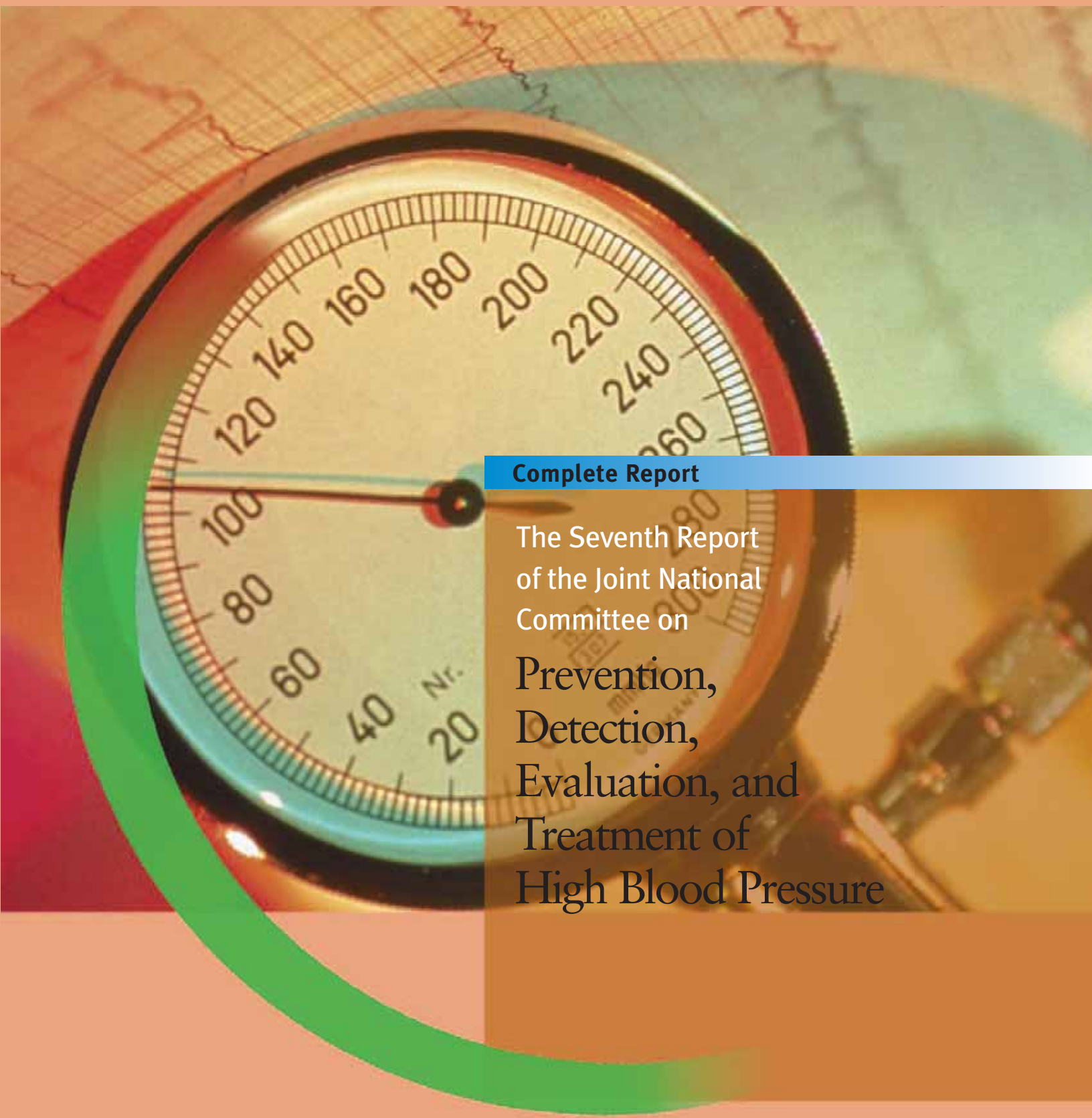


Complete Report

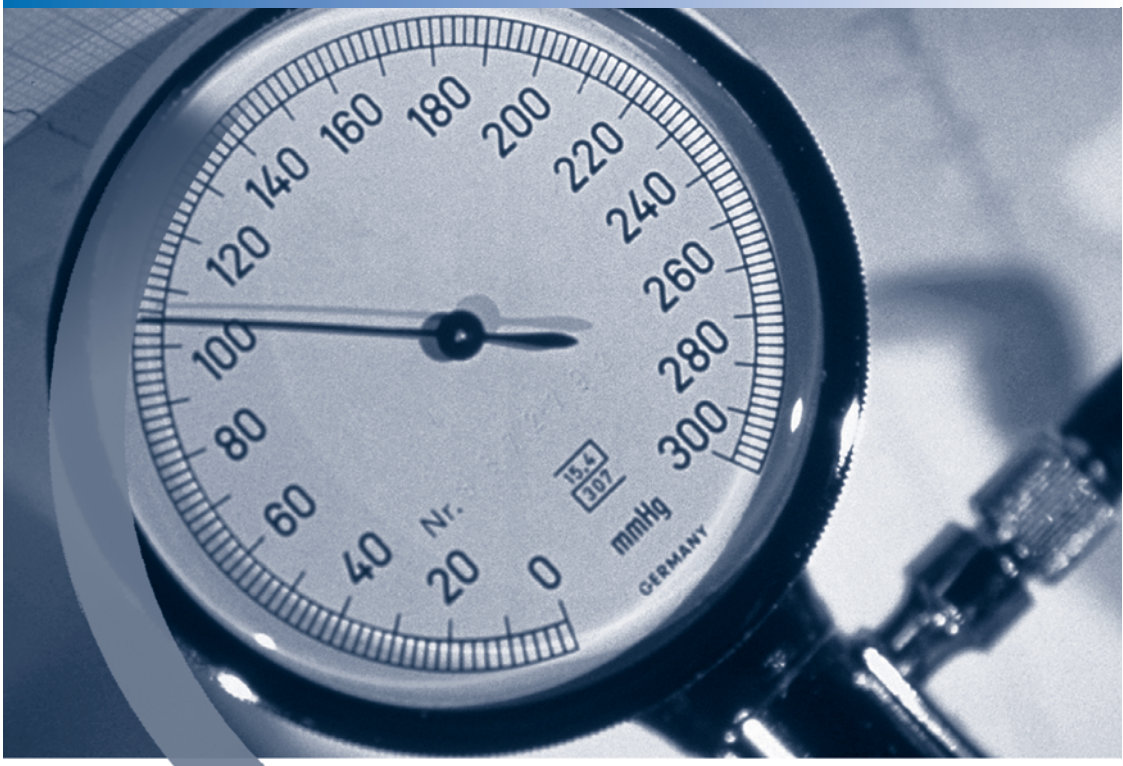
The Seventh Report of the Joint National Committee on

Prevention, Detection, Evaluation, and Treatment of High Blood Pressure

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health
National Heart, Lung, and Blood Institute

Complete Report



The Seventh Report of the Joint National Committee on

Prevention, Detection, Evaluation, and Treatment of High Blood Pressure

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
National Heart, Lung, and Blood Institute
National High Blood Pressure Education Program

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Dr. Chobanian has received honoraria for serving as a speaker from Monarch, Wyeth, Astra-Zeneca, Solvay, and Bristol-Myers Squibb.

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Dr. Carter has served as a consultant/advisor for Bristol-Myers Squibb.

Dr. Cushman has received funding/grant support for research projects from Astra-Zeneca, Merck, Pfizer, Kos, Aventis Pharma, King Pharmaceuticals, GlaxoSmithKline, and Boehringer-Ingelheim; he has served as a consultant/advisor for Bristol-Myers Squibb, Sanofi, GlaxoSmithKline, Novartis, Pfizer, Solvay, Pharmacia, Takeda, Sankyo, Forest, and Biovail.

Dr. Izzo has received honoraria for serving as a speaker from Boehringer-Ingelheim, Merck, Pfizer, Astra-Zeneca, Solvay, Novartis, Forest, and Sankyo; he has received funding/grant support for research projects from Boehringer-Ingelheim, Merck, Astra-Zeneca, Novartis, GlaxoSmithKline, and Biovail; he served as a consultant/advisor for Merck, Astra-Zeneca, Novartis, Intercure, Sankyo, and Nexcura; he has stock holdings in Intercure, Nexcura.

Dr. Jones has served as a consultant/advisor for Pfizer, Bristol-Myers Squibb, Merck, Forest, and Novartis.

Dr. Manger has served as a consultant/advisor for the NHBPEP Coordinating Committee.

Dr. Materson has served as a consultant/advisor for Unimed, Merck, GlaxoSmithKline, Novartis, Reliant, Tanabe, Bristol-Myers Squibb, Pfizer, Pharmacia, Noven, Boehringer-Ingelheim, and Solvay.

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Ayerst, Sankyo, Solvay, and Texas Biotechnology Corporation; she has served as a consultant/advisor for Bristol-Myers Squibb, Merck, Pfizer, Sanofi, Novartis, The Salt Institute, and Wyeth-Ayerst; she is also on the Board of Directors for the Texas Biotechnology Corporation.

Dr. Sowers has received honoraria for serving as a speaker from Med Com Vascular Biology Working Group and Joslin Clinic Foundation; he has received funding/grant support for research projects from Novartis and Astra-Zeneca.

Dr. Wright has received honoraria for serving as a speaker from Astra, Aventis, Bayer, Bristol-Myers Squibb, Forest, Merck, Norvartis, Pfizer, Phoenix Pharmaceuticals, GlaxoSmithKline, and Solvay/Unimed; he has received funding/grant support for research projects from Astra, Aventis, Bayer, Biovail, Bristol-Myers Squibb, Forest, Merck, Norvartis, Pfizer, Phoenix Pharmaceuticals, GlaxoSmithKline, and Solvay/Unimed.

National High Blood Pressure Education Program Coordinating Committee

Claude Lenfant, M.D. (National Heart, Lung, and Blood Institute, Bethesda, MD); George L. Bakris, M.D. (Rush University Medical Center, Chicago, IL); Henry R. Black, M.D. (Rush University Medical Center, Chicago, IL); Vicki Burt, Sc.M., R.N. (National Center for Health Statistics, Hyattsville, MD); Barry L. Carter, Pharm.D., F.C.C.P. (University of Iowa, Iowa City, IA); Francis D. Chesley, Jr., M.D. (Agency for Healthcare Research and Quality, Rockville, MD); Jerome D. Cohen, M.D. (Saint Louis University School of Medicine, St. Louis, MO); Pamela J. Colman, D.P.M. (American Podiatric Medical Association, Bethesda, MD); William C. Cushman, M.D. (Veterans Affairs Medical Center, Memphis, TN); Mark J. Cziraky, Pharm.D., F.A.H.A. (Health Core, Inc., Newark, DE); John J. Davis, P.A.-C. (American Academy of Physician Assistants, Memphis, TN); Keith Copelin Ferdinand, M.D., F.A.C.C. (Heartbeats Life Center, New Orleans, LA); Ray W. Gifford, Jr., M.D., M.S. (Cleveland Clinic Foundation, Fountain Hills, AZ); Michael Glick, D.M.D. (New Jersey Dental School, Newark, NJ); Lee A. Green, M.D., M.P.H. (University of Michigan, Ann Arbor, MI); Stephen Havas, M.D., M.P.H., M.S. (University of Maryland School of Medicine, Baltimore, MD); Thomas H. Hostetter, M.D. (National Institutes of Diabetes and Digestive and Kidney Diseases, Bethesda, MD); Joseph L. Izzo, Jr., M.D. (State University of New York at Buffalo School of Medicine, Buffalo, NY); Daniel W. Jones, M.D. (University of Mississippi Medical Center, Jackson, MS); Lynn Kirby, R.N., N.P., C.O.H.N. (Sanofi-Synthelabo Research, Malvern, PA); Kathryn M. Kolasa, Ph.D., R.D., L.D.N. (Brody School of Medicine at East Carolina University, Greenville, NC); Stuart Linas, M.D. (University of Colorado Health Sciences Center, Denver, CO); William M. Manger, M.D., Ph.D. (New York University Medical Center, New York, NY); Edwin C. Marshall, O.D., M.S., M.P.H. (Indiana University School of Optometry, Bloomington, IN); Barry J. Materson, M.D., M.B.A. (University of Miami, Miami, FL); Jay Merchant, M.H.A. (Centers for Medicare & Medicaid Services, Washington, DC); Nancy Houston Miller, R.N., B.S.N. (Stanford University School of Medicine, Palo Alto, CA); Marvin Moser, M.D. (Yale University School of Medicine, Scarsdale, NY); William A. Nickey, D.O. (Philadelphia College of Osteopathic Medicine, Philadelphia, PA); Suzanne Oparil, M.D. (University of Alabama at Birmingham, Birmingham, AL); Otelio S. Randall, M.D., F.A.C.C. (Howard University Hospital, Washington, DC); James W. Reed, M.D., F.A.C.P., F.A.C.E. (Morehouse School of Medicine, Atlanta, GA); Edward J. Roccella, Ph.D., M.P.H. (National Heart, Lung, and Blood Institute, Bethesda, MD); Lee Shaughnessy (National Stroke Association, Englewood, CO); Sheldon G. Sheps, M.D. (Mayo Clinic, Rochester, MN); David B. Snyder, R.Ph., D.D.S. (Health Resources and Services Administration, Rockville, MD); James R. Sowers, M.D., F.A.C.P., F.A.C.E. (SUNY Health Science Center at Brooklyn, Brooklyn, NY); Leonard M. Steiner, M.S., O.D. (Eye Group, Oakhurst, NJ); Ronald Stout, M.D., M.P.H. (Procter and Gamble, Mason, OH); Rita D. Strickland, Ed.D., R.N. (New York Institute of Technology,

Springfield Gardens, NY); Carlos Vallbona, M.D. (Baylor College of Medicine, Houston, TX); Howard S. Weiss, M.D., M.P.H. (Georgetown University Medical Center, Washington Hospital Center, Walter Reed Army Medical Center, Washington, DC); Jack P. Whisnant, M.D. (Mayo Clinic and Mayo Medical School, Rochester, MN); Laurie Willshire, M.P.H., R.N. (American Red Cross, Falls Church, VA); Gerald J. Wilson, M.A., M.B.A. (Citizens for Public Action on Blood Pressure and Cholesterol, Inc., Potomac, MD); Mary Winston, Ed.D., R.D. (American Heart Association, Dallas, TX); Jackson T. Wright, Jr., M.D., Ph.D. (Case Western Reserve University, Cleveland, OH)

Additional Contributors

Jan N. Basile, M.D., F.A.C.P. (Veterans Administration Hospital, Charleston, SC); James I. Cleeman, M.D. (National Heart, Lung, and Blood Institute, Bethesda, MD); Darla E. Danford, M.P.H, D.Sc. (National Heart, Lung, and Blood Institute, Bethesda, MD); Richard A. Dart, M.D., F.A.C.P., F.C.C.P., F.A.H.A. (Marshfield Clinic, Marshfield, WI); Karen A. Donato, S.M., R.D. (National Heart, Lung, and Blood Institute, Bethesda, MD); Mark E. Dunlap, M.D. (Louis Stokes Cleveland VA Medical Center, Cleveland, OH); Brent M. Egan, M.D. (Medical University of South Carolina, Charleston, SC); William J. Elliott, M.D., Ph.D. (Rush University Medical Center, Chicago, IL); Bonita E. Falkner, M.D. (Thomas Jefferson University, Philadelphia, PA); John M. Flack, M.D., M.P.H. (Wayne State University School of Medicine, Detroit, MI); David Lee Gordon, M.D. (University of Miami School of Medicine, Miami, FL); Philip B. Gorelik, M.D., M.P.H., F.A.C.P. (Rush Medical College, Chicago, IL); Mary M. Hand, M.S.P.H., R.N (National Heart, Lung, and Blood Institute, Bethesda, MD); Linda A. Hershey, M.D., Ph.D. (VA WNY Healthcare System, Buffalo, NY); Norman M. Kaplan, M.D. (University of Texas Southwestern Medical School at Dallas, Dallas, TX); Daniel Levy, M.D. (National Heart, Lung, and Blood Institute, Framingham, MA); James W. Lohr, M.D. (VA WNY Healthcare System and SUNY Buffalo, Buffalo, NY); Vasilios Papademetriou, M.D., F.A.C.P., F.A.C.C. (Veterans Affairs Medical Center, Washington, DC); Thomas G. Pickering, M.D., D.Phil. (Mount Sinai Medical Center, New York, NY); Ileana L. Piña, M.D., F.A.C.C. (University Hospitals of Cleveland, Cleveland, OH); L. Michael Prisant, M.D., F.A.C.C., F.A.C.P. (Medical College of Georgia, Augusta, GA); Clive Rosendorff, M.D., Ph.D., F.R.C.P. (Veterans Affairs Medical Center, Bronx, NY); Virend K. Somers, M.D., Ph.D. (Mayo Clinic and Mayo Foundation, Rochester, MN); Ray Townsend, M.D. (University of Pennsylvania School of Medicine, Philadelphia, PA); Humberto Vidaillet, M.D. (Marshfield Clinic, Marshfield, WI); Donald G. Vidt, M.D. (Cleveland Clinic Foundation, Cleveland, OH); William White, M.D. (The University of Connecticut Health Center, Farmington, CT)

Staff

Joanne Karimbakas, M.S., R.D. (American Institutes for Research Health Program, Silver Spring, MD)

We appreciate the assistance by: Carol Creech, M.I.L.S. and Gabrielle Gessner (American Institutes for Research Health Program, Silver Spring, MD).

National High Blood Pressure Education Program Coordinating Committee Member Organizations

American Academy of Family Physicians
American Academy of Neurology
American Academy of Ophthalmology
American Academy of Physician Assistants
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National Heart, Lung, and Blood Institute
National Institute of Diabetes and Digestive and Kidney Diseases

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Foreword

The complete version of the *Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure* (JNC7) provides additional scientific evidence to bolster other JNC 7 products: the *JNC 7 Express*; *Facts About the DASH Eating Plan; Your Guide to Lowering High Blood Pressure*; Reference Card from the JNC 7 for clinicians; Blood Pressure Wallet Card for patients; and Palm application of the JNC 7 recommendations. These educational materials are available on the NHLBI Web site http://www.nhlbi.nih.gov/.

The purpose of JNC reports is to synthesize the available scientific evidence and offer guidance to busy primary care clinicians. Readers of this report should remember that this document is intended as a guide, not a mandate. The National High Blood Pressure Education Program (NHBPEP) recognizes the responsible clinician's judgment regarding the management of patients remains paramount. Therefore, JNC documents are tools to be adopted and implemented in local and individual settings.

In the production of this report, much discussion was generated regarding the interpretation of the available scientific literature. However, after all of the discussions within the JNC 7 Executive Committee and the NHBPEP Coordinating Committee, as well as the many discussions at conferences and scientific meetings conducted in the United States and worldwide, the conclusion is that best management practice occurs when hypertension is treated to goal levels and blood pressure control is sustained over time. This is irrefutable but, unfortunately, hypertension treatment and control rates worldwide are simply not as good as they could be.

By developing this stellar landmark report, Dr. Aram Chobanian, the JNC 7 Executive Committee, and members of the NHBPEP Coordinating Committee, as well as the writers and the contributors to this document, have addressed the important public health issue of improving inadequate blood pressure control. Applying JNC 7 recommendations to clinical practice will prevent the devastating consequences of uncontrolled hypertension. I recommend this guideline to clinicians and public health workers with the conviction that its contents will indeed contribute to the further prevention of premature morbidity and mortality. Dr. Chobanian has our deep gratitude for leading the effort to develop this report in such a timely manner. His brilliant leadership is what made the JNC 7 and related materials possible. The NHBPEP will release other advisories as the scientific evidence becomes available.

Barbara M. Alving, M.D.
Acting Director
National Heart, Lung, and Blood Institute
and
Chair
National High Blood Pressure Education Program
Coordinating Committee

Abstract

The purpose of the *Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure* (JNC 7) is to provide an evidence-based approach to the prevention and management of hypertension. The key messages of this report are: in those older than age 50, systolic blood pressure (SBP) of >140 mmHg is a more important cardiovascular disease (CVD) risk factor than diastolic BP (DBP); beginning at 115/75 mmHg, CVD risk doubles for each increment of 20/10 mmHg; those who are normotensive at 55 years of age will have a 90 percent lifetime risk of developing hypertension; prehypertensive individuals (SBP 120–139 mmHg or DBP 80–89 mmHg) 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, which 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 mmHg, or <130/80 mmHg for patients with diabetes and chronic kidney disease); for patients whose BP is >20 mmHg above the SBP goal or 10 mmHg above the DBP 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 only be controlled 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.

Introduction

For more than three 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 [BP]).

Data from the National Health and Nutrition Examination Survey (NHANES) have indicated that 50 million or more Americans have high 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 mmHg SBP) is responsible for 62 percent of cerebrovascular disease and 49 percent of ischemic heart disease (IHD), with little variation by sex. In addition, suboptimal BP is the number one attributable risk factor 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 among Americans has improved from a level of 51 percent in the period 1976–1980 to 70 percent in 1999–2000 (table 1). The percentage of patients with hypertension receiving treatment has increased from 31 percent to 59 percent in the same period, and the percentage of persons with high BP controlled to below 140/90 mmHg has increased from 10 percent to 34 percent. Between 1960 and 1991, median SBP for individuals ages 60–74 declined by approximately 16 mmHg (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 percent and 50 percent, respectively (figures 2 and 3). These benefits have occurred independent of gender, age, race, or socioeconomic status. Within the last two 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.

Table 1. Trends in awareness, treatment, and control of high blood pressure, 1976–2000*

	National Health and Nutrition Examination Survey, Percent			
	1976–80[1]	1988–91[1]	1991–94[2]	1999–2000[3]
Awareness	51	73	68	70
Treatment	31	55	54	59
Control†	10	29	27	34

** Percentage of adults ages 18 to 74 years with SBP of 140 mmHg or greater, DBP of 90 mmHg or greater, or taking antihypertensive medication.*

† SBP below 140 mmHg and DBP below 90 mmHg, and on antihypertensive medication.

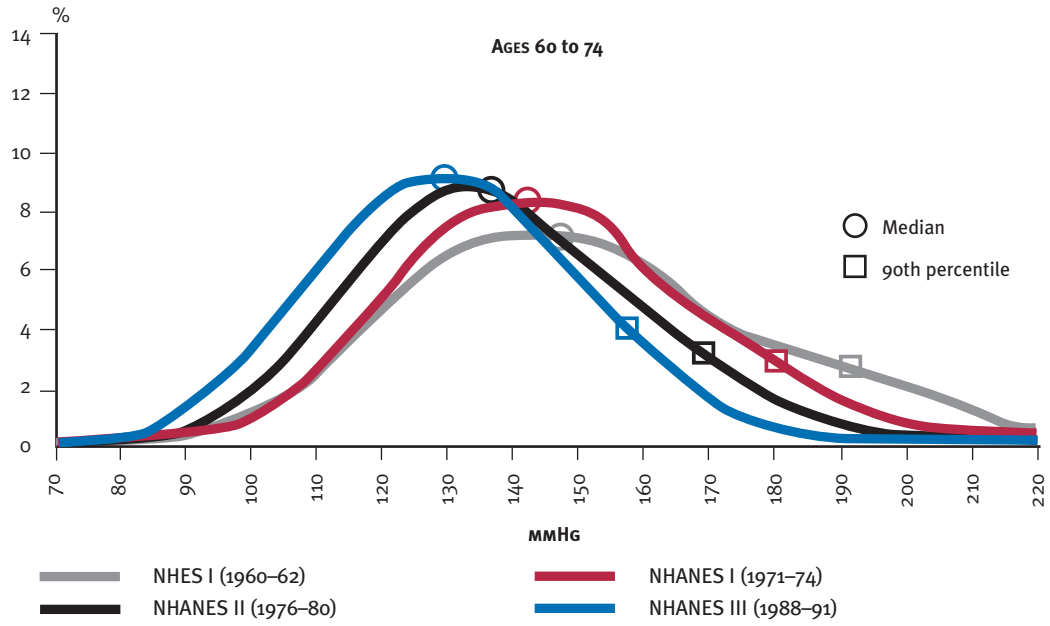
Sources:

1 *Data from Burt VL, et al. Prevalance of hypertension in the US adult population. Results from the Third National Health and Nutrition Examination Survey, 1988–1991.* Hypertension *1995;26:60–9.*

2 *Data from 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.*

3 *The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.* JAMA *2003;289:2560–71.*

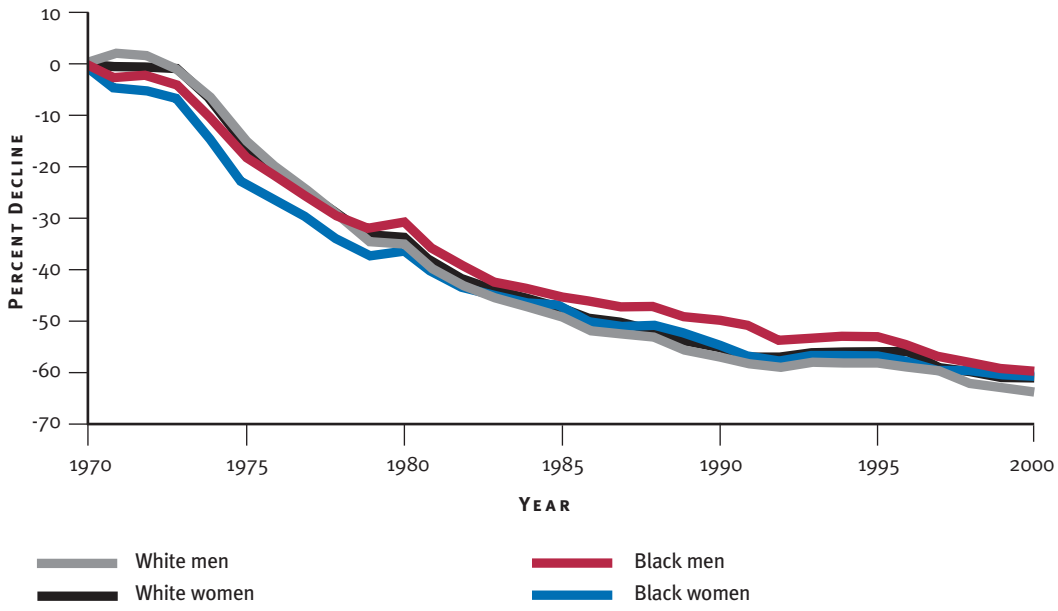
Figure 1. Smoothed weighted frequency distribution, median, and 90th percentile of systolic blood pressure for ages 60–74 years: United States, 1960–1991



NHANES, National Health and Nutrition Examination Survey; NHES, National Health Examination Survey

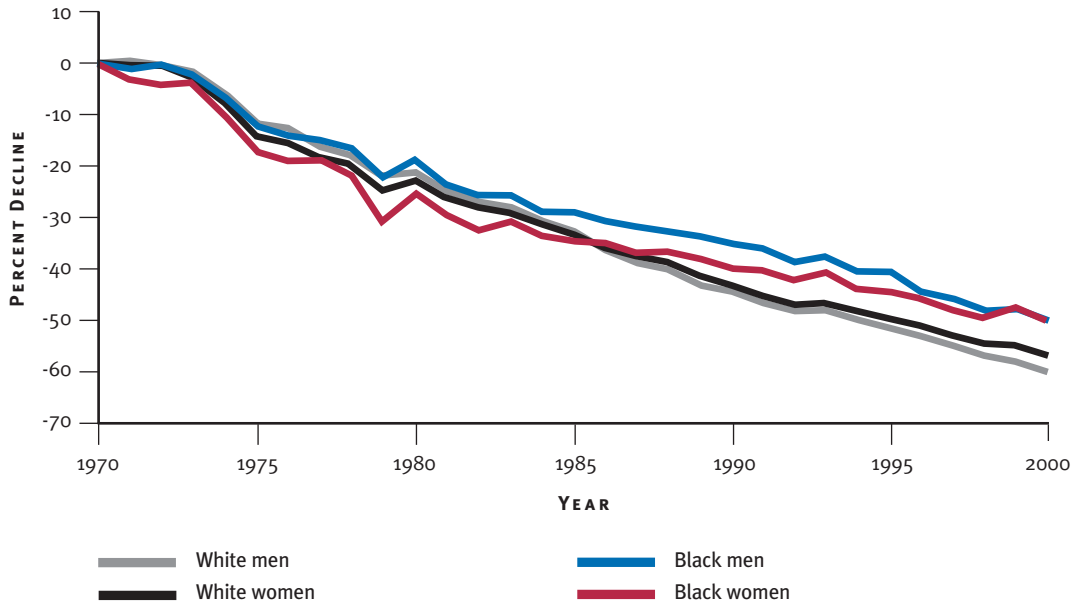
Source: Burt VL, et al. Trends in the prevalance, awareness, treatment, and control of hypertension in the adult US population. Data from the health examination surveys, 1960 to 1991. Erratum in: Hypertension *1996;7(5):1192.*

Figure 2. Percent decline in age-adjusted mortality rates for stroke by gender and race: United States, 1970–2000



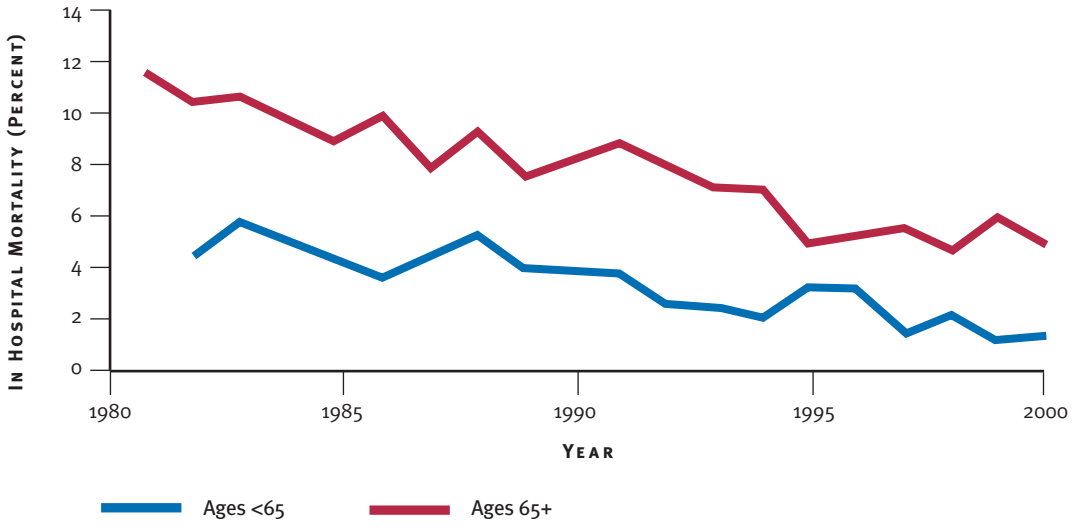
Source: Prepared by Thom T, National Heart, Lung, and Blood Institute from Vital Statistics of the United States, National Center for Health Statistics. Death rates are age-adjusted to the 2000 U.S. census population.

Figure 3. Percent decline in age-adjusted mortality rates for coronary heart disease by gender and race: United States, 1970–2000



Source: Prepared by Thom T, 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 U.S. census population.

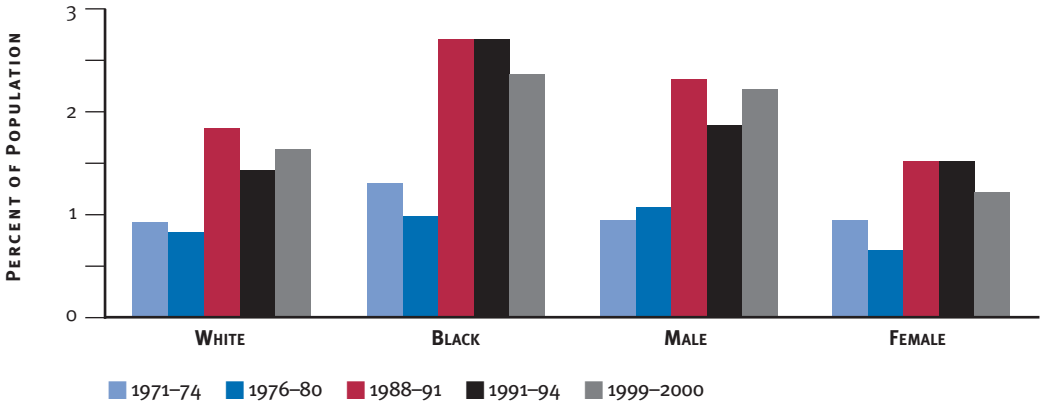
Figure 4. Hospital case-fatality rates for congestive heart failure for ages younger than 65 years and 65 years and older: United States, 1981–2000



Source: National Heart, Lung, and Blood Institute. Morbidity and Mortality: 2002 Chart Book on Cardiovascular, Lung, and Blood Diseases. *Chart 3-36. Accessed November 2003. http://www.nhlbi.nih.gov/resources/docs/cht-book.htm.*

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 percent of adults are still unaware of their hypertension, >40 percent of individuals with hypertension are not on treatment, and two-thirds of hypertensive patients are not being controlled to BP levels <140/90 mmHg (table 1). Furthermore, the decline rates in CHD- and stroke-associated deaths have slowed in the past decade. In addition, the prevalence and hospitalization rates of HF, wherein the majority of patients have hypertension prior to developing HF, 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.

Figure 5. Prevalence* of congestive heart failure by race and gender, ages 25–74 years: United States, 1971–74 to 1999–2000

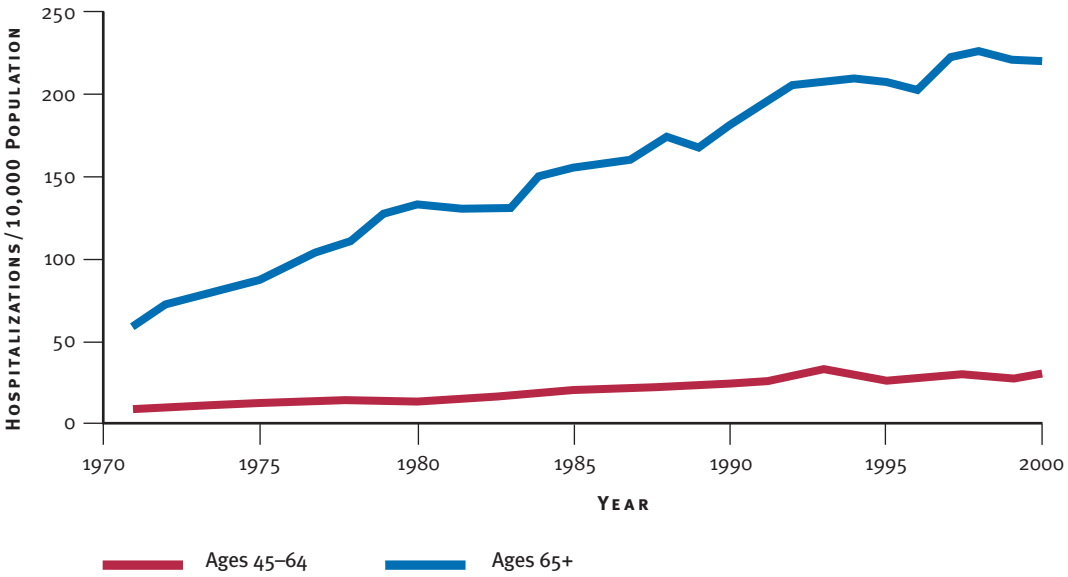


** Age-adjusted to 2000 U.S. census population.*

Note: White and Black in 1999–2000 exclude Hispanics.

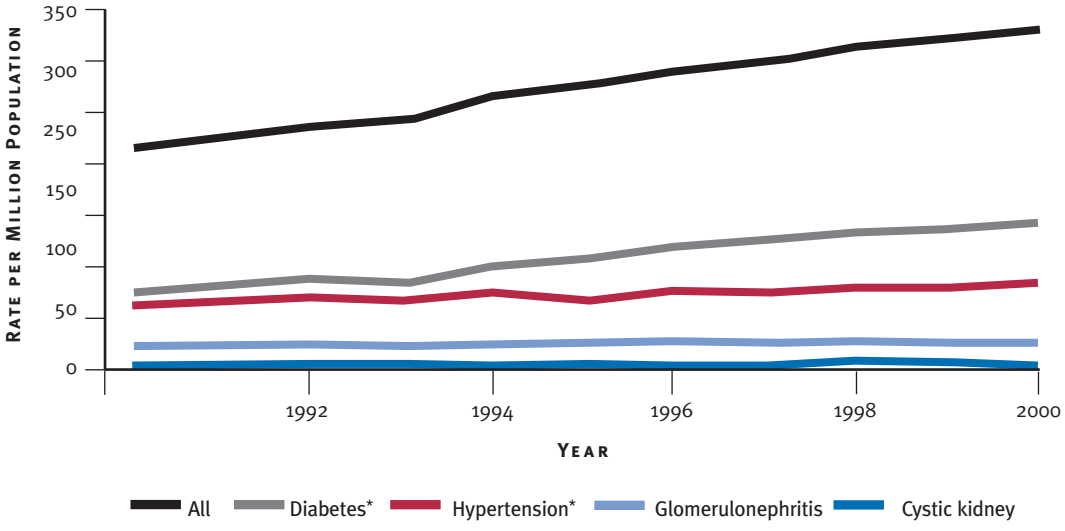
Source: National Heart, Lung, and Blood Institute. Morbidity and Mortality: 2002 Chart Book on Cardiovascular, Lung, and Blood Diseases. *Accessed November 2003. http://www.nhlbi.nih.gov/resources/docs/cht-book.htm and 1999–2000 unpublished data computed by Wolz M and Thom T, National Heart, Lung, and Blood Institute. June 2003.*

Figure 6. Hospitalization rates for congestive heart failure, ages 45–64 years and 65 years and older: United States, 1971–2000



Source: National Heart, Lung, and Blood Institute. Morbidity and Mortality: 2002 Chart Book on Cardiovascular, Lung, and Blood Diseases. *Chart 3-35. Accessed November 2003. http://www.nhlbi.nih.gov/resources/docs/cht-book.htm.*

Figure 7. Trends in incident rates of end-stage renal disease, by primary diagnosis (adjusted for age, gender, race)



* *These disease categories were treated as being mutually exclusive.*

Source: United States Renal Data System. 2002. Figure 1.14. Accessed November 2003. http://www.usrds.org/slides.htm.

Methods

The decision to appoint a committee for JNC 7 was based on four factors: the publication of many new hypertension observational studies and clinical trials since the last report was published in 1997;[4] 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 two 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 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 four 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 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 appointed the JNC 7 chair and an Executive Committee derived from the Coordinating Committee membership. The Coordinating Committee members served on one of five JNC 7 writing teams, which contributed to the writing and review of the document.

The concepts for the new report identified by the NHBPEP Coordinating Committee were used to create the report outline. Based on 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 Scheme Used for Classification of the Evidence).[11]

In reviewing the exceptionally large body of research literature on hypertension, the Executive Committee focused its deliberations on 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," or 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 daily living activities. These outcomes are strongly affected by nonfatal stroke, HF, CHD, and renal disease; hence, these outcomes were considered along with mortality in the committee's evidence-based deliberations. Studies of physiological endpoints ("disease-oriented evidence," or 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 six occasions, two of which included meetings with the entire NHBPEP 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 process[14] 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 NHBPEP 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.

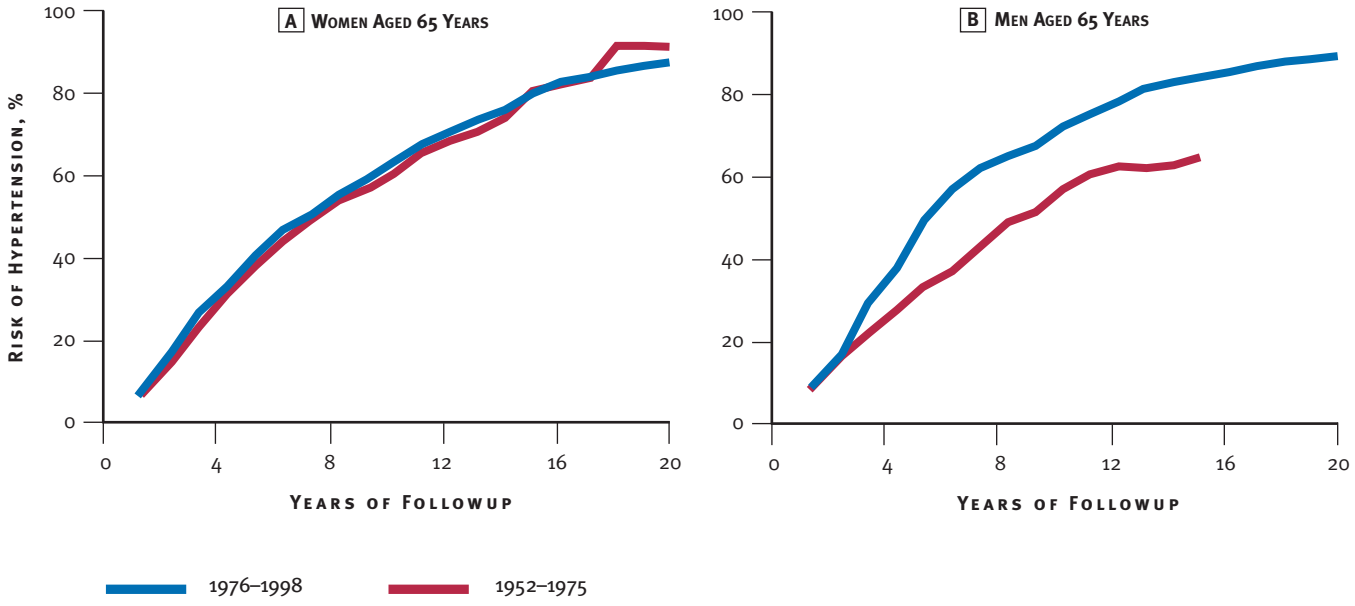
Lifetime Risk of Hypertension

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 60–69 years of age and approximately three-fourths of those 70 years of age 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 percent for men and women who were nonhypertensive at 55 or 65 years and survived to age 80–85 (figure 8).[16] Even after adjusting for competing mortality, the remaining lifetime risks of hypertension were 86–90 percent in women and 81–83 percent in men.

The impressive increase of BP to hypertensive levels with age is also illustrated by data indicating that the 4-year rates of progression to hypertension are 50 percent for those 65 years and older with BP in the 130–139/85–89 mmHg range and 26 percent for those with BP between 120–129/80–84 mmHg range.[17]

Figure 8. Residual lifetime risk of hypertension in women and men aged 65 years



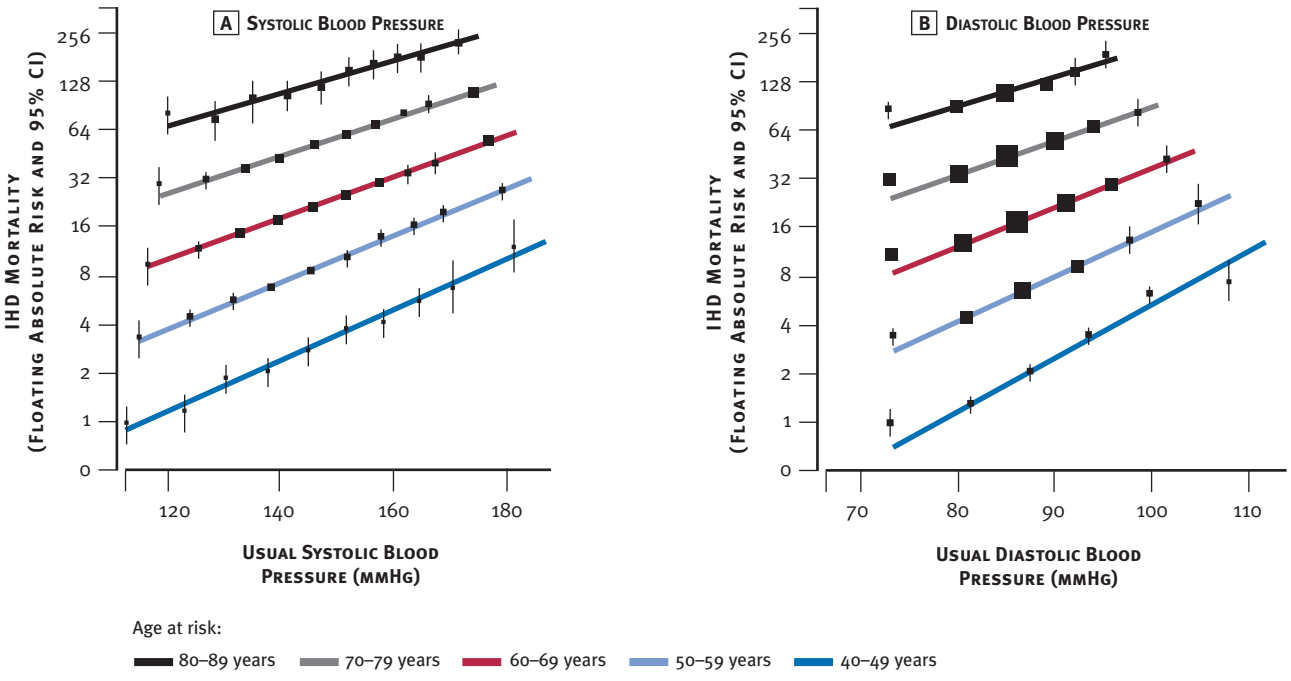
Cumulative incidence of hypertension in 65-year-old women and men. Data for 65-year-old men in the 1952–1975 period is truncated at 15 years since there were few participants in this age category who were followed up beyond this time interval.

Source: Vasan RS, et al. Residual lifetime risk for developing hypertension in middle-aged women and men: The Framingham Heart Study. JAMA *2002;287:1003–10. Copyright 2002, American Medical Association. All rights reserved.*

Data from observational studies involving more than 1 million individuals have indicated that death from both IHD and stroke increases progressively and linearly from levels as low as 115 mmHg SBP and 75 mmHg DBP upward (figures 9 and 10).[18] The increased risks are present in individuals ranging from 40 to 89 years of age. For every 20 mmHg systolic or 10 mmHg diastolic increase in BP, there is a doubling of mortality from both IHD and stroke.

In addition, longitudinal data obtained from the Framingham Heart Study have indicated that BP values between 130–139/85–89 mmHg are associated with a more than twofold increase in relative risk from cardiovascular disease (CVD) as compared with those with BP levels below 120/80 mmHg (figure 11).[19]

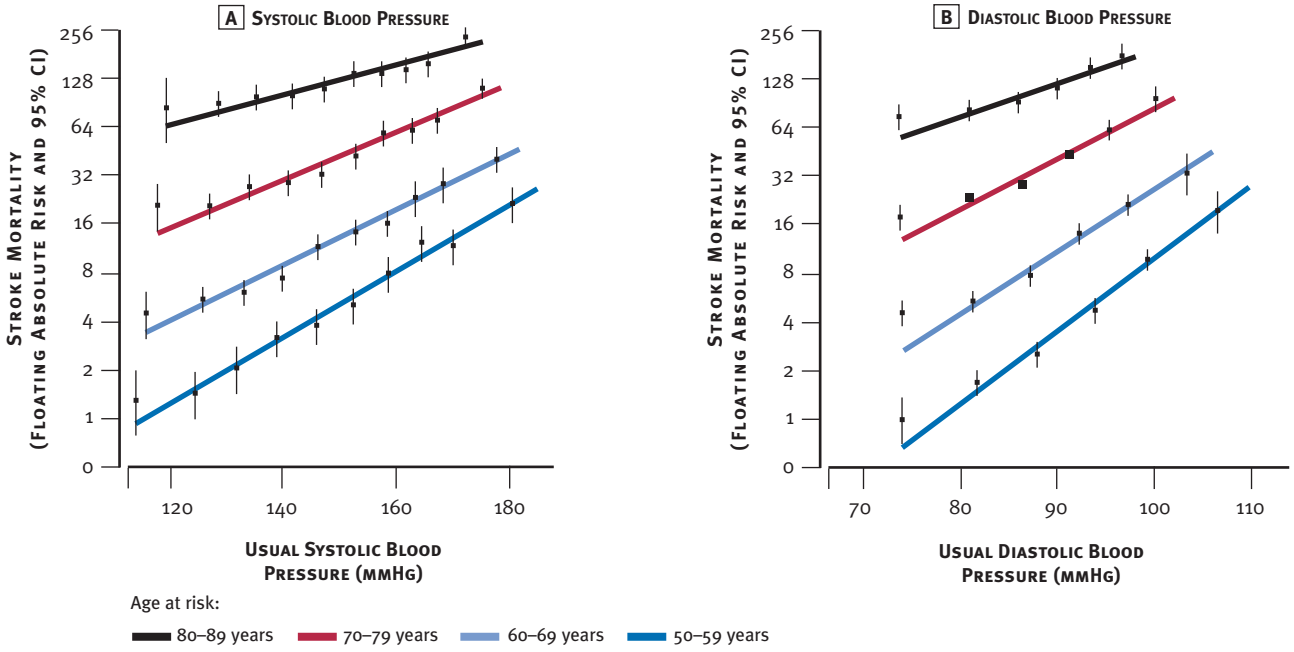
Figure 9. Ischemic heart disease mortality rate in each decade of age versus usual blood pressure at the start of that decade



IHD, ischemic heart disease

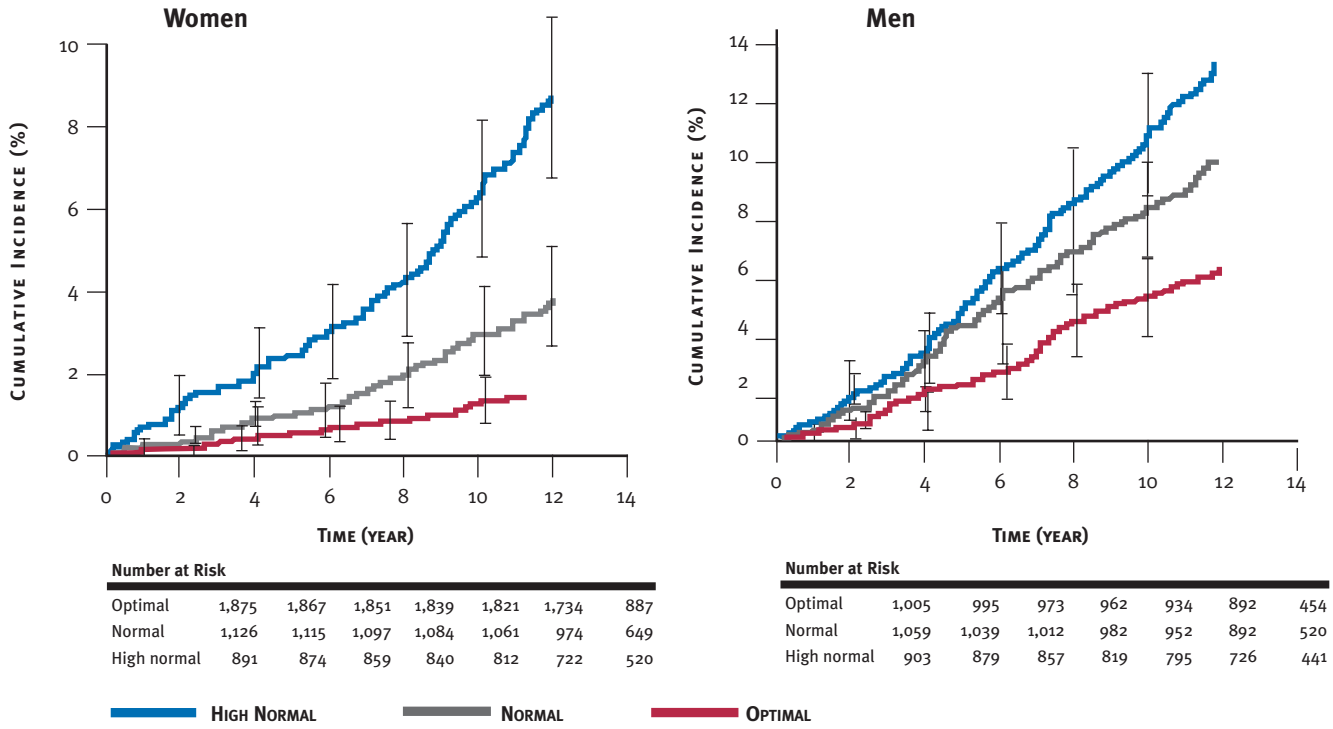
*Source: Reprinted with permission from Elsevier. Lewington S, et al. Age-specific relevance of usual blood pressure to vascular mortality: A meta-analysis of individual data for one million adults in 61 prospective studies. (*The Lancet *2002:360:1903–13).*

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. Lewington S, et al. Age-specific relevance of usual blood pressure to vascular mortality: A meta-analysis of individual data for one million adults in 61 prospective studies. (*The Lancet *2002; 360:1903–13).*

Figure 11. **Impact of high normal blood pressure on the risk of cardiovascular disease**



Number at Risk

Optimal	1,875	1,867	1,851	1,839	1,821	1,734	887
Normal	1,126	1,115	1,097	1,084	1,061	974	649
High normal	891	874	859	840	812	722	520

Number at Risk

Optimal	1,005	995	973	962	934	892	454
Normal	1,059	1,039	1,012	982	952	892	520
High normal	903	879	857	819	795	726	441

Cumulative incidence of cardiovascular events in women (panel A) and men (panel B) without hypertension, according to blood pressure category at the base-line examination. Vertical bars indicate 95 percent confidence intervals. Optimal BP is defined here as a systolic pressure of <120 mmHg and a diastolic pressure of <80 mmHg. Normal BP is a systolic pressure of 120–129 mmHg or a diastolic pressure of 80–84 mmHg. High-normal BP is a systolic pressure of 130–139 mmHg or a diastolic pressure of 85–89 mmHg. If the systolic and diastolic pressure readings for a subject were in different categories, the higher of the two categories was used.

Source: Vasan RS, et al. Impact of high-normal blood pressure on risk of cardiovascular disease. N Engl J Med *2001;345:1291–7. Copyright 2001, Massachusetts Medical Society. All rights reserved.*

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 120–139 mmHg systolic and/or 80–89 mmHg diastolic. 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).

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 1
Stage 2	160–179/100–109	→ Stage 2
Stage 3	≥180/110	

DBP, diastolic blood pressure; JNC, Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; SBP, systolic blood pressure

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;289:2560–71.*

Table 3 provides a classification of BP for adults 18 years and older. The classification is based on the average of two or more properly measured, seated, BP readings on each of two 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 based on 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 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 mmHg or less.

Table 3. Classification of blood pressure for adults

Blood Pressure Classification	SBP mmHg	DBP mmHg
Normal	<120	and <80
Prehypertension	120–139	or 80–89
Stage 1 Hypertension	140–159	or 90–99
Stage 2 Hypertension	≥160	or ≥100

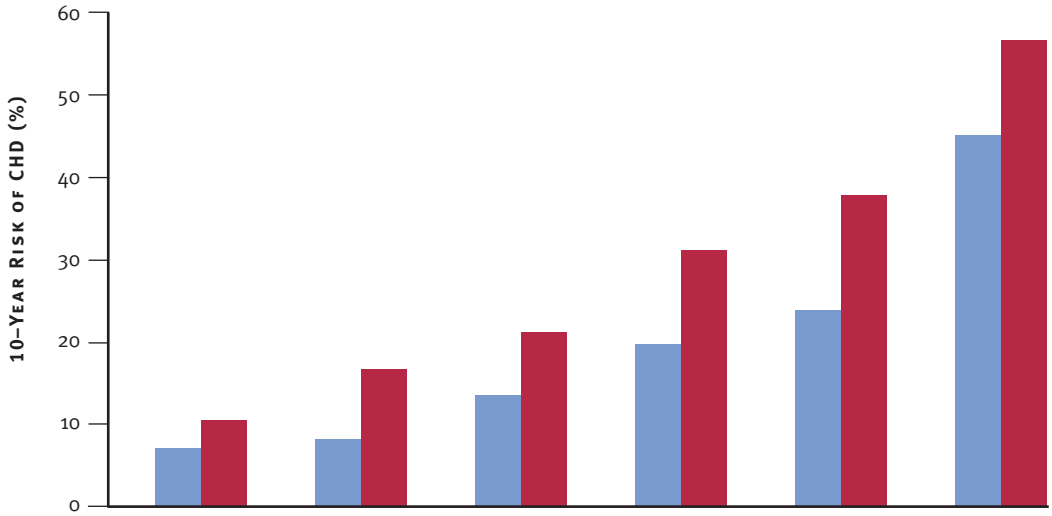
SBP, systolic blood pressure; DBP, diastolic blood pressure

This classification does not stratify hypertensive individuals by the presence or absence of risk factors or target organ damage in order to make different treatment recommendations, should either or both be present. JNC 7 suggests that **all** people with hypertension (stages 1 and 2) be treated. The treatment goal for individuals with hypertension and no other compelling conditions is <140/90 mmHg (see Compelling Indications). The goal for individuals with prehypertension and no compelling indications is to lower BP to normal levels with lifestyle changes, and prevent the progressive rise in BP using the recommended lifestyle modifications (see Lifestyle Modifications).

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 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 tables[21] 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.

Figure 12. Ten-year risk for coronary heart disease by systolic blood pressure and presence of other risk factors



Cholesterol	180	240	240	240	240	240
HDL	50	50	35	35	35	35
Smoking	No	No	No	Yes	Yes	Yes
Diabetes	No	No	No	No	Yes	Yes
LVH	No	No	No	No	No	Yes

SBP 120 **SBP 180**

CHD, coronary heart disease; HDL, high-density lipoprotein; LVH, left ventricular hypertrophy; SBP, systolic blood pressure

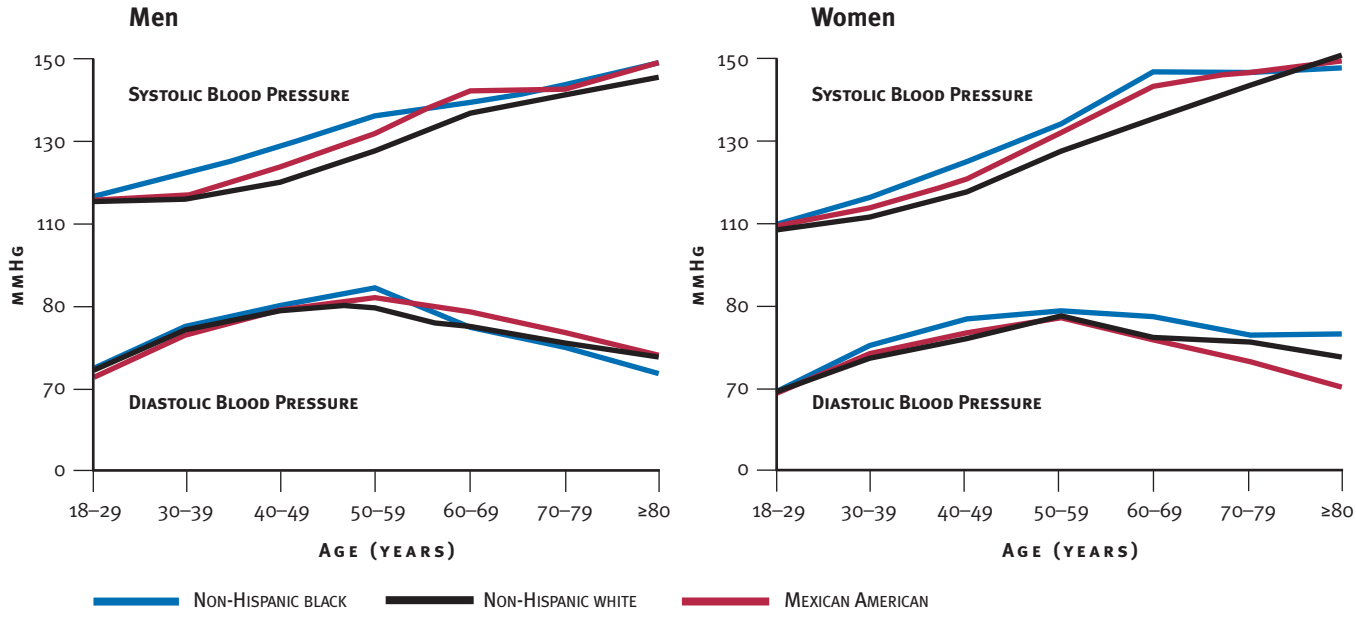
Source: Derived from Anderson KM, Wilson PWF, Odell PM, Kannel WB. An updated coronary risk profile. A statement for health professionals. Circulation *1991;83:356–62.*

Importance of Systolic Blood Pressure

Impressive evidence has accumulated to warrant greater attention to the importance of SBP as a major risk factor for CVDs. Changing patterns of BP occur with increasing age. The rise in SBP continues throughout life in contrast to DBP, which rises until approximately age 50, 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 age 50, either alone or in combination with SBP elevation. The prevalence of systolic hypertension increases with age, and above 50 years of age, 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 the Controlled Onset Verapamil Investigation of Cardiovascular End Points (CONVINCE) Trial, DBP control rates exceeded 90 percent, but SBP control rates were considerably less (60–70 percent).[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

Figure 13. Changes in systolic and diastolic blood pressure with age

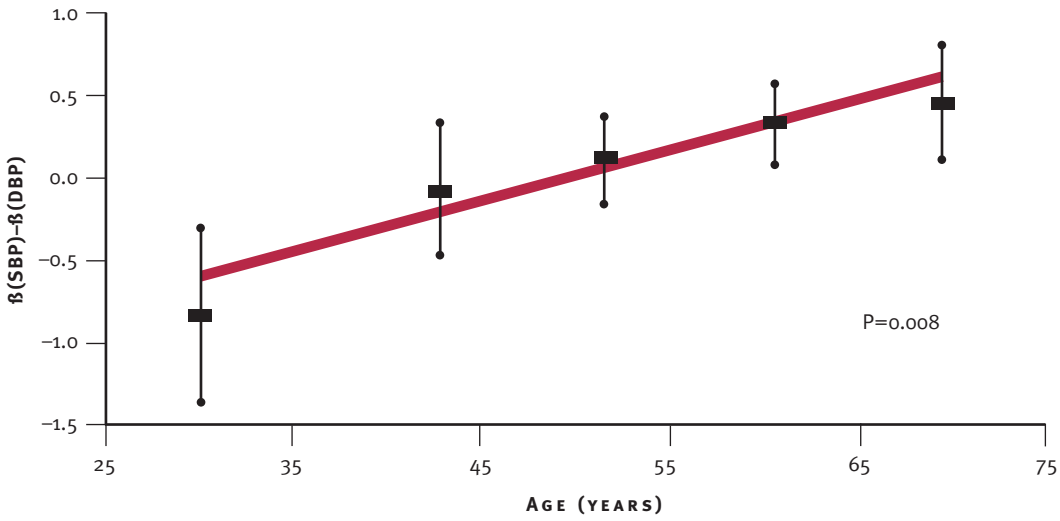


SBP and DBP by age and race or ethnicity for men and women over 18 years of age in the U.S. population. Data from NHANES III, 1988–1991.

Source: Burt VL, et al. Prevelance of hypertension in the U.S. adult population. Results from the Third National Health and Nutrition Examination Survey, 1988–1991. Hypertension *1995;25(3):305–13.*

antihypertensive therapy in older individuals with SBP of 140–159 mmHg, and most primary care physicians did not pursue control to <140 mmHg.[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 United States population becomes older, the toll of uncontrolled SBP will cause increased rates of CVDs and renal diseases.

Figure 14. Difference in coronary heart disease prediction between systolic and diastolic blood pressure as a function of age



DBP, diastolic blood pressure; SBP, systolic blood pressure

The strength of the relationship as a function of age is indicated by an increase in the ß coefficient. Difference in ß coefficients (from Cox proportional-hazards regression) between SBP and DBP is plotted as a function of age, obtaining this regression line: ß(SBP) – ß(DBP) = 1.4948 + 0.0290 x age (P=0.008). A ß coefficient level <0.0 indicates a stronger effect of DBP on CHD risk, while levels >0.0 suggest a greater importance of systolic pressure.

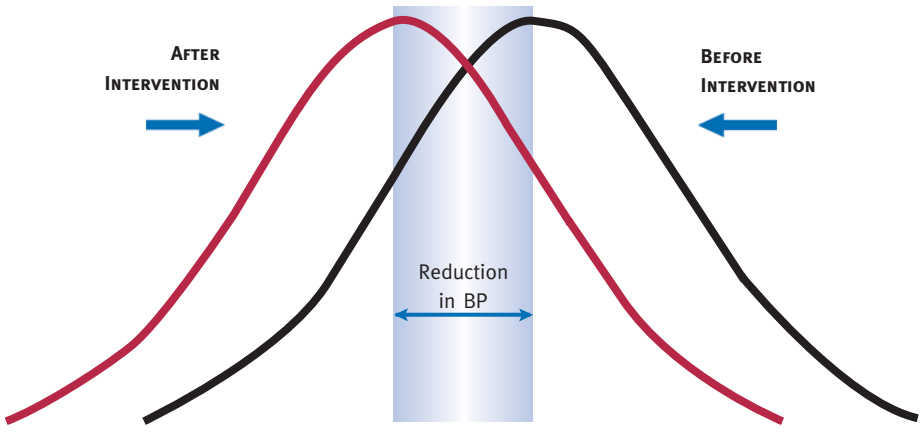
Source: Franklin SS, et al. Does the relation of blood pressure to coronary heart disease risk change with aging? The Framingham Heart Study. Circulation *2001;103:1245–9.*

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 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. At least 122 million Americans are overweight or obese.[33] Mean sodium intake is approximately 4,100 mg per day for men and 2,750 mg per day for women, 75 percent of which comes from processed foods.[34,35] Fewer than 20 percent of Americans engage in regular physical activity,[36] and fewer than 25 percent consume five 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, which complements the hypertension treatment strategy, is warranted. 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 mmHg reduction of SBP in the population would result in a 14 percent overall reduction in mortality due to stroke, a 9 percent reduction in mortality due to CHD, and a 7 percent decrease in all-cause mortality (figure 15).[10,38]

Figure 15. Systolic blood pressure distributions



Reduction in SBP mmHg	% Reduction in Mortality		
	Stroke	CHD	Total
2	-6	-4	-3
3	-8	-5	-4
5	-14	-9	-7

BP, blood pressure; CHD, coronary heart disease; SBP, systolic blood pressure

Source: Whelton PK, et al. Primary prevention of hypertension: Clinical and public health advisory from The National High Blood Pressure Education Program. JAMA *2002;288:1882–8.*

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 percent over the next decade is the type of approach which, 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 exam table), with feet on the floor, and arm supported at heart level. Caffeine, exercise, and smoking 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 upon standing. An appropriately sized cuff (cuff bladder encircling at least 80 percent 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 20–30 mmHg above this level for the auscultatory determinations; the cuff deflation rate for auscultatory readings should be 2 mmHg 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.

Followup of patients with various stages of hypertension is recommended as shown in table 4.

Table 4. Recommendations for followup based on initial blood pressure measurements for adults without acute end organ damage

Initial Blood Pressure (mmHg)*	Followup 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 (e.g., >180/110 mmHg), 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 followup (e.g., 160/86 mmHg should be evaluated or referred to source of care within 1 month).*

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

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

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 20–35 percent of patients diagnosed with hypertension.[61]

Ambulatory BP values are usually lower than clinic readings. Awake hypertensive individuals have an average BP of >135/85 mmHg, and during sleep, >120/75 mmHg. 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 10–20 percent 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 mmHg were nearly twice as likely to have a cardiovascular event as those with 24-hour mean BPs <135/85 mmHg, 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.

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

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 ABPM. For those whose out-of-office BPs are consistently <130/80 mmHg 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 ABPM may be particularly helpful in assessing BP in smokers. Smoking raises BP acutely, and the level returns to baseline about 15 minutes after stopping.

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; an examination of the optic fundi; a calculation of body mass index (BMI) (measurement of waist circumference is also very useful); an auscultation for carotid, abdominal, and femoral bruits; a palpation of the thyroid gland; a thorough examination of the heart and lungs; an examination of the abdomen for enlarged kidneys, masses, distended urinary bladder, and abnormal aortic pulsation; a palpation of the lower 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 cardiovascular event than the risk associated with lower heart rate levels.[64] Moreover, reduced heart-rate variability was also associated with an increase in cardiovascular mortality.[65]

No clinical trials have prospectively evaluated the impact of reduced heart rate on cardiovascular outcomes.

Table 6. Cardiovascular risk factors

Major Risk Factors
Hypertension*
Age (older than 55 years for men, 65 years for women)†
Diabetes mellitus*
Elevated LDL (or total) cholesterol, or low HDL cholesterol*
Estimated GFR <60 mL/min
Family history of premature CVD (men <55 years of age or women <65 years of age)
Microalbuminuria
Obesity* (BMI ≥30 kg/m^2)
Physical inactivity
Tobacco usage, particularly cigarettes
Target Organ Damage
Heart
LVH
Angina/prior MI
Prior coronary revascularization
Heart failure
Brain
Stroke or transient ischemic attack
Dementia
CKD
Peripheral arterial disease
Retinopathy

BMI, body mass index; CKD, chronic kidney disease; CVD, cardiovascular disease; GFR, glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LVH, left ventricular hypertrophy; MI, myocardial infarction

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

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

Table 7. Identifiable causes of hypertension

Chronic kidney disease
Coarctation of the aorta
Cushing's 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

Laboratory Tests and Other Diagnostic Procedures

Routine laboratory tests recommended before initiating therapy include a 12-lead electrocardiogram; urinalysis; blood glucose and hematocrit; serum potassium, creatinine (or the corresponding estimated glomerular filtration rate [eGFR]), and calcium;[66] and a lipoprotein profile (after a 9- to 12-hour fast) that includes high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides. Optional tests include measurement of urinary albumin excretion or albumin/creatinine ratio (ACR) except for those with diabetes or kidney disease where annual measurements should be made. More extensive testing for identifiable causes is not generally indicated unless BP control is not achieved or the clinical and routine laboratory evaluation strongly suggests an identifiable secondary cause (i.e., vascular bruits, symptoms of catecholamine excess, or unprovoked hypokalemia). (See 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 a LDL value within the range associated with low cardiovascular risk, who also had an elevated HS-CRP value, had a higher cardiovascular event rate as compared to those with low CRP and high LDL cholesterol.[73] Other studies also have shown that elevated CRP is associated with a higher cardiovascular event rate, especially in women.[74] Elevations in homocysteine have also been linked higher cardiovascular risk; however, the results with this marker are not as robust as those with high HS-CRP.[75,76]

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; and truncal obesity, glucose intolerance, and purple striae suggest Cushing's 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 age 30, 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

Table 8. Screening tests for identifiable hypertension

Diagnosis	Diagnostic Test
Chronic kidney disease	Estimated GFR
Coarctation of the aorta	CT angiography
Cushing's 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

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

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, noninvasive 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 recommend 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, 11beta-hydroxylase and 17alpha-hydroxylase deficiencies, Liddle's 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 (e.g., angiotensinogen, alpha-adducin, beta- and DA-adrenergic receptors, and beta-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.

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 mmHg and DBP <90 mmHg), though improved, are still far below the Healthy People goal of 50 percent, which was originally set as the year 2000 goal and has since been extended to 2010 (see 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 two 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 of age, 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 mmHg is associated with a decrease in CVD complications.[87] In patients with hypertension and diabetes or renal disease, the BP goal is <130/80 mmHg.[88,89]

Benefits of Lowering Blood Pressure

In clinical trials, antihypertensive therapy has been associated with reductions in (1) stroke incidence, averaging 35–40 percent; (2) myocardial infarction (MI), averaging 20–25 percent; and (3) HF, averaging >50 percent.[90] It is estimated that in patients with stage 1 hypertension (SBP 140–159 mmHg and/or DBP 90–99 mmHg) and additional cardiovascular risk factors, achieving a sustained 12 mmHg 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 nine patients would require such BP reduction to prevent one 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 (see 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 1,600 mg sodium DASH eating plan has BP effects similar to single drug therapy.[94] Combinations of two (or more) lifestyle modifications can achieve even better results.[100] For overall cardiovascular risk reduction, patients should be strongly counseled to quit smoking.

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/m²).	5–20 mmHg/10kg[92,93]
Adopt DASH eating plan	Consume a diet rich in fruits, vegetables, and lowfat dairy products with a reduced content of saturated and total fat.	8–14 mmHg[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 mmHg[94-96]
Physical activity	Engage in regular aerobic physical activity such as brisk walking (at least 30 min per day, most days of the week).	4–9 mmHg[97-98]
Moderation of alcohol consumption	Limit consumption to no more than 2 drinks (e.g., 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 mmHg[99]

DASH, Dietary Approaches to Stop Hypertension; SBP, systolic blood pressure

* *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.*

Pharmacologic Treatment

A large number of drugs are currently available for reducing BP. Tables 10 and 11 provide a list of the commonly used 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 percent of those whose BP was controlled to <140/90 mmHg received two or more agents, and only 30 percent overall were controlled on one drug.[28] In hypertensive patients with lower BP goals or with substantially elevated BP, three 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, beta 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) showed significant reductions in stroke and all CVD with the dihydropyridine CCB, nitrendipine, as compared with placebo.[113] The Heart Outcomes Prevention Evaluation (HOPE) Study, 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) study 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 alpha-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 percent 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 yet comparing an ARB with a diuretic. All of these trials 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.

Table 10. Oral antihypertensive drugs*

Class	Drug (Trade Name)	Usual Dose Range in mg/Day	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
	spironolactone (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 (Levatol)	10–40	1
	pindolol (generic)	10–40	2

Table 10. Oral antihypertensive drugs* (continued)

Class	Drug (Trade Name)	Usual Dose Range in mg/Day	Usual Daily Frequency*
Combined alpha- 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
CCBs—nondihydropyridines	diltiazem extended release (Cardizem CD, Dilacor XR, Tiazac†)	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
Alpha-1 blockers	doxazosin (Cardura)	1–16	1
	prazosin (Minipress†)	2–20	2–3
	terazosin (Hytrin)	1–20	1–2
Central alpha-2 agonists and other centrally acting drugs	clonidine (Catapres†)	0.1–0.8	2
	clonidine patch (Catapres-TTS)	0.1–0.3	1 wkly
	methyldopa (Aldomet†)	250–1,000	2
	reserpine (generic)	0.1–0.25	1
	guanfacine (Tenex†)	0.5–2	1
Direct vasodilators	hydralazine (Apresoline†)	25–100	2
	minoxidil (Loniten†)	2.5–80	1–2

ACEIs, angiotensin converting enzyme inhibitors; BBs, beta blockers; CCBs, calcium channel blockers

* *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 becoming available soon in generic preparations.*

Source: Physician's Desk Reference. *57th ed. Montvale, NJ: Thompson PDR, 2003.*

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
	Spironolactone-hydrochlorothiazide (25/25, 50/50)	Aldactazide
	Triamterene-hydrochlorothiazide (37.5/25, 75/50)	Dyazide, Maxzide

** ACEIs, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers; BBs, beta blockers; CCBs, calcium channel blockers*

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

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 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 African Americans who also had less BP lowering with lisinopril than diuretics. The incidence of HF was greater in CCB-treated and ACEI-treated individuals as compared with those receiving the diuretic in both African Americans 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 6,000 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 25–50 mg of hydrochlorothiazide or 12.5–25 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, and 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/day 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 VA Cooperative study did not document a significant difference in the occurrence of sexual dysfunction using diuretics when compared with other antihypertensive medications[103] (see section on erectile dysfunction). Adverse metabolic effects may occur with diuretics. In ALLHAT, diabetes incidence after 4 years of therapy was 11.8 percent with chlorthalidone therapy, 9.6 percent with amlodipine, and 8.1 percent with lisinopril. However, those differences did not translate to fewer cardiovascular events for the ACEI or CCB groups.[109] Those who were already diabetic had fewer cardiovascular events in the diuretic group than with ACEI treatment. Trials of longer than 1 year's 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 3.5mmol/L.[126] However, other studies 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 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.

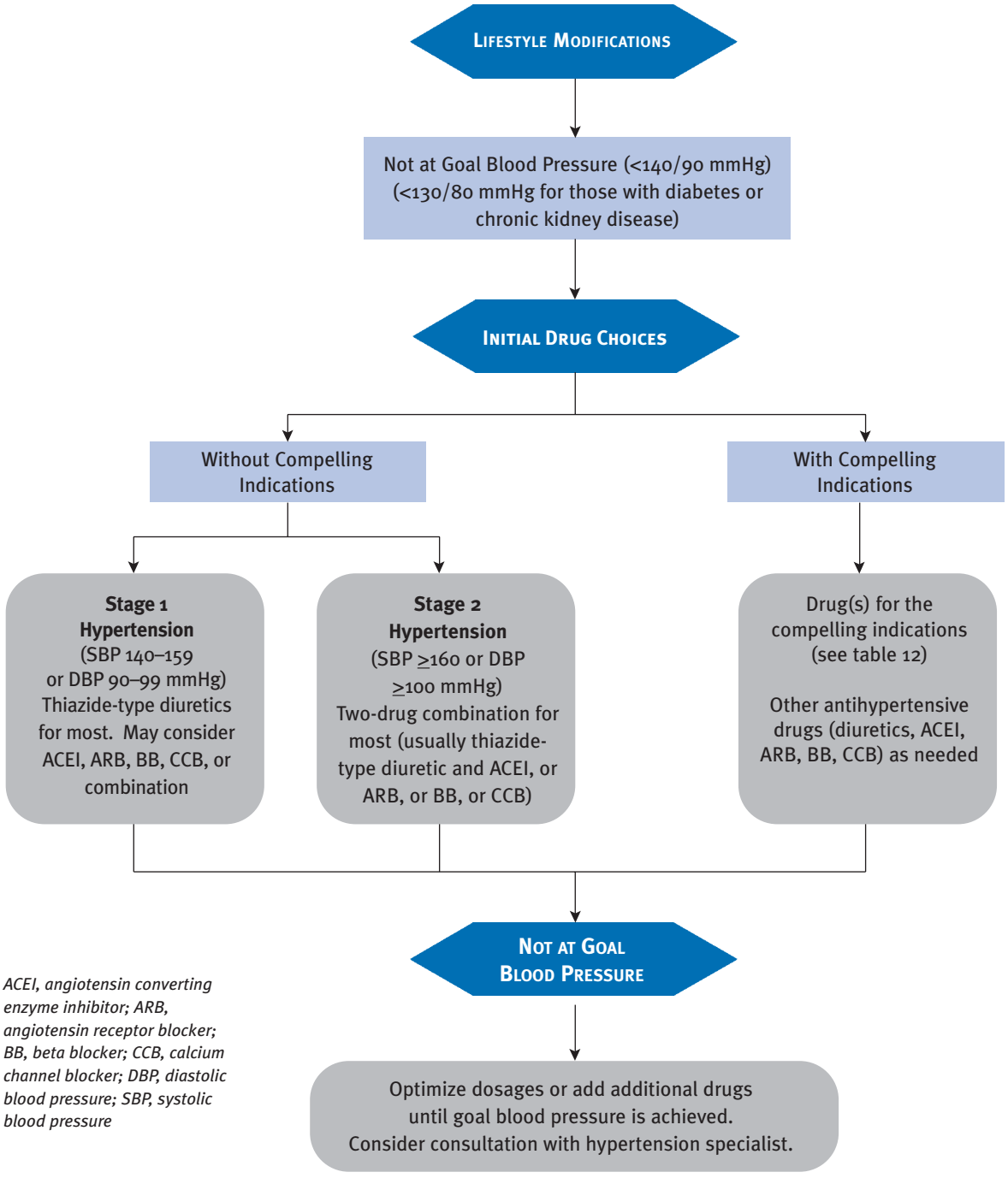
Since most hypertensive patients will require two or more antihypertensive medications to achieve their BP goals, addition of a second drug from a different class should be initiated when use of a single agent in adequate doses fails to achieve the goal. When BP is >20 mmHg above systolic goal or 10 mmHg above diastolic goal, consideration should be given to initiate therapy with two drugs, either as

separate prescriptions or in fixed-dose combinations.[129] (See figure 16.)

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 produce 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 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

Figure 16. Algorithm for treatment of hypertension



ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta blocker; CCB, calcium channel blocker; DBP, diastolic blood pressure; SBP, systolic blood pressure

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.

Followup and Monitoring

Once antihypertensive drug therapy is initiated, most patients should return for followup and adjustment of medications at monthly intervals or 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 one to two times per year. After BP is at goal and stable, followup 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]

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, IHD, chronic kidney disease, recurrent stroke) or commonly associated with hypertension (diabetes,

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]
Postmyocardial infarction		●	●			●	ACC/AHA Post-MI Guideline,[142] BHAT,[143] SAVE,[144] Capricorn,[145] EPHESUS[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]

AASK, African American Study of Kidney Disease and Hypertension; ACC/AHA, American College of Cardiology/American Heart Association; ACEI, angiotensin converting enzyme inhibitor; AIRE, Acute Infarction Ramipril Efficacy; Aldo ANT, aldosterone antagonist; ALLHAT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ANBP2, Second Australian National Blood Pressure Study; ARB, angiotensin receptor blocker; BB, beta blocker; BHAT, β-Blocker Heart Attack Trial; Capricorn, Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction; CCB, calcium channel blocker; CHARM, Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity; CIBIS, Cardiac Insufficiency Bisoprolol Study; CONVINCE, Controlled Onset Verapamil Investigation of Cardiovascular End Points; COPERNICUS, Carvedilol Prospective Randomized Cumulative Survival Study; EPHESUS, Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study; EUROPA, European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease; HOPE, Heart Outcomes Prevention Evaluation Study; IDNT, Irbesartan Diabetic Nephropathy Trial; INVEST, The International Verapamil-Trandolapril Study; LIFE, Losartan Intervention for Endpoint Reduction in Hypertension Study; MERIT-HF, Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure; NKF-ADA, National Kidney Foundation-American Diabetes Association; PROGRESS, Peridopril Protection against Recurrent Stroke Study; RALES, Randomized Aldactone Evaluation Study; REIN, Ramipril Efficacy in Nephropathy Study; RENAAL, Reduction of Endpoints in Non-Insulin Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan Study; SAVE, Survival and Ventricular Enlargement Study; SOLVD, Studies of Left Ventricular Dysfunction; TRACE, Trandolapril Cardiac Evaluation Study; UKPDS, United Kingdom Prospective Diabetes Study; ValHEFT, Valsartan Heart Failure Trial

* *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 the benefit of specific classes of antihypertensive drugs used as part of an antihypertensive regimen to achieve BP goal to test outcomes.*

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), 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 MI or other major coronary events and may be at higher risk of death following an acute MI. Myocardial oxygen supply in hypertensive individuals 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 mmHg 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, pharmacologic 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 airways 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 post-stenotic coronary perfusion. Nondihydropyridine CCBs also can decrease heart rate; when in combination with a BB however, 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 fifty percent 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 left ventricular dysfunction, but such activation may lead to abnormal ventricular

remodeling, further left ventricular enlargement, and reduced cardiac contractility. The inexorable progression to more severe stages of left ventricular dysfunction can be significantly reduced by effective therapy with ACEIs, BBs, and diuretics.

Hypertension precedes the development of HF in approximately 90 percent of patients and increases risk for HF by two- to threefold. Hypertension is especially important in HF affecting African American and elderly persons. 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 over the past 50 years.[158] However, HF hospitalization rates have more than doubled in the past 20 years[159] 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 guidelines are available to manage HF.[132] In the stage A group (New York Heart Association [NYHA] class I), for those at high risk for HF but with no demonstrable clinical symptoms or left ventricular dysfunction, treatment should include fastidious risk-factor management to control BP, hypercholesterolemia, and hyperglycemia. ACEIs may be appropriate due to 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), defined by the presence of reduced left ventricular function (ejection fraction [EF] ≤40 percent) in otherwise asymptomatic individuals, ACEIs and BBs are recommended. Stage C HF patients (NYHA class II–III) manifest left ventricular dysfunction and overt symptoms; 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 HF (NYHA class IV) 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 ACEI. 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 left ventricular dysfunction, usually late stage C (NYHA class III–IV). In the Radomized Aldactone Evaluation Study (RALES), low dose spironolactone (12.5–25 mg daily), when added to standard therapy, decreased mortality by 34 percent.[140] In the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS), eplerenone reduced mortality by 15 percent in patients following a recent MI with left ventricular ejection fraction (LVEF) ≤40 percent, 90 percent 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 Cr <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 110–130 mmHg. One trial demonstrated benefits of beta blockade in patients with SBP >85 mmHg,[134] suggesting that very low BPs (e.g., SBP <100 mmHg) may be desirable in some HF patients.

Digoxin continues to be used in HF despite inconsistent clinical results. In the 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 age 20 is 14.4 percent and is the leading cause of blindness, ESRD, and nontraumatic amputations.[161–165] Type 2 diabetes comprises >90 percent of diabetes in the United States and is associated with a 70–80 percent 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 two and a half 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 two 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 mmHg decrease in SBP was associated with average reductions in rates of diabetes-related mortality (15 percent), myocardial infarction (11 percent), and the microvascular complications of retinopathy or nephropathy (13 percent). Randomized controlled trials that have included large diabetic populations including UKPDS, Hypertension Optimal Treatment (HOT) Trial, SHEP, the Syst-EUR,[67] HOPE Study,[110] 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 (30–300 mg/day) is associated with increased CVD risk in diabetics and other high-risk patients.[67,181] Overt albuminuria (>300 mg/day or >200 mg/g creatinine on spot urine) or renal insufficiency (estimated GFR <60 mL/min, corresponding to serum creatinine >1.5 mg/dL 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 125–130 mmHg SBP and 70–75 mmHg 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 mmHg or lower (although available data are somewhat sparse to justify the low target level of 130/80 mmHg). 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 a 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 class of agent is superior for lowering BP is somewhat moot because the majority of diabetic patients will require two 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 endpoint 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 cardiovascular events compared to 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 older than 55 years of age 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 on to conventional therapy showed a reduction in combined MI, stroke, and CVD death of about 25 percent and a reduction in stroke by about 33 percent compared to 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 beta1-selective agents, are beneficial to diabetics as part of multidrug therapy, but their value as monotherapy is less clear. A BB is indicated in a diabetic with IHD 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.

CCBs may be useful to diabetics, particularly as part of combination therapy to control BP. They were shown to reduce CVD events in diabetics compared to 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) Trial 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 ABCD2 Trial, 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 1–2 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 4–8 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 diseases.

CKD is defined as either: (1) reduced excretory function with an eGFR <60 mL/min/1.73 m^2 (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 albumin/creatinine ratio (ACR) determined. Microalbuminuria is present when the spot urine ACR is between 30–200 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 an independent risk factor for CVD. Individuals with eGFR <60 mL/min have an approximate 16 percent increase in CVD mortality, and individuals with eGFR <30 mL/min have a 30 percent increase.[190] CVD risk also exhibits a continuous relationship with albuminuria; the presence of microalbuminuria confers a 50 percent increase in risk and the presence of macroalbuminuria, a 350 percent increase.[191]

Therapy. NHANES III data indicated that about 3 percent of adults (5.6 million people) in the United States had elevated serum creatinine values, and 70 percent of these people had hypertension.[192] While 75 percent of individuals received treatment, only 11 percent with hypertension and elevated serum creatinine had BPs <130/85 mmHg,

and only 27 percent had BPs <140/90 mmHg.[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 mmHg. A meta-analysis of individuals with CKD and albuminuria found that positive predictors of outcome were lower SBP levels (110–129 mmHg), lower albumin excretion ratio (AER) (<1.0 g/day), and the presence of ACEI therapy.[194,195] However, in the African American Study of Kidney Disease and Hypertension (AASK) study of African Americans with hypertensive CKD, those achieving a mean BP of 128/78 mmHg experienced renal deterioration at the same rate as those achieving a mean of 141/85 mmHg.[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 provide useful guidelines for management of hypertensive patients with CKD. They recommend a goal BP for all CKD patients of <130/80 mmHg and the need for more than one 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 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 been 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 percent 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 percent reduction in stroke occurence.[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 mmHg lower than in the control group.

The management of BP during an acute stroke remains controversial. BP is often elevated in the immediate poststroke period and is thought by some to be a compensatory physiologic 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 upon 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 mmHg or DBP 120–140 mmHg, cautious reduction of BP by about 10–15 percent is suggested, while carefully monitoring the patient for neurologic deterioration related to the lower pressure. If the DBP is >140 mmHg, carefully monitored infusion of sodium nitroprusside should be used to reduce the BP by 10–15 percent.[198]

BP control affects the use of thrombolytic agents in ischemic stroke. SBP >185 mmHg or diastolic pressures >110 mmHg are contraindications to the use of tissue plasminogen activator (tPA) 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 ≥180 mmHg or DBP ≥105 mmHg 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 U.S. 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 etiology 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 minorities' traditional diets may be very high.[205] The low-sodium DASH eating plan was associated with greater reductions in BP in African Americans than in 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, ACEI was less effective in lowering blood pressure than either the thiazide-type diuretic or the CCB. This was associated with a 40 percent greater risk of stroke, 32 percent greater risk of HF, and 19 percent 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 the incidence of antihypertensive drug side effects may occur; African Americans and Asians have a three- to fourfold higher risk of angioedema[109,209,210] and have more cough attributed to ACEIs than Caucasians.[211]

Several other benefits of treatment have been demonstrated in minority populations. A 28 percent reduction in mortality was observed in African Americans who received BB therapy after acute MI compared to 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 to a 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, in minority groups the use of combination or multiple antihypertensive drug therapy that usually includes a thiazide-type diuretic will lower BP and reduce the burden of hypertension-related CVD 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 2001[21] is the presence of three or more of the five 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-cholesterol 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]

Table 13. Clinical criteria defining the metabolic syndrome in Adult Treatment Panel III

- Waist circumference:
  >102 cm (>40 inches) for men
  >88 cm (>35 inches) for women
- Blood pressure:
  ≥130 mmHg systolic and/or
  ≥85 mmHg 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

HDL, high-density lipoprotein

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;285:2486–97.*

Prevalence

When the ATP III criteria were applied to the data from the NHANES III survey (1988–1994), the prevalence of the metabolic syndrome in adults in the United States was estimated at 23.7 percent or about 47 million individuals.[221] BMI, kg/m^2 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 of 25–29.9 kg/m^2 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.

Table 14. Estimated prevalence of the metabolic syndrome using the Adult Treatment Panel III definition among normal weight, overweight, and obese men and women in the National Health and Nutrition Examination Survey III

Category	BMI, kg/m^2	Metabolic Syndrome Prevalence, Percent	
		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%

BMI, body mass index

Source: Park YW, et al. The metabolic syndrome: Prevalance and associated risk factor findings in the US population from The Third National Health and Nutrition Examination Survey, 1988–1994. Arch Intern Med *2003;163:427–36.*

Age Trends

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

Clinical Impact

The metabolic syndrome is associated in men with a fourfold increase in risk for fatal CHD, and a twofold greater risk of CVD and all-cause mortality, even after adjustment for age, LDL-cholesterol, 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 five- to nine-fold increased risk of developing diabetes.[225,226]

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 Prevention and Lifestyle Modification 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 mmHg, pharmacological therapy is indicated as described in the hypertension treatment algorithm (figure 16).

Lipids. Elevated triglycerides 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 percent in high-risk individuals.[229] Management guidelines published by the ADA are appropriate for individuals with impaired fasting glucose and diabetes.[230]

Lipids

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

Overweight and Obesity

Prevalence and epidemiology. Using the NHANES databases for the periods 1988–1994 vs. 1999–2000, the age-adjusted prevalence of obesity (BMI ≥30 kg/m^2) among U.S. adults increased from 22.9 percent to 30.5 percent,[33] while the prevalence of overweight (BMI ≥25 kg/m^2) increased from 55.9 percent to 64.5 percent. 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 Caucasians in the United States. These demographic differences extend to children, where obesity and related health problems are increasing at nearly double the rate in ethnic minorities compared to Caucasians.[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 encouraged.

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 body mass index

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

BMI, body mass index; CVA, cerebrovascular accident

Source: Field AE, et al. Impact of overweight on the risk of developing common chronic diseases during a 10-year period. Arch Intern Med *2001;161:1581–6.*

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 the 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 plan[94] 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 lbs or greater was associated with reductions in cardiovascular risk of about 40 percent.[235] A 10 percent 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; 60–90 minutes per week of walking can reduce CHD mortality by about 50 percent.[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 percent.[237] Although aerobic fitness may negate much of the cardiovascular risk associated with obesity,[238] studies report that individuals who are obese have much lower levels of physical activity and poorer aerobic fitness than leaner individuals.[239]

Table 16. Lifestyle changes beneficial in reducing weight*

- Decrease time in sedentary behaviors such as watching television, playing video games, or spending time online.
- Increase physical activity such as walking, biking, aerobic dancing, tennis, soccer, basketball, etc.
- Decrease portion sizes for meals and 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—The Evidence Report. *National Institutes of Health.* Obes Res *1998;6(suppl)2:51S–209S.*

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 a 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, 30–50 percent of individuals with stages 1 and 2 hypertension have impaired left ventricular relaxation, and in more severe forms of hypertension, about two-thirds have abnormal left ventricular 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 left ventricular mass reduction during treatment were higher pretreatment left ventricular mass, greater fall in SBP or DBP, and longer duration of treatment. The most consistent reduction in left ventricular 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 left ventricular mass reduction.[245,246] The LIFE study found that LVH, defined by ECG, 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 PAD 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, alpha-adrenergic blockers, and direct vasodilators do not improve walking distance or symptoms of claudication.[247–249] This lack of efficacy may be due to: (1) inability of maximally dilated diseased vessels to dilate further during exercise; (2) 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 (3) 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, heart failure, and death.[253] A structured walking program has been shown to increase the pain-free and maximum walking distance in patients with intermittent claudication.[254] Smoking cessation may be the single most important factor 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.

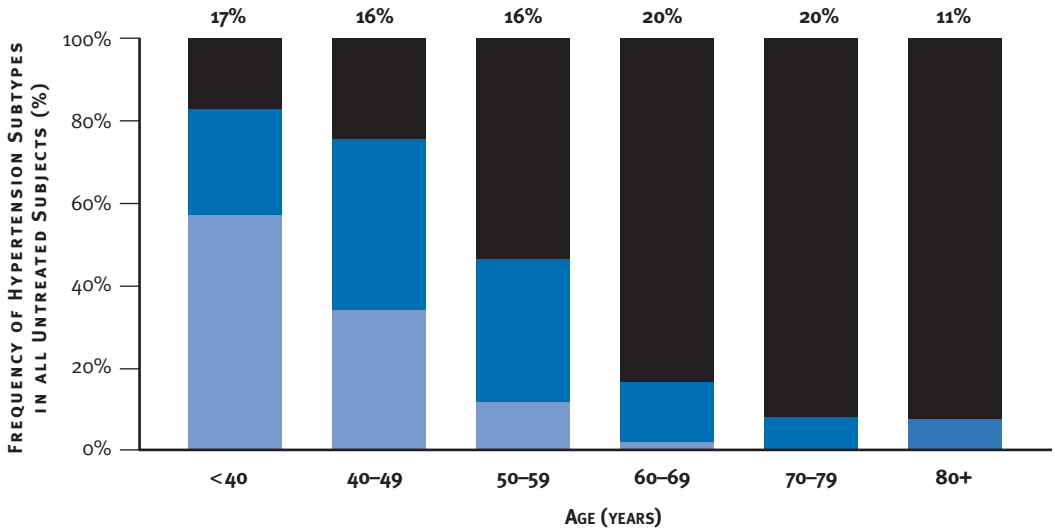
Table 17. Medical therapies of peripheral arterial disease

- Stop smoking.
- Achieve ideal body weight.
- Engage in structured exercise program.
- Achieve goal blood pressure.
- Control lipids (goal: low-density lipoprotein <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.

Hypertension in Older People

The number of Americans 65 years of age 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 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; by age 75, almost all hypertensive

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 mmHg and DBP <90 mmHg);* ■ *SDH (SBP ≥140 mmHg and DBP ≥90 mmHg);* ■ *IDH (SBP <140 mmHg and DBP ≥90 mmHg).*

Source: Franklin SS, et al. Predominance of isolated systolic hypertension among middle-aged and elderly US hypertensives. Analysis based on National Health and Nutrition Examination Survey (NHANES III). Hypertension *2001;37:869–74.*

individuals have systolic hypertension and about three-fourths have ISH.

Individuals over age 60 represent the most rapidly growing segment of the U.S. population, and even in those who remain normotensive between 55 and 65 years of age, there remains a lifetime risk of developing hypertension that exceeds 90 percent.[16] At the same time, there is a three- to fourfold increase in CVD risk in older compared to 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 mmHg and diastolic <90 mmHg) are only about 20 percent in older hypertensive individuals, largely due to poor control of SBP.[257]

Treatment benefits. In the SHEP study involving hypertensive individuals over age 60 with pretreatment SBP >160 and DBP <90 mmHg, individuals treated with chlorthalidone (with or without BB) had reductions in the primary endpoint of stroke (36 percent), as well as HF events (54 percent), MI (27 percent), and overall CVD (32 percent)[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 percent) as well as overall CVD events (31 percent).[113] A meta-analysis of eight placebo-controlled trials in 15,693 elderly patients followed for 4 years found that active antihypertensive treatment reduced coronary events (23 percent), strokes (30 percent), cardiovascular deaths (18 percent), and total deaths (13 percent), with the benefit particularly great in those older than 70 years.[258] Benefits of therapy have been demonstrated even in individuals over 80 years of age.[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 Accurate Blood Pressure Measurement in the Office). BP is more variable in older patients, 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 next section), 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 percent of adults over the age of 60, while DBP alone correctly classified 66 percent.[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 endpoint. 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 no randomized prospective clinical trial has conclusively proven the benefits of treatment in individuals with stage 1 systolic hypertension (140–159 mmHg), 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 mmHg by treatment.[155]

Treatment. Weight loss and reduced sodium intake are particularly beneficial in older people. In the Trial of Nonpharmacologic Interventions in the Elderly (TONE), reducing sodium to 80 mmol (2 grams) per day reduced BP over 30 months, and about 40 percent 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 to remain as physically active as is 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 (OH). 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 OH. Normally, standing is accompanied by a small increase in DBP and a small decrease in SBP when compared to supine values. OH is present when there is a supine-to-standing BP decrease >20 mmHg systolic or >10 mmHg diastolic. There is more OH in diabetic individuals. OH occurred in about 7 percent of men over 70 years of age in the Honolulu Heart Study, was highly age-dependent, and carried with it a 64 percent 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 incidents of falls and fractures.[265-267] The causes of OH include severe volume depletion, baroreflex dysfunction, autonomic insufficiency, and certain venodilator antihypertensive drugs, especially alpha blockers and alpha-beta 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 age 50. 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 three-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 Accurate Blood Pressure Measurement in the Office). 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" hypertension 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 (see prior sections).

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 medication doses. Causes and approaches to nonadherence are discussed in subsequent sections.

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, 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 nontraditional 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 the next logical 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.

Table 18. Causes of resistant hypertension

Improper Blood Pressure 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 (e.g., ephedra, ma huang, bitter orange)

Associated conditions

- Obesity
- Excess alcohol intake

Identifiable causes of hypertension (see table 7).

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. Magnetic resonance imaging (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]

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 135–150 mmHg and DBP 70–79 mmHg 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 >75 percent of women older than 75 years of age.[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 percent of hypertensive Black and White women were aware of their high BP in contrast to 65 percent of hypertensive men in these ethnic groups. Overall, 61 percent of hypertensive women, but only 44 percent of men, were being treated with antihypertensive medications. The higher treatment rates in women have been attributed to increased numbers of physician contact.

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 to premenopausal women until the sixth decade, when the rate of increase tended to slow. Staessen et al. reported that, even after adjustment for age and BMI, postmenopausal women are more than twice as likely to have hypertension as premenopausal women.[296] In a prospective study of conventional and ambulatory BP levels, postmenopausal women had higher SBP (4–5 mmHg) than pre- and perimenopausal controls.[297] The increase in SBP per decade was 5 mmHg 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 mmHg increase in SBP over 5.6 years of followup among 8,506 postmenopausal women randomized to conjugated equine estrogen and medroxyprogesterone acetate as compared to 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 50–79 years of age, current hormone use was associated with a >25 percent likelihood of having hypertension compared to 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 used 24-hour ABPM to evaluate the effects of HRT on BP, while overall results were 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 hyper-

tensive women treated with HRT should have their BP monitored closely at first and then at 6-month intervals.

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 µg estrogen. The Nurses' Health Study found that current users of oral contraceptives had a significantly increased (relative risk [RR]=1.8; 95 percent confidence interval [CI]=1.5–2.3) risk of hypertension compared with those who had never used oral contraceptives.[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 (e.g., 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 to 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 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, women reported twice as many adverse effects as men.[305] Women are more likely to develop diuretic-induced hyponatremia, and men are 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 one of five 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]

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 due to the high morbidity and mortality of this condition if not diagnosed antepartum.

Table 19. Classification of hypertension in pregnancy

Chronic hypertension	■ BP ≥140 mmHg systolic or 90 mmHg diastolic prior to pregnancy or before 20 weeks gestation ■ Persists >12 weeks postpartum
Preeclampsia	■ BP ≥140 mmHg systolic or 90 mmHg diastolic with proteinuria (>300 mg/24 hrs) after 20 weeks gestation ■ Can progress to eclampsia (seizures) ■ More common in nulliparous women, multiple gestation, women with hypertension for ≥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 two- to threefold 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, alanine aminotransferase; AST, aspartate aminotransaminase; BP, blood pressure

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 pharmacologic 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 based on 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 antihypertensive medications while maintaining close observation, including use of home BP monitoring. This approach reflects concern about the safety of antihypertensive drug treatment during pregnancy. A meta-analysis of 45 randomized controlled studies of treatment with several classes of antihypertensive drugs in stages 1 and 2 hypertension during 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 re-instituted once BP reaches 150–160 mmHg systolic or 100–110 mmHg 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 percent 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 followup) 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 percent. Risk factors for superimposed preeclampsia include renal insufficiency, a history of hypertension for 4 years or longer, and hypertension in a previous pregnancy. Prevention of preeclampsia relies on: (1) identification of high-risk women; (2) close clinical and laboratory monitoring aimed at its early recognition; and

Table 20. Treatment of chronic hypertension in pregnancy

Agent	Comments
Methyldopa	■ Preferred based on long-term followup studies supporting safety
BBs	■ Reports of intrauterine growth retardation (atenolol) ■ Generally safe
Labetalol	■ Increasingly preferred to methyldopa due to 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, angiotensin converting enzyme inhibitors; BBs, beta-blockers

(3) 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 (i.e., 150/100 mmHg) 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 <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, and 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 away, oral methyldopa is preferred due to its safety record. Oral labetalol is an alternative, and other BBs and calcium antagonists are also acceptable based on 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 105–110 mmHg or higher, aiming for levels of 95–105 mmHg.

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. Propanolol and labetalol are preferred if a BB is indicated. ACEIs and ARBs should be avoided, based on 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 (20–50 percent) of subsequent

Table 21. Treatment of acute severe hypertension in preeclampsia

Hydralazine	■ 5 mg iv bolus, then 10 mg every 20–30 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 two 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 blood pressure drop ■ Short-acting nifedipine is not approved by the Food and Drug Administration for managing hypertension
Sodium nitroprusside (rarely, when others fail)	■ 0.25 ug/kg/min to a maximum of 5 ug/kg/min ■ Fetal cyanide poisoning may occur if used for more than 4 hours

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 mmHg 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. As in 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 persistant hypertension.

Lifestyle interventions should be recommended for all children with hypertension, with pharmacologic 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 choice of drugs are generally similar in 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 is not 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 (e.g., obesity, lack of physical activity, smoking), and vigorous interventions should be made when these factors are 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]

Table 22. The 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

DBP, diastolic blood pressure; SBP, systolic blood pressure

Source: Adapted from the National High Blood Pressure Education Program. 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. National High Blood Pressure Education Program Working Group on Hypertension Control in Children and Adolescents. Pediatrics *1996;98(pt 1):649–58.*

Hypertensive Crises: Emergencies and Urgencies

Hypertensive emergencies are characterized by severe elevations in BP (>180/120 mmHg) 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 MI, 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 hypertensive individuals, 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 percent of all patient visits to busy urban emergency rooms (ERs).[315]

Patients with hypertensive emergencies 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 percent (within minutes to 1 hour), then if stable, to 160/100–110 mmHg within the next 2–6 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 24–48 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 mmHg if tolerated, and patients in whom BP is lowered to enable the use of thrombolytic agents (see 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 ER 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 reinstitution of medications if noncompliance is a problem. Most importantly, patients should not leave the ER without a confirmed followup visit within several 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 ER. Patients who continue to be noncompliant will often return to the ER 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 age 50 and is even more common if they are hypertensive.[316] In a survey of over 3,000 health professionals, the frequency of ED was 4 percent in men under age 50, 26 percent in those 50–59, and 40 percent in those 60–69.[316] The frequency was significantly higher if they were hypertensive, diabetic, obese, 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

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 µg/kg/min as IV infusion‡	Immediate	1–2 min	Nausea, vomiting, muscle twitching, sweating, thiocynate 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 hrs	Tachycardia, headache, flushing, local phlebitis	Most hypertensive emergencies except acute heart failure; caution with coronary ischemia
Fenoldopam mesylate	0.1–0.3 µg/kg per min IV infusion	<5 min	30 min	Tachycardia, headache, nausea, flushing	Most hypertensive emergencies; caution with glaucoma
Nitroglycerin	5–100 µg/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 hrs IV	15–30 min	6–12 hrs	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 10–40 mg IM	10–20 min IV 20–30 min IM	1–4 hrs IV 4–6 hrs IM	Tachycardia, flushing, headache, vomiting, aggravation of angina	Eclampsia
Adrenergic Inhibitors					
Labetalol hydrochloride	20–80 mg IV bolus every 10 min 0.5–2.0 mg/min IV infusion	5–10 min	3–6 hrs	Vomiting, scalp tingling, bronchoconstriction, dizziness, nausea, heart block, orthostatic hypotension	Most hypertensive emergencies except acute heart failure
Esmolol hydrochloride	250–500 µg/kg/min IV bolus, then 50–100 µg/kg/min by infusion; may repeat bolus after 5 min or increase infusion to 300 µg/min	1–2 min	10–30 min	Hypotension, nausea, asthma, first degree heart block, heart failure	Aortic dissection, perioperative
Phentolamine	5–15 mg IV bolus	1–2 min	10–30 min	Tachycardia, flushing, headache	Catecholamine excess

h or hr, hour; IM, intramuscular; IV, intravenous; min, minute(s)

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

† *Hypotension may occur with all agents*

‡ *Require special delivery system*

regarding individual effects of antihypertensive drug therapy are confounded by age, vascular disease, and hormonal status. In the TOHMS 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 on incidence of sexual dysfunction was noted

between a CCB, ACEI, hydrochlorothiazide, or BB compared to placebo.[103] In other studies centrally acting alpha 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 work-up. 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 alpha-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 mmHg 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 particularly benefit from treatment with beta-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 prior section).[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 and is 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 Hypertensive Individuals

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 topic[325] 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 hypertensive individuals 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 2–4 percent of the adult population, and >50 percent 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/m^2.[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 an 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, MI, 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 BP[351] 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 hypertensive individuals 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 affect 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 percent.[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, which are calcineurin inhibitors (cyclosporin 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 decline in GFR 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 mmHg or less. Because of the absence of compelling data, no particular class of antihypertensives can be considered 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 1–2 weeks following initiation or escalation in therapy with ACEIs or ARBs. A >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 radiocontrast-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 hypertensive individuals. Consequently, searching for the presence of these agents in a person's 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 agents that may alter BP. They may affect BP in several ways, such as affecting sodium balance; increasing adrenergic or suppressing parasympathetic neural activity; altering the production, release, or effectiveness of vasoactive hormones; or exerting direct effects on the endothelium or vascular smooth muscle.

Table 24. Common substances associated with hypertension in humans

Prescription Drugs	Street Drugs and Other "Natural Products"
Cortisone and other steroids (both cortico- and mineralo-), ACTH	**Cocaine and cocaine *withdrawal***
Estrogens (usually just oral contraceptive agents with high estrogenic activity)	**Ma Huang, "herbal ecstasy," and other phenyl propanolamine analogues**
Nonsteroidal anti-inflammatory drugs	**Nicotine and *withdrawal***
Phenylpropanolamines and analogues	Anabolic steroids
Cyclosporine and Tacrolimus	Narcotic *withdrawal*
Erythropoietin	Methylphenidate
Sibutramine	Phencyclidine
Ketamine	Ketamine
Desflurane	Ergotamine and other ergot-containing herbal preparations
Carbamazepine	St. John's Wort
Bromocryptine	**Food Substances**
Metoclopramide	**Sodium chloride**
Antidepressants (especially venlafaxine)	**Ethanol**
Buspirone	Licorice
Clonidine, BB combination	Tyramine-containing foods (with MAO-I)
Pheochromocytoma: BB without alpha blocker first; glucagon	**Chemical Elements and Other Industrial Chemicals**
Clozapine	Lead
	Mercury
	Thallium and other heavy metals
	Lithium salts, especially the chloride

ACTH, adrenocorticotropic hormone; BB, beta blocker

Note: Bold-faced items within the list represent the substances of more current clinical importance.

Alcohol

Modest consumption of alcohol (e.g., <30 grams 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 normotensive subjects.[10] The use of ABPM has highlighted the biphasic effects of alcohol on BP, underscoring the importance of the timing of BP measurement. A large intake of alcohol (>30 grams) may lower BP in the first 4 hours after ingestion. Approximately 10–15 hours later (perhaps at the time a patient is seen for an office visit or in the ER 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 predominantly to result from sympathetic neural activation, although changes in cortisol and cellular calcium concentrations also may play a role.

Nonaspirin Nonsteroidal Anti-Inflammatory Drugs

Nonaspirin nonsteroidal anti-inflammatory drugs (NANSAIDs) represent one of the most common medication classes consumed by hypertensive patients. Among the NANSAIDs, older agents like Indomethacin are the most extensively studied. BP responses vary within the class of the NANSAIDs; 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 are another mechanism. Cyclooxygenase-2 (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 because diabetic patients are often older and obese, and both obesity and aging predispose to osteoarthritis as well as diabetes.

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 experiences with, and trust in, their clinicians. Better communication improves outcomes; empathy builds trust and is a potent motivator (table 25).[374]

Table 25. Provide empathetic reinforcement

- Adopt an attitude of concern coupled with hope and interest in the patient's future.
- Provide positive feedback for blood pressure and behavioral improvement.
- If blood pressure is not at goal, ask about behaviors to achieve blood pressure 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 blood pressure.

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, such as 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 patients' 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 which 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]

Table 26. Clinician awareness and monitoring

- Anticipate adherence problems for young men.
- Consider nonadherence as a cause of:
  - Failure to reach goal blood pressure
  - 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.

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 personal digital assistant-based) or paper-based (flow charts, algorithms, guidelines). Feedback reminders from any source (computer-based, automated telephone-based, nurse 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]

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 with patients who missed appointments.
- Use an office-based system approach for monitoring and followup (e.g., educate staff to provide patient encouragement, computer or chart reminders, disease management aids).

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.

Table 28. Patient education about treatment

- Assess the patient's understanding and acceptance of the diagnosis of hypertension.
- Discuss patient's concerns, and clarify misunderstandings.
- Tell the patient the blood pressure reading, and provide a written copy.
- Come to agreement with the patient on goal blood pressure.
- Ask the patient to rate from 1 to 10 his or her chance of staying on treatment.
- Inform the 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 blood pressure is elevated by "feeling or symptoms"; blood pressure must be measured.

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 of BBs in patients who have suffered an MI. NCQA now monitors physician records for the percent of patients whose BP is <140/90 mmHg.[381] BP control rates by monitored physicians have increased to as high as 59 percent. Patients should be told their BP on each visit and encouraged not only to ask for those numbers but to also 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 Health Care Professionals

Clinicians must work with other health care professionals (e.g., nurse case managers and other nurses, physician assistants, pharmacists, dentists, registered dietitians, licensed nutritionists, 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 are also helpful through their efforts to screen, identify cases, refer and track followup 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, pharmacologic therapies, and adherence to treatment.

Table 29. Collaborate with other health professionals

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

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.

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; e.g., 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 blood pressure 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.

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 a 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 percent) was health-oriented, informed about hypertension, and took their medication. The second group (16 percent) tended to rely on medication rather than lifestyle to control their BP. The third group (22 percent) had the highest BMI, did not practice health-promoting lifestyles (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 with achieving lifestyle modifications; they will likely require more frequent office visits or contact with nurses or other providers. The patients in the last group (23 percent) were more likely to be male and young, knew less about hypertension, were least afraid of the consequences of hypertension or failure to take their medication, and were most likely to consume alcohol, abuse tobacco, and stop medication without informing their physician. This last group will probably require persistent reinforcement, information on the hazards related to 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).

Table 31. Promote social support systems

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

Goal Setting and Behavioral Change

The clinician and patient must agree upon BP goals and an estimated achievement time, 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 behavioral changes, they progress through a series of stages (precontemplation, contemplation, preparation, action, and maintenance). Behavioral changes are 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 to use a 1–10 ranking to indicate 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. Clinicians must calibrate these devices (see 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 mmHg lower than office BP, and this information should be considered when assessing progress toward the goal. However, office BP should still be used to determine whether a patient is at goal.

Patient satisfaction with 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 (e.g., 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

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 studies; also known as cohort studies, including historical or prospective followup studies

X Cross-sectional surveys; also known as prevalence studies

PR Previous review or position statements

C Clinical interventions (nonrandomized)

These symbols are appended to the citations in the reference list. 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]

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NHLBI Health Information Center
P.O. Box 30105
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