women (eg, if other contraceptive methods are not suitable) and combined with antihypertensive therapy.

Outcomes of Antihypertensive Trials in Women. Relative benefits of antihypertensive therapy do not appear to differ between the sexes.³⁰³ Absolute risk reduction for stroke was

also similar in men and women, but for coronary events, it was greater in men. Similarly, a placebo-controlled trial of CCB treatment showed treatment benefits for both sexes.^{113,304} More recent outcome trials comparing ACEIs, ARBs, or CCBs with diuretics and BBs in older, high-risk patients have generally shown similar benefits for women and men.^{101,102,109} The current evidence indicates that the sex of the patient should not play a role in decisions about whether or not to treat high BP.

Choice of Antihypertensive Drugs for Women. While women generally respond to antihypertensive drugs similarly to men, some special considerations may dictate treatment choices for women. ACEIs and ARBs are contraindicated for women who are or intend to become pregnant because of the risk of fetal developmental abnormalities. Diuretics are particularly useful in elderly individuals because of a decreased risk of hip fracture. Some antihypertensive drugs have gender-specific adverse effect profiles. For example, in the TOMHS study, women reported twice as many adverse effects as men.³⁰⁵ Women are more likely to develop diuretic-induced hyponatremia, and men more likely to develop gout. Hypokalemia is more common in women taking a diuretic. ACEI-induced cough is twice as common in women as in men, and women are more likely to complain of CCB-related peripheral edema and minoxidil-induced hirsutism.

Pregnant Women

Hypertensive disorders in pregnancy are a major cause of maternal, fetal, and neonatal morbidity and mortality. Hypertension in pregnancy is classified into 1 of 5 categories (Table 19), and it is critical to differentiate preeclampsia, a pregnancy-specific syndrome of exaggerated vasoconstriction and reduced organ perfusion, from pre-existing chronic hypertension.^{7,306}

TABLE 20. Treatment of Chronic Hypertension in Pregnancy

Agent	Comments
Methyldopa	Preferred on the basis of long-term follow-up studies supporting safety
BBs	Reports of intrauterine growth retardation (atenolol) Generally safe
Labetalol	Increasingly preferred to methyldopa because of reduced side effects
Clonidine	Limited data
Calcium antagonists	Limited data No increase in major teratogenicity with exposure
Diuretics	Not first-line agents Probably safe
ACEIs, angiotensin II receptor antagonists	Contraindicated Reported fetal toxicity and death

ACEIs indicate angiotensin-converting enzyme inhibitor; BBs, beta blockers.

Prepregnancy Assessment. Women should be evaluated prior to conception to define their BP status, and, if hypertensive, to assess its severity, possible secondary causes, and presence of target organ damage and to plan treatment strategies. Many hypertensive women who plan to become pregnant should be screened for pheochromocytoma because of the high morbidity and mortality of this condition if not diagnosed antepartum. In hypertensive women planning to become pregnant, it may be prudent prior to conception to change to antihypertensive medications known to be safe during pregnancy, such as methyldopa or BBs. ACEIs and ARBs should be discontinued prior to attempts at conception or as soon as pregnancy is confirmed. Those with progressive renal diseases should be encouraged to complete their childbearing while their renal function is relatively well preserved. Mild renal disease (serum creatinine <1.4 mg/dL) has a minimal effect on fetal survival, and the underlying renal disease does not generally worsen during pregnancy. However, moderate or severe renal insufficiency in pregnancy may accelerate both hypertension and the underlying disease and markedly reduce fetal survival.

Treatment of Chronic Hypertension During Pregnancy. Women with Stage 1 hypertension are at low risk for cardiovascular complications during pregnancy and are candidates for lifestyle modification therapy only, as there is no evidence that pharmacological treatment improves neonatal outcomes. Further, BP usually falls during the first half of pregnancy; therefore, hypertension may be easier to control with reduced or no medications. With lifestyle modification, aerobic exercise should be restricted on the basis of theoretical concerns that inadequate placental blood flow may increase the risk of preeclampsia, and weight reduction should not be attempted, even in obese pregnant women. Although the data on pregnant women are sparse, many experts recommend restriction of sodium intake to the same 2.4 g sodium intake recommended for those with primary hypertension.⁷ Use of alcohol and tobacco must be strongly discouraged. Use of antihypertensive drugs in pregnant women with chronic hypertension varies greatly among centers. Some clinicians prefer to stop antihyperten-

sive medications while maintaining close observation, including use of home BP monitoring. This approach reflects concern about the safety of antihypertensive drug treatment in pregnancy. A meta-analysis of 45 randomized controlled studies of treatment with several classes of antihypertensive drugs in Stage 1 and 2 hypertension in pregnancy showed a direct linear relationship between treatment-induced fall in mean arterial pressure and the proportion of small-for-gestational-age infants.³⁰⁷ This relationship was independent of type of hypertension, type of antihypertensive agent, and duration of therapy.

However, for pregnant women with target organ damage or a prior requirement for multiple antihypertensive agents for BP control, antihypertensive medication should be continued as needed to control BP. In all cases, treatment should be reinstated once BP reaches 150 to 160 mm Hg systolic or 100 to 110 mm Hg diastolic, in order to prevent increases in BP to very high levels during pregnancy. Aggressive treatment of severe chronic hypertension in the first trimester is critical, since fetal loss rates of 50% and significant maternal mortality have been reported in these patients.³⁰⁸ Most of the poor outcomes are related to superimposed preeclampsia (Table 19). Further, women with chronic hypertension are also at higher risk for adverse neonatal outcomes if proteinuria is present early in pregnancy. Fetal loss and acceleration of maternal renal disease increase at serum creatinine levels >1.4 mg/dL at conception.

Antihypertensive Drug Selection. The primary goal of treating chronic hypertension in pregnancy is to reduce maternal risk, but the choice of antihypertensive agent(s) is largely driven by the safety of the fetus. Methyldopa is preferred by many as first-line therapy, based on reports of stable uteroplacental blood flow and fetal hemodynamics and the absence of long-term (7.5-year follow-up) adverse effects on development of children exposed to methyldopa in utero.^{309,310} Other treatment options are summarized in Table 20.

Preeclampsia. Preeclampsia is more common in women with chronic hypertension, with an incidence of approximately 25%. Risk factors for superimposed preeclampsia include

TABLE 21. Treatment of Acute Severe Hypertension in Preeclampsia

Hydralazine	5 mg IV bolus, then 10 mg every 20 to 30 minutes to a maximum of 25 mg, repeat in several hours as necessary
Labetalol (second-line)	20 mg IV bolus, then 40 mg 10 minutes later, 80 mg every 10 minutes for 2 additional doses to a maximum of 220 mg
Nifedipine (controversial)	10 mg PO, repeat every 20 minutes to a maximum of 30 mg Caution when using nifedipine with magnesium sulfate, can see precipitous BP drop Short-acting nifedipine is not approved by US Food and Drug Administration for managing hypertension
Sodium nitroprusside (rarely when others fail)	0.25 μ g/kg/min to a maximum of 5 μ g/kg/min Fetal cyanide poisoning may occur if used for more than 4 hours

renal insufficiency, a history of hypertension for 4 years or longer, and hypertension in a previous pregnancy. Prevention of preeclampsia relies on identification of high-risk women and close clinical and laboratory monitoring aimed at its early recognition, and institution of intensive monitoring or delivery when indicated. Treatment of preeclampsia includes hospitalization for bed rest, control of BP, seizure prophylaxis in the presence of signs of impending eclampsia, and timely delivery. Importantly, many women with preeclampsia have previously been normotensive, so acute BP elevations even to modest levels (ie, 150/100 mm Hg) may cause significant symptomatology and require treatment. Treatment does not alter the underlying pathophysiology of the disease, but it may slow its progression and provide time for fetal maturation. Preeclampsia rarely remits spontaneously and in most cases worsens with time.

While delivery may be appropriate therapy for the mother, it may compromise a fetus of less than 32 weeks gestation. Regardless of gestational age, delivery should be strongly considered when there are signs of fetal distress or intrauterine growth retardation or signs of maternal problems, including severe hypertension, hemolysis, elevated liver enzymes, low platelet count, deteriorating renal function, visual disturbance, headache, or epigastric pain. Vaginal delivery is preferable to cesarean delivery to avoid the added stress of surgery.

Antihypertensive Drug Therapy. Antihypertensive therapy should be prescribed only for maternal safety; it does not improve perinatal outcomes and may adversely affect uteroplacental blood flow. Selection of antihypertensive agents and route of administration depends on anticipated timing of delivery. If delivery is likely more than 48 hours off, oral methyldopa is preferred because of its safety record. Oral labetalol is an alternative, and other BBs and calcium antagonists are also acceptable on the basis of limited data (Table 20). If delivery is imminent, parenteral agents are practical and effective (Table 21). Antihypertensives are administered before induction of labor for persistent DBPs of 105 to 110 mm Hg or higher, aiming for levels of 95 to 105 mm Hg.

Treating Hypertension During Lactation. Hypertensive mothers can usually breast-feed safely. However, all antihypertensive drugs that have been studied are excreted into human breast milk. Therefore, in mothers with stage 1 hypertension who wish to breast-feed for a few months, it

might be prudent to withhold antihypertensive medication, with close monitoring of BP, and reinstitute antihypertensive therapy following discontinuation of nursing. No short-term adverse effects have been reported from exposure to methyldopa or hydralazine. Propranolol and labetalol are preferred if a BB is indicated. ACEIs and ARBs should be avoided on the basis of reports of adverse fetal and neonatal renal effects. Diuretics may reduce milk volume and thereby suppress lactation. Breast-fed infants of mothers taking antihypertensive agents should be closely monitored for potential adverse effects.

Recurrence of Hypertension. Hypertension recurs in a large proportion (20% to 50%) of subsequent pregnancies. Risk factors for recurrence include early onset of hypertension in the first pregnancy, a history of chronic hypertension, persistent hypertension beyond 5 weeks postpartum, and elevated BP early in pregnancy. Women with preeclampsia have a greater tendency to develop hypertension than those with normotensive pregnancies.

Hypertension in Children and Adolescents

In children and adolescents, hypertension is defined as elevated BP that persists on repeated measurement at the 95th percentile or greater for age, height, and gender (Table 22). As with adults, the fifth Korotkoff sound is used to define DBP.³¹¹

Clinicians should be alert to the possibility of identifiable causes of hypertension in younger children. Secondary forms of hypertension are more common in children and in individuals with severe hypertension (>20 mm Hg above the 95th percentile). Chronic hypertension is becoming increasingly common in adolescence and is generally associated with obesity, sedentary lifestyle, and a positive family history of hypertension and other CVDs. Like adults, children and adolescents with established hypertension develop target organ damage, including LVH. Appropriate assessment for LVH, including echocardiography, should be considered in children who have significant and persisting hypertension.

Lifestyle interventions should be recommended for all children with hypertension, with pharmacological therapy instituted for higher levels of BP or if insufficient response to lifestyle modifications occurs. Teenage children with BP below but near the 95th percentile should adopt healthy lifestyles similar to adults with prehypertension. Although the recommendations for drug choices are generally similar in

TABLE 22. 95th Percentile of Blood Pressure by Selected Ages, by the 50th and 75th Height Percentiles, and by Gender in Children and Adolescents

Age	Girls' SBP/DBP		Boys' SBP/DBP	
	50th Percentile for Height	75th Percentile for Height	50th Percentile for Height	75th Percentile for Height
1	104/58	105/59	102/57	104/58
6	111/73	112/73	114/74	115/75
12	123/80	124/81	123/81	125/82
17	129/84	130/85	136/87	138/88

Source: Adapted from Update on the 1987 Task Force Report on High Blood Pressure in Children and Adolescents: A working group report from the National High Blood Pressure Education Program. *Pediatrics*. 1996;98:649–658.

children and adults, dosages of antihypertensive medication for children should be smaller and adjusted very carefully. ACEIs and ARBs should not be used if the patient is pregnant. These agents should be used with extreme caution in sexually active teenage girls and only when careful counseling and effective pregnancy precautions are established.

The presence of uncomplicated hypertension should not be a reason to restrict children from participating in physical activities, particularly because exercise may lower BP. Use of anabolic steroid hormones for the purpose of bodybuilding should be strongly discouraged. Efforts should be made to identify other modifiable risk factors in children (eg, obesity, lack of physical activity, smoking), and vigorous interventions should be made when present. Detailed recommendations regarding hypertension in children and adolescents can be found in the 1996 *NHBPEP Working Group Report on Hypertension Control in Children and Adolescents*.³¹¹

Hypertensive Crises: Emergencies and Urgencies

Hypertensive emergencies are characterized by severe elevations in BP (>180/120 mm Hg) complicated by evidence of impending or progressive target organ dysfunction. They require immediate BP reduction (not necessarily to normal) to prevent or limit target organ damage.^{312,313} Examples include hypertensive encephalopathy, intracerebral hemorrhage, acute myocardial infarction, acute left ventricular failure with pulmonary edema, unstable angina pectoris, dissecting aortic aneurysm, or eclampsia. Hypertensive urgencies are those situations associated with severe elevations in BP without progressive target organ dysfunction. Examples include upper levels of stage II hypertension associated with severe headache, shortness of breath, epistaxis, or severe anxiety. The majority of these patients present as noncompliant or inadequately treated hypertensives, often with little or no evidence of target organ damage.

Early triage to establish the appropriate therapeutic strategies for these patients is critical to limiting morbidity and mortality.³¹⁴ Patients presenting with severe hypertension may represent as much as 25% of all patient visits to busy urban emergency rooms.³¹⁵

Patients with a hypertensive emergency should be admitted to an Intensive Care Unit for continuous monitoring of BP and parenteral administration of an appropriate agent (Table 23). The initial goal of therapy in hypertensive emergencies is

to reduce mean arterial BP by no more than 25% (within minutes to 1 hour), then, if stable, to 160/100 to 110 mm Hg within the next 2 to 6 hours. Excessive falls in pressure that may precipitate renal, cerebral, or coronary ischemia should be avoided. For this reason, short-acting nifedipine is no longer considered acceptable in the initial treatment of hypertensive emergencies or urgencies. If this level of BP is well tolerated and the patient is clinically stable, further gradual reductions toward a normal BP can be implemented in the next 24 to 48 hours. There are exceptions to the above recommendation—patients with an ischemic stroke in which there is no clear evidence from clinical trials to support the use of immediate antihypertensive treatment, patients with aortic dissection who should have their SBP lowered to <100 mm Hg if tolerated, and patients in whom BP is lowered to enable the use of thrombolytic agents (see the section on stroke).

Some patients with hypertensive urgencies may benefit from treatment with an oral, short-acting agent such as captopril, labetalol, or clonidine followed by several hours of observation. However, there is no evidence to suggest that failure to aggressively lower BP in the emergency room is associated with any increased short-term risk to the patient who presents with severe hypertension. Such a patient may also benefit from adjustment in their antihypertensive therapy, particularly the use of combination drugs, or reinstatement of medications if noncompliance is a problem. Most importantly, patients should not leave the emergency room without a confirmed follow-up visit within 1 to a few days.

Unfortunately, the term “urgency” has led to overly aggressive management of many patients with severe, uncomplicated hypertension. Aggressive dosing with intravenous drugs or even oral agents to rapidly lower BP is not without risk. Oral loading doses of antihypertensive agents can lead to cumulative effects causing hypotension, sometimes following discharge from the emergency room. Patients who continue to be noncompliant will often return to the emergency room within weeks.

Erectile Dysfunction and Hypertension

Erectile dysfunction (ED), defined as the inability to have and maintain an erection adequate for intercourse, becomes increasingly common in men over 50 years old and is even more common if they are hypertensive.³¹⁶ In a survey of over 3000 health professionals, the frequency of ED was 4% in

TABLE 23. Parenteral Drugs for Treatment of Hypertensive Emergencies*

Drug	Dose	Onset of Action	Duration of Action	Adverse Effects†	Special Indications
Vasodilators					
Sodium nitroprusside	0.25–10 $\mu\text{g}/\text{kg}/\text{min}$ as IV infusion‡	Immediate	1–2 min	Nausea, vomiting, muscle twitching, sweating, thiocyanate and cyanide intoxication	Most hypertensive emergencies; caution with high intracranial pressure or azotemia
Nicardipine hydrochloride	5–15 mg/h IV	5–10 min	15–30 min, may exceed 4 h	Tachycardia, headache, flushing, local phlebitis	Most hypertensive emergencies except acute heart failure; caution with coronary ischemia
Fenoldopam mesylate	0.1–0.3 $\mu\text{g}/\text{kg}$ per min IV infusion	<5 min	30 min	Tachycardia, headache, nausea, flushing	Most hypertensive emergencies; caution with glaucoma
Nitroglycerin	5–100 $\mu\text{g}/\text{min}$ as IV infusion§	2–5 min	5–10 min	Headache, vomiting, methemoglobinemia, tolerance with prolonged use	Coronary ischemia
Enalaprilat	1.25–5 mg every 6 h IV	15–30 min	6–12 h	Precipitous fall in pressure in high-renin states; variable response	Acute left ventricular failure; avoid in acute myocardial infarction
Hydralazine hydrochloride	10–20 mg IV	10–20 min IV	1–4 h IV	Tachycardia, flushing, headache, vomiting, aggravation of angina	Eclampsia
	10–40 mg IM	20–30 min IM	4–6 h IM		
Adrenergic inhibitors					
Labetalol hydrochloride	20–80 mg IV bolus every 10 min	5–10 min	3–6 h	Vomiting, scalp tingling, bronchoconstriction, dizziness, nausea, heart block, orthostatic hypotension	Most hypertensive emergencies except acute heart failure
Esmolol hydrochloride	0.5–2.0 mg/min IV infusion	1–2 min	10–30 min	Hypotension, nausea, asthma, first-degree heart block, HF	Aortic dissection, perioperative
	250–500 $\mu\text{g}/\text{kg}/\text{min}$ IV bolus, then 50–100 $\mu\text{g}/\text{kg}/\text{min}$ by infusion; may repeat bolus after 5 min or increase infusion to 300 $\mu\text{g}/\text{min}$				
Phentolamine	5–15 mg IV bolus	1–2 min	10–30 min	Tachycardia, flushing, headache	Catecholamine excess

*These doses may vary from those in the *Physicians' Desk Reference* (51st edition).

†Hypotension may occur with all agents.

‡Requires special delivery system.

men under age 50, 26% in those 50 to 59, and 40% in those 60 to 69.³¹⁶ The frequency was significantly higher if they were hypertensive, diabetic, obese, or smokers or were taking antidepressants or BBs.

Whereas hypertension per se may be associated with ED,³¹⁷ the use of various antihypertensive medications may increase the incidence, in part because BP lowering itself may cause reduction of perfusion of genital organs. Available data regarding individual effects of antihypertensive drug therapy are confounded by age, vascular disease, and hormonal status. In the TOMHS study involving antihypertensive drugs from five different classes (excluding ARBs), participants randomized to chlorthalidone reported a significantly higher incidence of erection problems at 24 months of the study than participants randomized to placebo. Incidence rates through 48 months were more similar among treatment groups than at 24 months, with nonsignificant differences between chlorthalidone and placebo groups.¹²³ In the VA Cooperative trial, no difference in incidence of sexual dysfunction was noted

between a CCB, ACEI, hydrochlorothiazide, or BB compared with placebo.¹⁰³ In other studies, centrally acting α -agonists have been associated with ED, while ACEIs, ARBs, and CCBs have not been observed to increase its incidence.^{317,318}

A lower risk of ED was reported among men who were physically active, not obese, and nonsmokers.³¹⁶ Therefore, lifestyle modifications should be encouraged to forestall ED. If ED appears after institution of antihypertensive drug therapy, the offending agent should be discontinued and treatment restarted with another agent. Sildenafil or other phosphodiesterase-5 inhibitors may be prescribed without a significant likelihood of adverse reactions in those with concomitant antihypertensive therapy so long as nitrates are avoided.³¹⁹

There are no definitive data on a relation between sexual dysfunction and hypertension in women. Regardless of gender, clinicians should be willing to discuss sexual dysfunction problems and offer counseling to improve the patient's quality of life.

Urinary Outflow Obstruction

Symptoms of urinary outflow obstruction or a known history of obstruction should be elicited as part of the hypertension workup. When a normal bladder is distended beyond approximately 300 mL, sympathetic nervous system stimulation may cause a substantial increase in BP. Patients with high spinal cord injuries in particular may exhibit large acute BP increases similar to individuals with autonomic dysfunction. BP control can be improved by keeping the bladder volume below 300 mL and by the use of sympatholytic drugs. Nonsurgical treatment of patients with urinary outflow obstruction includes the use of α_1 -blockers such as terazosin, doxazosin, or prazosin, which indirectly dilate prostatic and urinary sphincter smooth muscle and also lower BP.³²⁰

Patients Undergoing Surgery

Uncontrolled hypertension is associated with wider fluctuations of BP during induction of anesthesia and intubation and may increase the risk for perioperative ischemic events. BP levels of 180/110 mm Hg or greater should be controlled prior to surgery.³²¹ For elective surgery, effective BP control can be achieved over several days to weeks of outpatient treatment. In urgent situations, rapidly acting parenteral agents such as sodium nitroprusside, nicardipine, and labetalol can be utilized to attain effective control very rapidly.

Surgical candidates with controlled hypertension should maintain their medications until the time of surgery, and therapy should be reinstated as soon as possible postoperatively. Adequate potassium supplementation should be provided, if needed, to correct hypokalemia well in advance of surgery. Older patients may gain particular benefit from treatment with β_1 -selective BBs before and during the perioperative period.³²²

Sudden intraoperative hypertension is managed by many of the same parenteral antihypertensive agents that are utilized in the management of hypertensive emergencies (see the section on emergencies and urgencies).³²³ Intravenous infusions of sodium nitroprusside, nicardipine, and labetalol can be effective. Nitroglycerin is often an agent of choice in patients with coronary ischemia, while the very short-acting BB esmolol may be of benefit in managing intraoperative tachycardia.

Hypertension is very common in the early postoperative period, related to increased sympathetic tone and vascular resistance.³²⁴ Contributing factors include pain and increased intravascular volume, which may require parenteral dosing with a loop diuretic such as furosemide. If resumption of oral treatment must be interrupted postoperatively, periodic dosing with intravenous enalaprilat or transdermal clonidine hydrochloride may be useful.

Dental Issues in the Hypertensive Subjects

A concern in dental care is the use of epinephrine in local anesthetic solutions. Many dental providers do not use catecholamine-containing local anesthetic formulations for any patient with elevated BP, as they are concerned with an adverse cardiovascular response. A systematic review of this topic³²⁵ concluded that although adverse events may occur in uncontrolled hypertensive patients during dental procedures, the use of epinephrine had a minimal effect. BP should be

monitored closely in the dental office if general anesthesia is administered to hypertensives because of potential wide fluctuations in BP and the risk of hypotension in those receiving antihypertensive drugs. CCBs and other vasodilators may cause hypertrophy of the gums.

Obstructive Sleep Apnea

Obstructive sleep apnea (OSA) occurs in 2% to 4% of the adult population, and over 50% of individuals with OSA have hypertension.^{263,326–333} Obesity is so common in OSA that the index of suspicion for OSA should be high in any hypertensive patient whose BMI is above 27 kg/m².³³¹ These individuals should be questioned thoroughly for symptoms of OSA, including snoring, witnessed apnea, irregular breathing during sleep, restless sleeping, and chronic morning fatigue. Frequently it is the sleep partner who provides the most reliable history, especially regarding snoring, because the affected individual may deny or be unaware of the problem. If the diagnosis is suspected clinically, confirmation by a formal sleep study is indicated. The impact of sleep apnea on CVD is probably related in large part to its association with elevated BP. However, OSA may act through a number of mechanisms to elicit myocardial and vascular damage, including increase in catecholamine release,^{333,334} activation of inflammatory mechanisms,³³⁵ insulin resistance,^{336,337} and endothelial dysfunction.³³⁸ Other cardiovascular conditions associated with OSA include arrhythmias, HF, myocardial infarction, and stroke.^{331,332,339–344}

Previous debate about whether OSA is an etiologic factor in hypertension has focused largely around the strong association of OSA with obesity. While obesity is known to contribute in large part to OSA,^{345–348} patients with OSA may also be at increased risk for weight gain,³⁴⁹ and treatment of OSA may reduce visceral fat.³⁵⁰ It now appears that the potential causal association between OSA and hypertension involves both the obesity-hypertension link and an independent role of OSA in chronic BP elevation. Episodes of apnea with repeated oxygen desaturation in OSA have been shown to stimulate strong sympathetic nervous system discharges that directly elevate BP.^{333,334} Poorer quality of sleep and shorter sleep periods may play a reinforcing role in the fatigue and daytime somnolence. Sleep deprivation alone may raise BP³⁵¹ and impair glucose tolerance.³⁵² There is also a direct relationship between the severity of sleep apnea and the level of BP. Finally, sustained and effective treatment of OSA with continuous positive airway pressure (CPAP) has been reported to lower nighttime and daytime BP in hypertensives with OSA.^{353–355}

In addition to weight loss, improvements in the quality of sleep in OSA patients can occur as a result of a variety of positioning measures during sleep, particularly sleeping on one's side. Treatment with CPAP can be useful in overall BP lowering and may also improve cardiac ischemia^{356,357} and HF symptoms.^{331,332} The role of oral prostheses and surgical approaches remains to be fully defined.³⁵⁴ No specific class of antihypertensive drugs has yet been demonstrated to be superior for BP lowering in OSA patients.³⁵⁴

Hypertension and the Eye

Hypertension can effect the retina, choroid, and optic nerve of the eye, particularly with stage 2 hypertension. These changes

can be appreciated with inspection of the retinal vessels by direct ophthalmoscopy, photography, or angiography.

Hypertensive retinopathy is most commonly manifested by generalized or focal narrowing of retinal arterioles. In acute or advanced hypertension, the retinal vasculature may be injured sufficiently to cause occlusion or leakage. These changes may be manifested as nerve fiber layer infarcts (soft exudates or cotton-wool patches), extravascular edema (hard exudates), intraretinal hemorrhages, and retinal arterial macroaneurysms.

Hypertensive choroidopathy is most frequently seen in young patients with acute hypertension, including cases of eclampsia or pheochromocytoma. Findings include Elschnig spots (nonperfused areas of the choriocapillaris) and Siegrist streaks (linear hyperpigmentation over choroidal arteries).

Hypertensive optic neuropathy occurring with severe hypertension may present with flame hemorrhages, optic disc edema, venous congestion, and macular exudates.³⁵⁸⁻³⁶⁰

Renal Transplantation

Hypertension is a relatively common occurrence in patients receiving organ transplants; in those receiving kidney allografts, the prevalence of hypertension probably exceeds 65%.³⁶¹ Nocturnal hypertension, a reversal of diurnal BP rhythm, may be present in these individuals who may need ABPM to evaluate overall BP control. Hypertension is less common in other forms of transplantation. The mechanisms of hypertension in transplant patients are multifactorial, but vasoconstriction and long-term vascular structural changes caused by chronic immunosuppressive drugs that are calcineurin inhibitors (cyclosporine and tacrolimus) and corticosteroids are among the most important.³⁶² Impaired renal function is another exacerbating factor; despite successful renal transplantation, most patients have enough impairment in renal function to cause relative salt and water retention. Transplant renal artery stenosis may also be a factor.

Observational studies suggest that hypertension correlates with deterioration in graft function. Large-scale, controlled clinical trials on the effects of BP control on GFR decline or on CVD incidence are lacking in this population. The high risk of graft occlusion and cardiovascular events has suggested that BP should be lowered to 130/80 mm Hg or less. Because of the absence of compelling data, no particular class of antihypertensives can be considered to be superior to any other. The difficulty of lowering BP in this group makes combination drugs necessary in almost all patients. As with other renal diseases, serum creatinine and potassium should be monitored 1 to 2 weeks following initiation or escalation in therapy with ACEIs or ARBs. A greater than 1 mg/dL increase in serum creatinine should raise the question of renal artery stenosis.

Patients with Renovascular Disease

Hemodynamically significant renal artery stenosis may be associated with all stages of hypertension, but it is more commonly recognized in patients with stage 2 or resistant hypertension, since these are the individuals in whom special evaluation for the problem is carried out. If present bilaterally,

renal artery stenosis can lead to reduced kidney function (ischemic nephropathy).³⁶³

Clinical clues to renovascular disease include (1) onset of hypertension before age 30 (especially without a family history) or recent onset of significant hypertension after age 55; (2) an abdominal bruit, particularly if it continues into diastole and is lateralized; (3) accelerated or resistant hypertension; (4) recurrent (flash) pulmonary edema; (5) renal failure of uncertain etiology, especially with a normal urinary sediment; (6) coexisting diffuse atherosclerotic vascular disease, especially in heavy smokers; or (7) acute renal failure precipitated by antihypertensive therapy, particularly ACEIs or ARBs.^{78,79,81}

In patients with indications of renovascular disease, captopril-enhanced radionuclide renal scan, duplex Doppler flow studies, and magnetic resonance angiography may be used as noninvasive screening tests. Three-dimensional images can be obtained by spiral computed tomography, a technique that necessitates the use of intravenous contrast.⁸¹ Definitive diagnosis of renovascular disease requires renal angiography, which carries some risk, particularly of radioccontrast-induced acute renal failure or atheroembolism.³⁶⁴

In patients, usually women, with fibromuscular dysplasia, results of percutaneous transluminal renal angioplasty (PTRA) have been excellent and comparable to surgical revascularization.³⁶⁵ Patients with normal renal function and atherosclerotic renal artery stenosis that is focal, unilateral, and nonostial also may be managed by angioplasty.³⁶⁵ Renal artery stenting has become an important adjunct to PTRA, being used to counteract elastic recoil and to abolish the residual stenosis often observed after PTRA.³⁶⁶

Even though many patients with high-grade renal artery stenosis remain stable for prolonged periods if BP is well controlled,³⁶⁷ surgical revascularization or PTRA with renal artery stenting may be needed to preserve renal function.⁸¹

Drugs and Other Agents Affecting Blood Pressure

Many prescription drugs and some over-the-counter agents and herbal supplements may affect BP and complicate BP control in treated hypertensives. Consequently, searching for the presence of these agents in the medical history can identify a secondary component contributing to BP elevation. Such recognition may negate the need to employ unnecessary and potentially hazardous testing.

Use of agents that can affect BP in a given patient should be suspected in the following situations: (1) loss of control of previously well-controlled hypertension, (2) presence of comorbidities (particularly osteoarthritis), (3) biochemical evidence of intercurrent drug usage (such as an increase in serum potassium or creatinine concentrations with nonsteroidal anti-inflammatory drugs), and (4) atypical hypertension (such as severe but transient hypertension in a young patient presenting with chest pain and ECG changes accompanying possible cocaine usage).

Table 24 provides a list of those agents that may alter BP. They may affect BP in several ways. They may affect sodium balance; increase adrenergic or suppress parasympathetic neural activity; alter the production, release, or effectiveness

TABLE 24. Common Substances Associated With Hypertension in Humans

Prescription Drugs

Cortisone and other steroids (both cortico- and mineralo-), ACTH

Estrogens (usually just oral contraceptive agents with high estrogenic activity)

Nonsteroidal anti-inflammatory drugs

Phenylpropanolamines and analogues

Cyclosporine and tacrolimus

Erythropoietin

Sibutramine

Ketamine

Desflurane

Carbamazepine

Bromocryptine

Metoclopramide

Antidepressants (especially venlafaxine)

Buspirone

Clonidine, BB combination

Pheochromocytoma: BB without α -blocker first; glucagon

Clozapine

Street drugs and other “natural products”

Cocaine and cocaine withdrawal

Ma huang, “herbal ecstasy,” and other phenylpropanolamine analogs

Nicotine and withdrawal

Anabolic steroids

Narcotic withdrawal

Methylphenidate

Phencyclidine

Ketamine

Ergotamine and other ergot-containing herbal preparations

St. John’s wort

Food substances

Sodium chloride

Ethanol

Licorice

Tyramine-containing foods (with MAO-I)

Chemical elements and other industrial chemicals

Lead

Mercury

Thallium and other heavy metals

Lithium salts, especially the chloride

Boldfaced items within the list represent the substances of more current clinical importance.

of vasoactive hormones; or exert direct effects on the endothelium or vascular smooth muscle.

Alcohol

Modest consumption of alcohol (eg, <30 g of ethanol a day or approximately two drinks daily) is not generally associated with BP increases. Larger amounts of alcohol ingestion have a dose-related effect on BP, both in hypertensive and normo-

tensive subjects.¹⁰ The use of ambulatory BP monitoring has highlighted the biphasic effects of alcohol on BP, underscoring the importance of the timing of BP measurement. A large intake of alcohol (>30 g) may lower BP in the first 4 hours after ingestion. Approximately 10 to 15 hours later (perhaps at the time a patient is seen for an office visit or in the emergency room during withdrawal), BP increase may be noted. This accounts for some of the discrepancies reported in the literature about alcohol’s effect on BP. The mechanism(s) of alcohol’s effect on BP are unclear but appear to result predominantly from sympathetic neural activation, although changes in cortisol and cellular calcium concentrations also may play a role.

Nonaspirin Nonsteroidal Anti-Inflammatory Drugs (NANSAs)

NANSAs represent one of the most common medication classes consumed by hypertensive patients. Among the NANSAs, older agents like indomethacin are the most extensively studied. BP responses vary within the class of the NANSAs; however, increases in pressure are often accompanied by peripheral edema and weight gain, supporting a salt-retention mechanism of hypertension associated with the loss of natriuretic prostaglandins such as PGE₂.^{368,369} Reduction in the well-described vasodilatory effects of some prostaglandins is another mechanism. COX-2 inhibitors also may cause elevation in BP.^{370–372} Recently, a double-blind randomized trial was conducted evaluating the effects of celecoxib, rofecoxib, and naproxen on 24-hour BP in type 2 diabetic patients with osteoarthritis whose hypertension was treated with ACEIs or ARBs. At equally efficacious doses for the management of osteoarthritis, treatment with rofecoxib, but not celecoxib or naproxen, induced a significant increase in average 24-hour SBP in type 2 diabetic patients receiving ACEIs or angiotensin II receptor blockers.³⁷³ Thus, current data suggest that certain NSAIDs and COX 2 inhibitors may have destabilizing effects on BP control in diabetic hypertensive patients. This is a major concern, as diabetic patients are often older and obese, and both obesity and aging predispose to osteoarthritis as well as diabetes.

Improving Hypertension Control**Issues Dealing with Adherence to Regimens**

Behavioral models suggest that the most effective therapy prescribed by the most careful clinician will control hypertension only if the patient is motivated to take the medication as directed and to establish and maintain a health-promoting lifestyle. Motivation improves when patients have positive

TABLE 25. Provide Empathetic Reinforcement

Adopt an attitude of concern coupled with hope and interest in the patient’s future

Provide positive feedback for BP and behavioral improvement

If BP is not at goal, ask about behaviors to achieve BP control

Hold exit interviews to clarify regimen. A patient may tell you that they understand but tell the exit interviewer that they do not.

Schedule more frequent appointments and health care personnel contact with patients who are not achieving goal BP

TABLE 26. Clinician Awareness and Monitoring

Anticipate adherence problems for young men
Consider nonadherence as a cause of
Failure to reach goal BP
Resistant hypertension
Sudden loss of control
Encourage patients to bring in all medications from all physicians and other sources, whether prescription, complementary, or over-the-counter, to each visit for review and to rule out iatrogenic causes of elevated blood pressure
Ask what the patient takes for pain
Recognize depression and other psychiatric illnesses, including panic attacks, and manage appropriately
Be willing to change unsuccessful regimens and search for those more likely to succeed

experiences with, and trust in, their clinicians. Better communication improves outcomes. Empathy builds trust and is a potent motivator (Table 25).³⁷⁴

What Can the Clinician Do?

Clinician-patient partnerships that are based on trust, respect, and a holistic knowledge of the patient correlate with positive outcomes of care: adherence, satisfaction, and improved health status. Patients often evaluate a clinician's competence by their customer service skills, not their clinical skills.³⁷⁵ Customer service includes ease of access, minimal waiting time, and a positive regard from the office staff; all are known to influence provider satisfaction and patient adherence. Clinicians are the role model and should train staff by providing a positive, interactive, empathetic environment. This will increase patient comfort and willingness to participate in their own care.

Clinical Inertia

There is a broad range of clinician commitment to optimal hypertension therapy (Table 26). Failure to titrate or combine medications and to reinforce lifestyle modifications despite knowing that the patient is not at goal BP represents clinical inertia that must be overcome. This may be due in part to clinician focus on relieving symptoms, a lack of familiarity with clinical guidelines, or discomfort in titrating to a goal.³⁷⁶

A number of approaches are available to overcome clinical inertia. One of the most effective is to use decision support systems that prompt the clinician to advance therapy when a goal has not been achieved (Table 27). Such systems can be electronic (computer- or PDA-based) or paper-based (flow charts, algorithms, guidelines). Feedback reminders from any source (computer-based, automated telephone-based, nurse

TABLE 27. Organize Care Delivery Systems

Schedule next appointment before patient leaves office
Use appointment reminders, preferably computer-based, and contact patients to confirm appointments
Follow up patients who missed appointments
Use an office-based systems approach for monitoring and follow-up (eg, educate staff to provide patient encouragement, computer or chart reminders, disease management aids)

TABLE 28. Patient Education About Treatment

Assess patient's understanding and acceptance of the diagnosis of hypertension
Discuss patient's concerns and clarify misunderstandings
Tell patient the BP reading and provide a written copy
Come to agreement with the patient on goal BP
Ask patient to rate (1 to 10) his or her chance of staying on treatment
Inform patient about recommended treatment and provide specific written information about the role of lifestyle including diet, physical activity, dietary supplements, and alcohol intake. Use standard brochures when available.
Elicit concerns and questions and provide opportunities for the patient to state specific behaviors to carry out treatment recommendations
Emphasize:
Need to continue treatment
Control does not mean cure
One cannot tell if BP is elevated by feeling or symptoms; BP must be measured

care managers, outside auditors) can be very effective in not only helping to achieve BP goals but to alert clinicians to missed patient appointments, necessary prescription refills, and laboratory abnormalities.³⁷⁷

Patient-centered behavioral interventions such as counseling improve BP control (Table 28).³⁷⁸ Nurse clinicians and pharmacists have proven their effectiveness in helping to achieve goal BP.³⁷⁹ Commercial health plans may provide resources for chart auditing or other assistance to improve BP control.³⁸⁰ Clinicians should periodically audit their own patient files to assess their degree of compliance and success with established goals and treatment interventions.

The National Committee for Quality Assurance (NCQA) has established the Health Plan Employer Data and Information Set (HEDIS), a set of standardized performance measures designed to ensure that purchasers and consumers have the information they need to reliably assess quality of health care (<http://www.ncqa.org/Programs/HEDIS>). Enforcement of HEDIS guidelines by managed care organizations has successfully increased the appropriate use of ACEIs in HF and BBs in patients who have suffered a myocardial infarction. NCQA now monitors physician records for the percent of patients whose BP is less than 140/90 mm Hg.³⁸¹ BP control rates by physicians so monitored have increased to as high as 59%. Patients should be told their BP on each visit and be encouraged not only to ask for those numbers but to inquire as to why BP is above the goal, if that is the case. They also should be given a written record to keep as their part of this commitment.

Role of Other Healthcare Professionals

Clinicians must work with other healthcare professionals (eg, nurse case managers and other nurses, physician assistants, pharmacists, dentists, registered dietitians, licensed nutrition-

TABLE 29. Collaborate With Other Health Professionals

Use complimentary skills and knowledge of nurses, physician assistants, pharmacists, registered dietitians, optometrists, dentists, and podiatrists
Refer selected patients for more intensive counseling

TABLE 30. Individualize the Regimen

Include patient in decision-making
Simplify the regimen to once-daily dosing, if possible
Incorporate treatment into patient's daily lifestyle; eg, take medications just before or after brushing teeth
Agree with the patient on realistic short-term objectives for specific components of the medication and lifestyle modification plan
Encourage discussion of diet and physical activity
Encourage discussion of adverse drug effects and concerns
Encourage self-monitoring with validated BP devices
Minimize the cost of therapy. Recognize financial issues and enlist local community and national programs to assist in affording medications.
Indicate that adherence to the regimen will be a subject of discussion at each visit
Encourage gradual sustained weight loss

ists, nutrition educators, optometrists, and podiatrists) to influence or reinforce instructions to improve patient lifestyles and BP control (Table 29). Nurse-managed hypertension clinics, worksite Occupational Health departments, managed care organizations, pharmacists, and lay community workers have all contributed to better hypertension control. Public health nurses and community outreach workers in high-risk communities also are helpful through their efforts to screen, identify cases, refer and track follow-up appointments, and educate patients. All health care professionals must be committed to enhancing BP control through reinforcing messages about the risks of hypertension, the importance of managing both SBP and DBP and achieving goal BP, education about effective lifestyle interventions, pharmacological therapies, and adherence to treatment.

Patient Factors

Patient attitudes are greatly influenced by cultural differences, beliefs, and previous experiences with the health system.³⁸² These attitudes must be understood and respected if the clinician is to build trust and increase communication with patients and families (Table 30). Clinicians should explain to patients that the terms “hypertension” and “high BP” are used interchangeably and that neither indicates an anxiety state. In addition to motivation, patients need specific education designed to help them modify their lifestyle and to take medications as prescribed to feel better and to reduce risks.

Characterization of Patients Leading to Tailored Therapy

There is a broad range of patient involvement in, and commitment to, hypertension therapy. Management strategies need to be focused on the patient's goals when providing advice and encouraging adherence. Optimal management strategies are likely to differ for patient types. Healthy lifestyles influence adherence to medication as well as patient's beliefs and involvement with behaviors including food, beverages, physical activity, healthy weight, salt and alcohol consumption, and smoking. A cluster analysis of 727 hypertensive patients found that the individuals fell into 4 categories.³⁸³ The largest group (39%) was health-oriented, informed about hypertension, and took their medication. A

TABLE 31. Promote Social Support Systems

With full permission of the patient, involve caring family members or other social support (ie, faith-based or community organizations) in the treatment process
Suggest common interest group activities (eg, a walking group) to enhance mutual support and motivation

second group (16%) tended to rely on medication rather than lifestyle to control their BP. The third group (22%) had the highest BMI, did not practice health-promoting lifestyle except for low rates of alcohol consumption and tobacco abuse, often forgot to take their medication, and had a lower BP control rate. These patients may benefit most from clinical counseling and help in achieving lifestyle modifications and will likely require more frequent office visits or contact with nurses or other providers. The last group (23%) was more likely to be male and young, knew less about hypertension, was least afraid of consequences of hypertension or failure to take their medication, and was most likely to consume alcohol, abuse tobacco, and stop medication without informing their physician. They probably require persistent reinforcement, information on the hazards of lack of BP control, and small incremental goal-setting by allied health care personnel. Involvement of family members or other social supports also may be useful (Table 31).

Goal Setting and Behavioral Change

The clinician and patient must agree on BP goals and estimated time to reach them, and those goals should be clearly recorded in the chart. With the support of the clinician, the patient must be empowered with the understanding that making behavioral changes is ultimately his or her responsibility. As people make behavior change, they progress through a series of stages (precontemplation, contemplation, preparation, action, and maintenance). Behavior change is more successfully facilitated using this approach along with motivational interviewing rather than assigning the same intervention to every patient.^{384,385}

Patients can be asked, using a 1 to 10 ranking, how likely they are to follow the plan. If not likely, the clinician can use motivational interviewing to identify the barriers to adherence. At visits where BP is above goal, alterations in the treatment plan should be made and documented accordingly. Home BP devices can be very useful in involving many patients in their own care. Devices must be calibrated by the clinician (see the section Self Measurement). This should be done, in part, by having the patient determine their BP with the device in the presence of the clinician. Home-determined BP tends to be approximately 5 mm Hg lower than office BP, and this information should be considered when assessing progress toward goal. But office BP should still be used to determine that a patient is at goal.

Patient satisfaction with their health care providers predicts compliance with treatment. All clinicians need to provide positive, patient-centered care to satisfy and enable their patients to follow treatment. Some patient-centered behavioral interventions, like counseling, have been shown to improve BP control, while the evidence for structured training or self-monitoring is less clear.

Economic Barriers

The cost of medications may be a barrier to effective treatment. Patients often perceive that lifestyle modifications such as following the DASH eating plan are expensive, but following these plans can be accomplished even on modest budgets. Nutrition educators offer classes in schools, communities, and worksites on food budgeting and meal planning. Clinicians should refer their patients to these classes. Medical nutrition therapy by registered dietitians improves the health of patients who have high cholesterol, diabetes, obesity, or other chronic disease risk factors.³⁸⁶ Patients should be advised that most lifestyle modifications may be cost-free or may even save money (eg, smoking cessation and reduction of alcohol consumption). Further, the beneficial effects of lifestyle modification may include reduction in the amount and cost of prescribed medications and the cost of insurance. A patient adhering to the DASH eating plan may require less medication and save money. Patients need to understand the important difference between the price of a medication and the cost of nonadherence. The price of medication is the amount of money needed for purchase, and the cost is the outcome or consequences of not adhering to this treatment advice, which may include impaired quality of life, CVD, kidney failure, stroke, and even premature death. The identification of persons who can assist the patient with insurance concerns and social services may be important to overall adherence. Most pharmaceutical companies have special needs programs that are often handled through their marketing departments.

Additional Sources of Information

Additional information is available at the NHLBI web site: <http://www.nhlbi.nih.gov/>.

Scheme Used for Classification of the Evidence

The studies that provided evidence supporting the recommendations of this report were classified and reviewed by the staff and the executive committee. The classification scheme is from the JNC 6 report and other NHBPEP Working Group Reports.^{3,4,6,9}

These symbols are appended to the citations in the reference list:

M: Meta-analysis; use of statistical methods to combine the results from clinical trials.

RA: Randomized controlled trials; also known as experimental studies.

RE: Retrospective analyses; also known as case-control studies.

F: Prospective study; also known as cohort studies, including historical or prospective follow-up studies.

X: Cross-sectional survey; also known as prevalence studies.

PR: Previous review or position statements.

C: Clinical interventions (nonrandomized).

Appendix

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