SECTION I

EPIDEMIOLOGY AND PATHOPHYSIOLOGY

CHAPTER 1

Epidemiology of Hypertension

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Systemic arterial hypertension is the condition of persistent, non-physiologic elevation of systemic blood pressure (BP). It is currently defined as a resting systolic BP (SBP) ≥140 mm Hg or diastolic BP (DBP) ≥90 mm Hg, or receiving therapy for the indication of lowering BP.[1] Hypertension afflicts a substantial proportion of the adult population worldwide and a growing number of children. Numerous genetic, environmental, and behavioral factors influence the development of hypertension. In turn, hypertension has been identified as one of the major causal risk factors for cardiovascular disease (CVD); including heart disease, vascular disease and stroke, and renal disease. An understanding of the basic epidemiology of hypertension is essential for effective public health and clinical efforts to detect, treat, and control this common condition.

Epidemiology and Risk Factors

An epidemiologic association between a proposed risk factor and a disease is likely to be causal if it fulfills the following criteria: (1) exposure to the proposed risk factor precedes the onset of disease, (2) there is a strong association between exposure and incidence of disease, (3) the association is dose dependent, (4) exposure is consistently predictive of disease in a variety of populations, (5) the association is independent of other risk factors, and (6) the association is biologically and pathogenetically plausible and is supported by animal experiments and clinical investigation.[2] Further, more definitive support for a causal association between a proposed risk factor and disease may arise from clinical trials in which intervention to modify or abolish the risk factor (by behavioral or therapeutic means) is associated with a decreased incidence of the disease. As discussed below, hypertension fulfills all of these criteria and represents an important target for intervention in reducing the population and individual burden of CVD and renal disease.

Several different measures are used to describe the influence of a risk factor on disease. *Prevalence* describes the proportion of a population or group that is affected with a trait or disease at any one time, and thus represents a cross-sectional measure of exposure. *Incidence* is a measure of the rate of new cases in a population or group within a defined time period. Thus the prevalence is a function of both the incidence of disease as well as the rate at which people with the disease die or are cured. In the case of hypertension, the vast majority of individuals who are diagnosed as having hypertension have it for the remainder of their lives.

The *relative risk* of disease is often reported in epidemiologic studies of risk factors, and it is defined as the ratio of disease incidence among exposed, compared with nonexposed, individuals. As such, relative risk measures the strength of the association between exposure and disease, but it gives no indication of the *absolute risk* of disease. Absolute risk of disease associated with a given exposure is often expressed as the rate of development of new cases of disease per unit of time (or incidence) in exposed individuals. This proportion may be compared with the proportion among unexposed subjects in a variety of ways. The *attributable risk* of a given exposure describes the proportion of the incidence of disease in a population that can be ascribed to the exposure, assuming a causal relationship exists. Attributable risk may be calculated by subtracting the incidence in unexposed individuals from the incidence in exposed individuals. However, this does not take into account other coexisting risk factors. The *population attributable risk percent* takes into account the proportion of individuals in the population who are exposed, as well as the relative risk, and the influence of other risk factors. Therefore attributable risk is a useful concept in determining the public health impact of a given risk factor and in selecting risk factors that should be targeted for prevention programs.[3]

Prevalence and Secular Trends

Data from recent U.S. National Health and Nutrition Examination Surveys (NHANES) from 2005 to 2008 indicate that the prevalence of hypertension among adults 18 years of age and older in the United States was 30.9%, or nearly 1 in 3 adults. In the context of the entire population, over 76 million U.S. adults are estimated to have hypertension.[4,5] Despite significant advances in our understanding of the risk factors, pathogenesis, and sequelae of hypertension, and multiple trials over the past three decades indicating the benefits of antihypertensive therapy, hypertension remains a significant public health problem. Although steady and significant

TABLE 1-1 Trends in Prevalence, Awareness, Treatment and Control of Hypertension in the United States, from the National Health and Nutrition Examination Surveys

	NHANES II 1976-1980 (%)	NHANES III 1988-1991 (%)	NHANES III 1991-1994 (%)	NHANES 1999-2000 (%)	NHANES 2007-2008 (%)
Prevalence	31.8	25.0	24.5	28.7	29.6
Awareness	51	73	68	69	80.6
Treatment	31	55	54	60	73.7
Control to <140/90 mm Hg	10	29	27	30	48.4

NHANES, National Health and Nutrition Examination Survey.

reductions occurred over the last four decades in population levels of BP and prevalence of hypertension in the United States[6,7] as well as many of its sequelae,[8] recent data indicate a slowing or reversal of these favorable trends. For example, between the late 1970s and the early 1990s, the prevalence of hypertension in the United States declined from about 32% to 25%. However, more recent survey data indicate an increase in prevalence between 1988 and 1994 and between 1999 and 2002. The prevalence appears to have been approximately stable during the last decade from 1999 to 2008, however, at approximately 30%.[9] The current pandemic of obesity and aging of the population are likely to increase rates of hypertension substantially over the next decades.

African Americans, and especially African American women, have a prevalence of hypertension that is among the highest in the world. Currently, it is estimated that 38.6% of African American adults have hypertension, compared with 32.3% of non-Hispanic whites and 17.3% of Mexican Americans.[4] Asian Americans and most other ethnic groups tend to have similar BP levels and hypertension prevalence as whites. The prevalence of hypertension increased to a similar extent in all ethnicities during the decade of the 1990s.[7] Prevalence rates are similar between men and women, but they increase dramatically with age, from 7.4% to 35.6% to 69.7% among those aged 18 to 39, 40 to 64, and ≥65 years, respectively.[4]

There have been substantial improvements in awareness, treatment, and control of hypertension over the last several decades, but the number of hypertensive individuals who are aware of their hypertension, are receiving treatment, or are treated and controlled remain far below optimal levels (Table 1-1). Data from NHANES 2007-2008 indicate that approximately 78% of hypertensive individuals were aware of their elevated BP, 73.7% of them were receiving antihypertensive therapy, but only 48.4% had a BP of <140/90 mm Hg—the level considered to be "controlled" or at goal.[9] These data reflect a recent significant increase in treatment and control rates from approximately 30% and 60% to the current levels of treatment and control. Nonetheless, extrapolating these data to the current estimate of 76 million Americans with hypertension,[5] over 39 million hypertensive individuals are unaware of their diagnosis, are aware but untreated, or are treated but uncontrolled (Fig. 1-1). As noted later, data from Europe, where clinical practice guidelines have typically recommended higher BP thresholds before initiation of drug therapy, suggest even lower rates of treatment and control of BP.[10,11]

Rates of awareness, treatment, and control of BP differ by age, sex, and race/ethnicity. After years of relative stagnation, trends in awareness, treatment, and control have shown remarkable progress in the last decade among all age, sex, and race groups.[9] Overall, awareness of elevated BP increased significantly from 69.6% to 80.6% between 1999 and 2008, with women and non-Hispanic African American adults being more likely to be aware, and Mexican Americans being the least likely to be aware, of their hypertension.[9] Currently, women are significantly more likely than men to receive treatment with antihypertensive drug therapy and to be at goal BP (Table 1-2). Compared with non-Hispanic whites, non-Hispanic African Americans have similar overall levels of treatment, but slightly lower rates of control, whereas Mexican Americans have substantially lower levels of treatment and control to BPs <140/90 mm Hg, with only 36.9% of hypertensive Mexican Americans at goal BP.[4]

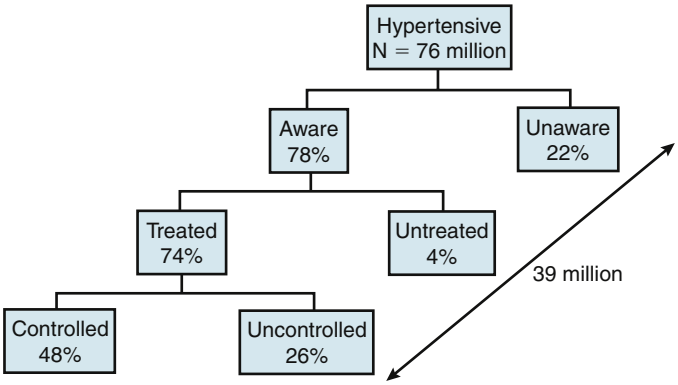

FIGURE 1-1 Number and percentage of Americans who are aware of their hypertension, treated, and controlled to goal levels from the National Health and Nutrition Examination Surveys (NHANES) 2007-2008. *(Data from Roger VL, Go AS, Lloyd-Jones DM, et al. Heart Disease and Stroke Statistics—2011 Update: A report from the American Heart Association.* Circulation. *2011;123:e18-e209; and Yoon S, Otschega Y, Louis T.* Recent Trends in the Prevalence of High Blood Pressure and Its Treatment and Control, 1999-2008. *Hyattsville, MD: National Center for Health Statistics; 2010.)*

TABLE 1-2 Treatment and Control of Hypertension in the United States, 2005-2008, by Sex and Race/Ethnicity

	PREVALENCE OF ANTIHYPERTENSIVE TREATMENT (%)	CONTROL TO <140/90 MM HG (%)
Men	63.8	43.8
Women	75.3*	47.7*
Non-Hispanic white	71.2	47.7
Non-Hispanic African American	71.7	42.7†
Mexican American	56.1†	36.9†

*P <0.01 compared with men.
†P <0.001 compared with non-Hispanic whites.
Data from Gillespie C, Kuklina EV, Briss PA, et al. Vital signs: prevalence, treatment, and control of hypertension: United States, 1999-2002 and 2005-2008. *Morbidity & Mortality Weekly Report.* 2011;60:103-108.

Global Burden of Hypertension

International data indicate that hypertension is even more prevalent in other countries, including developed countries. Whereas the prevalence of hypertension in adults aged 35 to 74 years in Canada in the 1990s was similar to that of the United States (at approximately 28%), concurrent data from six European countries revealed an overall prevalence of 44%. Of the European countries studied, Italy had the lowest prevalence (38%), whereas Germany

had the highest (55%).[12] The increase in BP and in prevalence of hypertension with age was steeper in European countries compared with the United States and Canada. The correlation between hypertension prevalence and stroke mortality rates was very strong (r = 0.78), with a stroke mortality rate of 27.6 per 100,000 in North America and 41.2 per 100,000 in European countries.[12] Furthermore, treatment rates in Europe in the 1990s were substantially lower, in association with higher BP thresholds for treatment in clinical practice guidelines promulgated in Europe and Canada. Among 35- to 64-year-old hypertensives, over half (53%) were treated in the United States, compared with 36% in Canada and 25% to 32% in European countries. The associated differences in levels of BP control were dramatic, with 66%, 49%, and 23% to 38% of U.S., Canadian, and European individuals with hypertension, respectively, controlled to BP levels of <160/95 mm Hg, and 29%, 17%, and ≤10%, respectively, controlled to levels of <140/90 mm Hg.[10]

Whereas data from low- and middle-income countries around the world had been sparse, in recent years the scope and trends in the global burden of hypertension have become clearer. Danaei and colleagues[11] described the current levels and trends in SBP for adults 25 years and older in 199 countries using data from published and unpublished health examination surveys and epidemiologic studies including 5.4 million participants. In 2008, they estimated that the age-standardized mean SBP worldwide was 128.1 mm Hg in men (95% confidence interval [CI], 126.7-129.4 mm Hg) and 124.4 mm Hg in women (123.0-125.9 mm Hg). Systolic BP is currently highest in low- and middle-income countries. In 2008, female SBP was highest in some east- and west-African countries, with means ≥135 mm Hg, whereas male SBP was highest in Baltic and east- and west-African countries, where mean SBP was ≥138 mm Hg. Men and women in western Europe had the highest SBP among high-income regions. Globally, between 1980 and 2008, Danaei and colleagues[11] estimated that SBP decreased by 0.8 mm Hg per decade in men and 1.0 mm Hg per decade in women. However, there were wide variations in this pattern by sex, region, and country. Female SBP decreased by 3.5 mm Hg or more per decade in Western Europe and Australasia. Male SBP fell most in high-income North America, by 2.8 mm Hg per decade, followed by Australasia and Western Europe, where it decreased by more than 2.0 mm Hg per decade. On average, SBP rose in Oceania, East Africa, and southern and Southeast Asia for both sexes, and in West Africa for women, with the increases ranging from 0.8 to 2.7 mm Hg.[11]

Risk Factors for Hypertension

Hypertension is a complex phenotype with multiple genetic and environmental risk factors, as well as important gene–environment interactions. Age, with its concomitant changes in the vasculature and demographic and socio-economic variables, is among the strongest risk factors for hypertension.

Age

The prevalence of hypertension increases sharply with advancing age. Whereas only 11.1% of men and 6.8% of women ages 20 to 34 years are affected, 66.7% of men and 78.5% of women aged 75 years and over have hypertension (Fig. 1-2). Thus, in older patients, hypertension is by far the most prevalent risk factor for CVD. About 81% of hypertensive individuals in the United States are age 45 years and older, although this group comprises only 46% of the U.S. population.[13] With the aging of the population, the overall prevalence of hypertension in the population is sure to increase.

Viewed from another perspective, hypertension already affects more individuals during their lifespan than any other trait or disease studied to date. The concept of the "lifetime risk" of a given disease provides a useful measure of the absolute burden and public health impact of a disease and provides an average risk for an individual during his or her lifetime. Lifetime risk estimates

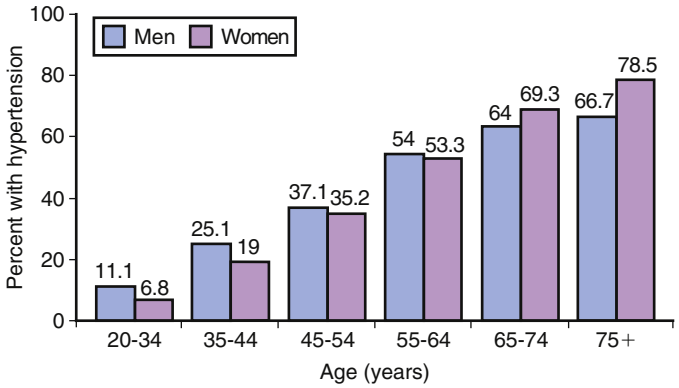

FIGURE 1-2 Prevalence of hypertension among men and women aged 18 years and over, from National Health and Nutrition Examination Surveys 2005-2008. *(Data from Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke statistics—2011 update: a report from the American Heart Association.* Circulation. *2011;123:e18-e209.)*

account for the risk of developing disease during the remaining lifespan and the competing risk of death from other causes before developing the disease of interest. Data from the Framingham Heart Study (FHS), a long-standing study of CVD epidemiology, indicate that, for adults free of hypertension at age 55, the remaining lifetime risks for development of hypertension through age 80 are 93% for men and 91% for women. In other words, more than 9 out of 10 older adults will develop hypertension before they die. Even those who reach age 65 free of hypertension still have a remaining lifetime risk of 90%.[14]

In Western societies, SBP tends to rise monotonically and inexorably with advancing age. Conversely, DBP levels rise until about age 50 to 55 years, after which there is a plateau for several years and then a steady decline to the end of the usual lifespan.[12,15,16] A variety of factors, particularly related to changes in arterial compliance and stiffness,[17,18] contribute to the development of systolic hypertension and to decreasing DBP with age. Both of these phenomena contribute to a marked increase in pulse pressure (PP), defined as SBP minus DBP, after age 50. Thus hypertension, and particularly systolic hypertension, is a nearly universal condition of aging, and few individuals escape its development. Only in societies where salt intake is low, physical activity levels are very high, and obesity is rare are age-related increases in SBP avoided.

Weight

Increasing weight is one of the major determinants of increasing BP. The prevalence of hypertension among obese individuals, with a body mass index (BMI) ≥30 kg/m^2, is 42.5%, compared with 27.8% for overweight individuals (25.0-29.9 kg/m^2), and 15.3% for individuals with BMI <25 kg/m^2.[19] Comparing NHANES 1988-1994 to NHANES 1999-2004, Cutler and associates[20] found an overall increase in the prevalence of hypertension of 13% in men and 24% in women. After adjustment for BMI, there was no statistically significant change in hypertension in men, indicating that the increase in BMI accounted for nearly all of the increase in hypertension in men. For women, after adjustment for BMI, there continued to be large relative increases in the prevalence of hypertension, indicating that some of the increases in hypertension in women were attributable to factors other than their increases in BMI.

Data from FHS also reveal marked increases in risk for development of hypertension with increasing BMI. Compared with normal-weight adult men and women, the multivariable-adjusted relative risks for development of hypertension in long-term follow-up were 1.48 and 1.70 for overweight men and women, and 2.23 and 2.63 for obese men and women, respectively.[21]

Numerous studies have also demonstrated the important role of weight gain in BP elevation and weight reduction in BP lowering.

As discussed previously, SBP and DBP tend to rise with age beginning at around age 25 years in most adults.[15,16] However, recent data indicate that these "age-related" increases in SBP and DBP may be avoided in young adults who maintain stable BMI over long-term follow-up. In the Coronary Artery Risk Development In Young Adults (CARDIA) Study, those who maintained a stable BMI at all six examinations over 15 years had no significant changes in either SBP or DBP, whereas those who had an increase in their BMI of ≥2 kg/m^2 had substantial increases in BP.[22]

The influence of weight gain on BP, as well as the benefits of maintaining stable weight or losing weight, extend down even to young children. One large birth cohort study of children examined BMI at ages 5 and 14 and the association with SBP and DBP at age 14. Children who were overweight at age 5 but had normal BMI at age 14 had similar mean SBP and DBP to those who had a normal BMI at both time points. Conversely, children who were overweight at both ages, or who had a normal BMI at age 5 and were overweight at age 14, had higher SBP and DBP at age 14 than those who had a normal BMI at both ages, even after adjustment for potential confounders.[23]

Other Risk Factors

As discussed previously, gender influences the prevalence of hypertension in an age-dependent fashion. Until about the sixth decade of life, men have a higher prevalence, after which women increasingly predominate (see Fig. 1-2). Overall, more women than men are affected by hypertension, in part because of their longer life expectancy.

Race/ethnicity has also been shown to be a risk factor for hypertension. Whereas non-Hispanic white persons make up about two thirds of the U.S. adult hypertensive population, this is consistent with their representation in the overall population. African Americans are disproportionately affected and have among the highest rates of hypertension in the world, with mean SBP levels approximately 5 mm Hg higher than whites, and prevalence rates at least 10% higher than whites.[5,20] Other racial/ethnic groups in the United States, including Mexican Americans, have prevalences of hypertension that are similar to those of whites.[5,13,15,20] Education status also affects rates of hypertension, with lower education levels being strongly associated with hypertension. However, much of this inverse association of education with BP appears to be explained by differences in diet and in BMI between less-educated and more-educated individuals.[24]

Among dietary influences on BP level, high dietary sodium intake has been related consistently to rates of hypertension in numerous epidemiologic cohorts. Conversely, higher potassium, calcium, and magnesium intakes appear to be associated with lower rates of hypertension in various populations.[25] Patients with omnivorous diets have higher BP levels than those who are vegetarian, but the types of dietary fat do not appear to influence BP levels directly (with the possible exception of mild lowering by omega-3 fatty acids). The evidence linking heavy alcohol intake to hypertension is unequivocal. More than 50 epidemiologic studies have demonstrated an association between intake of three or more drinks per day and hypertension, although regular alcohol intake is associated with a lower risk of atherothrombotic CVD events.

Genetic Factors

Numerous studies have examined potential genetic susceptibilities for hypertension. Data consistently indicate that BP levels are heritable. Using data from the multi-generational FHS cohorts, Levy and associates[26] estimated that heritability for single-examination measures was 0.42 for SBP and 0.39 for DBP. Using data from multiple examinations, long-term SBP and DBP phenotypes had high heritability estimates, at 0.57 and 0.56, respectively.

The availability of high-throughput technology has recently allowed for genome-wide association studies to be performed in large pooled cohorts to assess for linkage between identified areas of the genome and BP levels. A large consortium of studies[27] tested 2.5 million genotyped and imputed single-nucleotide polymorphisms (SNPs) across the genome for association with SBP and DBP levels in 34,433 subjects of European ancestry and followed up findings with direct genotyping in 71,225 participants of European ancestry and 12,889 of Indian Asian ancestry. The investigators also performed in silico comparison in another large consortium (N = 29,136). This group identified associations between SBP or DBP and common variants in eight genomic regions near a number of potential genes of interest: *CYP17A1* ($P = 7 \times 10\text{-}24$), *CYP1A2* ($P = 1 \times 10\text{-}23$), *FGF5* ($P = 1 \times 10\text{-}21$), *SH2B3* ($P = 3 \times 10\text{-}18$), *MTHFR* ($P = 2 \times 10\text{-}13$), *c10orf107* ($P = 1 \times 10\text{-}9$), *ZNF652* ($P = 5 \times 10\text{-}9$), and *PLCD3* ($P = 1 \times 10\text{-}8$) genes. All variants associated with continuous BP were associated with the phenotype of dichotomous hypertension as well. The authors concluded that these associations between common variants and BP and hypertension could offer mechanistic insights into the regulation of BP and may point to novel targets for interventions to prevent CVD.[27]

Similarly, rare inherited genetic syndromes are associated with hypertension, including Liddle syndrome and 11β-hydroxylase and 17α-hydroxylase deficiencies. However, because hypertension is a complex phenotype, and BP levels are determined by the complex interactions of multiple neurologic, renal, endocrine, cardiac, and vascular processes, no single-gene polymorphisms have been discovered that explain more than a small fraction of hypertension alone or jointly in the population at large.

Classification of Blood Pressure

Formal classification of BP stages by consensus panels began to take shape in the early 1970s with the first National Conference on High Blood Pressure Education. The first report of the Joint National Committee (JNC) was published in 1977 and has been followed by six subsequent reports in 1980, 1984, 1988, 1993, 1997, and 2003. The Seventh Report (JNC 7, published in 2003)[1,28] was the clinical standard for the prevention, detection, evaluation, and treatment of hypertension in the United States until recently. JNC 7 recognized several important concepts that have evolved in our understanding of hypertension over the past decades. First, systolic hypertension confers at least as much, and usually greater, risk for adverse events as diastolic hypertension, which was not fully appreciated in the first four JNC reports. Thus the JNC report recommends that for middle-aged and older hypertensives (who represent the vast majority of hypertensives in the population), SBP should be the primary target for staging of BP and initiation of therapy. Second, hypertension rarely occurs in isolation and is usually present in the context of one or more other CVD risk factors. Therefore, in recommending treatment for hypertension, the JNC 7 report recommended some consideration of global risk for CVD.

It has long been recognized that BP confers risk for CVD beginning at levels well within the clinically "normal" range, with risk increasing in a continuous, graded fashion to the highest levels, as discussed in detail later. Thus, although clinical practice guidelines impose certain thresholds for considering individuals to be hypertensive, and for initiation of therapy, this conception is an artificial construct designed to assist clinicians and patients with treatment decisions.

The JNC 7 scheme for classifying BP stages is shown in Table 1-3. From JNC-VI to JNC 7, the committee elected to change the terminology for BP levels below the hypertensive range. Whereas BP <120/80 had previously been termed "optimal," it is now termed "normal." A new category of "prehypertension" was defined, including individuals with SBP of 120 to 139 or DBP of 80 to 89 mm Hg. In addition, the prior classification of stage 3 hypertension was dropped because of its relatively uncommon occurrence, and all individuals with SBP ≥160 or DBP ≥100 mm Hg are now classified as having stage 2 hypertension.[1]

Individuals are classified into their BP stages on the basis of both SBP and DBP levels. When a disparity exists between SBP

TABLE 1-3 Blood Pressure Staging System of the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure

JNC 7 BLOOD PRESSURE STAGE	BLOOD PRESSURE RANGE
Normal	SBP <120 *and* DBP <80 mm Hg
Prehypertension	SBP 120-139 *or* DBP 80-89 mm Hg
Stage 1 hypertension	SBP 140-159 *or* DBP 90-99 mm Hg
Stage 2 hypertension	SBP ≥160 *or* DBP ≥100 mm Hg

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

and DBP stages, patients are classified into the higher stage. Several studies[29-31] have examined this phenomenon of "up-staging" based on disparate SBP and DBP levels. In one study,[29] 3656 FHS participants not receiving therapy for hypertension were examined between 1990 and 1995, and their JNC-VI BP stages were classified on the basis of SBP alone, DBP alone, or both. In this sample, 64.6% of subjects had congruent stages of SBP and DBP, 31.6% were up-staged on the basis of SBP, and 3.8% on the basis of DBP. Thus, among all participants, 96% were correctly classified by knowledge of their SBP alone, whereas only 68% were correctly classified by knowledge of the DBP alone. In subjects under 60 years of age, the numbers were 95% for SBP alone and 81% for DBP alone; for those over age 60, they were 99% for SBP alone and 47% for DBP alone. Of 1488 subjects with high-normal BP or hypertension, who were potentially eligible for drug therapy, 13.0% had congruent elevations of SBP and DBP, 77.7% were up-staged on the basis of SBP, and 9.3% were up-staged on the basis of DBP; the SBP alone correctly classified 91%, whereas the DBP alone correctly classified only 22%. Thus SBP elevation out of proportion to DBP is common in middle-aged and older persons, and SBP appears to play a greater role in the determination of BP stage and eligibility for therapy.[29] Similar results were also observed in data from the NHANES III sample.[31] Among younger individuals, up-staging resulting from DBP is somewhat more common. However, after the age of 50 years, which includes the vast majority of hypertensives, up-staging resulting from SBP clearly occurs for an overwhelming proportion of the population and determines hypertensive status and/or eligibility for therapy.[31]

Isolated systolic hypertension (ISH) in older people reflects progressive large artery stiffening seen with aging. In younger hypertensive patients, isolated diastolic hypertension (SBP <140 and DBP ≥90 mm Hg) and systolic-diastolic hypertension (SBP ≥140 and DBP ≥90 mm Hg) tend to predominate, whereas beyond age 50, ISH (SBP ≥140 and DBP <90 mm Hg) predominates. ISH is the most common form of hypertension over age 60, being present in more than 80% of untreated hypertensive men and women.[31]

These observations, coupled with data on risks of systolic hypertension and the benefits of treating systolic hypertension, prompted the National High Blood Pressure Education Program's Advisory Panel to recommend a major paradigm shift in 2000 in urging that SBP become the major criterion for the diagnosis, staging, and therapeutic management of hypertension, particularly in middle-aged and older Americans.[18] This recommendation was incorporated into the staging system and treatment guidelines for JNC 7.[1,28]

Sequelae and Outcomes with Hypertension

Hypertension is a major risk factor for all forms of atherosclerotic and atherothrombotic CVD. Increasing the BP level generally increases risk in a continuous and graded fashion for total mortality, CVD mortality, coronary heart disease (CHD) mortality, myocardial infarction (MI), heart failure (HF), left ventricular hypertrophy (LVH), atrial fibrillation, stroke/transient ischemic attack, peripheral vascular disease, and renal failure. For many of these endpoints, there is effect modification by gender, with male hypertensives being at higher absolute risk for CVD events than female hypertensives (HF being a notable exception). There is also substantial effect modification by age, with older hypertensives being at similar or higher relative risk, but at much greater absolute risk than younger ones.[32] As discussed later, hypertension rarely occurs in isolation, and it confers increased risk for CVD across the spectrum of overall risk factor burden, but with increasing importance in the setting of other risk factors.[33]

As shown in Figure 1-3, absolute levels of risk for CHD increase substantially with increasing risk factor burden and are augmented still further by elevated BP. Furthermore, the slope of increasing CHD risk is greater with higher BP levels when the burden of other risk factors is greater (see Fig. 1-3). Thus BP levels, and the risk they confer, must always be considered in the context of other risk factors and the patient's global risk for CVD. For example, because the combination of hypertension and diabetes mellitus (DM) is particularly dangerous, JNC 7 recommended lower goal BP levels for patients with DM (<130/80 mm Hg) than for those without DM (<140/90 mm Hg).[1]

Individuals with hypertension have a twofold to threefold increased relative risk for CVD events compared with age-matched normotensives. Hypertension increases relative risks for all manifestations of CVD, but its *relative* impact is greatest for stroke and HF (Fig. 1-4). Because CHD incidence is greater than incidence of stroke and HF, however, the *absolute* impact of hypertension on CHD is greater than for other manifestations of CVD, as demonstrated by the excess risks shown in Figure 1-4.

To illustrate the importance of hypertension as a risk factor, let us consider the case of HF. Between 75% and 91% of individuals who develop HF have antecedent hypertension.[8,34] In the FHS, hypertension conferred a hazard ratio for the development of HF of approximately 2 for men and 3 for women over the ensuing 18 years.[34] As shown in Figure 1-5, the hazard ratios for HF associated with hypertension (2 to 3) were far lower than the hazard ratios for HF associated with MI, which were greater than 6 for both men and women. However, the population prevalence of hypertension was 60%, compared with approximately 6% for MI. Therefore the population-attributable risk (PAR) of HF—in other words, the fraction of HF in this population that resulted from hypertension—was 59% in women and 39% in men. The PARs for MI were 13% and 34% for women and men, respectively.[34]

Investigators from the comprehensive Olmsted County cohort in Minnesota have also estimated PARs for various HF risk factors. In that study, the relative risks for HF were again high for CHD and DM, with odds ratios of 3.05 and 2.65, respectively, whereas the odds ratio associated with hypertension was 1.44. However, hypertension was prevalent in two thirds of the cohort. The PAR was highest for CHD and hypertension; each accounted for 20% of HF cases in the population overall, although CHD accounted for the greatest proportion of cases in men (PAR 23% for CHD vs. 13% for hypertension) and hypertension was of greatest importance in women (PAR 28% for hypertension vs. 6% for CHD).[35]

Importance of Systolic Blood Pressure

For four decades, elevated SBP has been recognized as conferring at least as great risk for CVD—and, in most groups studied, substantially greater risk—as an elevated DBP.[36] However, translation of this knowledge into clinical guidelines and clinical practice has been slow. In numerous studies, increasing SBP has consistently been associated with higher risk for adverse events than increasing DBP, whether these BP variables are considered separately or together, and whether they are treated as linear covariates or in quintiles, deciles, or JNC stages. For example, in the Cardiovascular Health Study of older Americans (Table 1-4), a 1 standard deviation (SD) increment in SBP was associated with higher adjusted risk for CHD and stroke than was

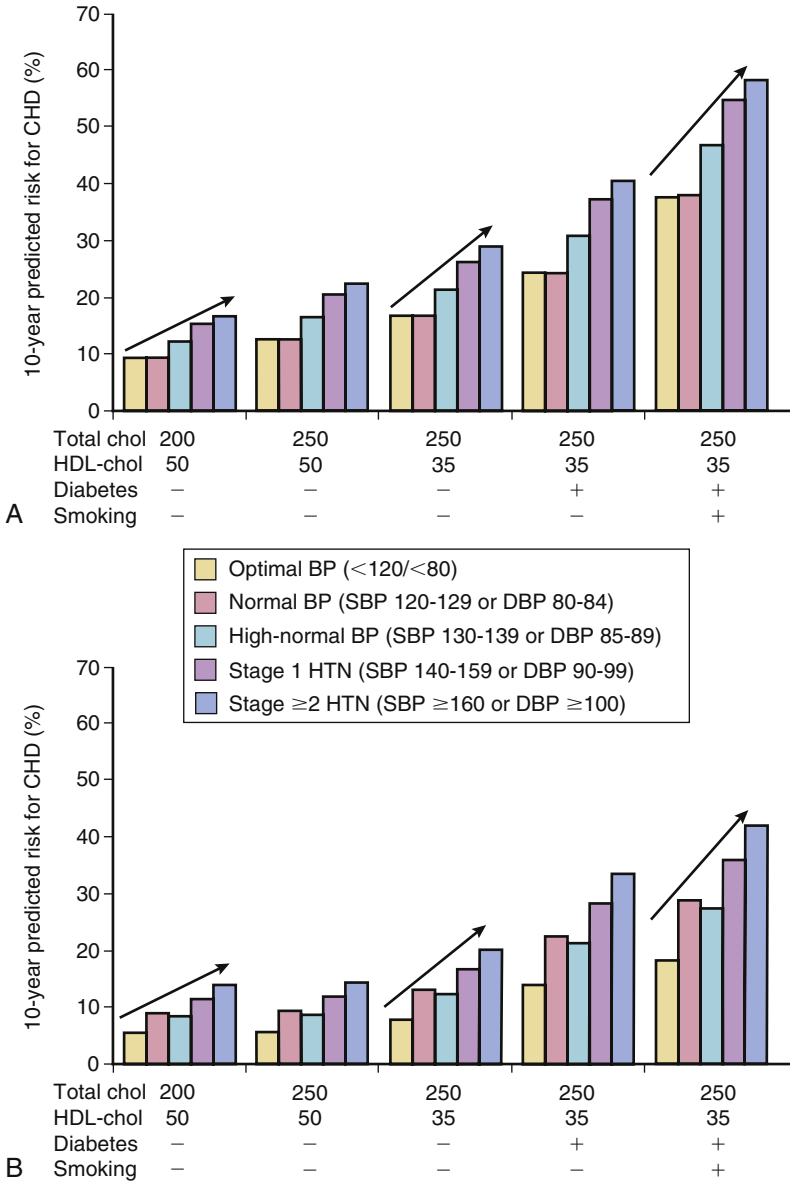

FIGURE 1-3 Predicted Framingham 10-year risk[33] for coronary heart disease (CHD) by increasing burden of risk factors and systolic blood pressure (SBP), in a 60-year-old man (**A**) and woman (**B**). HDL-chol, high-density lipoprotein cholesterol.

a 1 SD increment in DBP (or PP). In models with SBP and DBP together or SBP and PP together, SBP consistently dominated as the greater risk factor.[37] When men who were screened for inclusion in the Multiple Risk Factor Intervention Trial (MRFIT) were stratified into quintiles of SBP or DBP, risks for each SBP quintile were the same or higher than for the corresponding quintile of DBP (Fig. 1-6, *A*).[38] Similar findings were observed when MRFIT screenees were stratified into deciles of SBP and DBP; at every level, SBP was consistently associated with higher risk for CHD mortality than the corresponding decile of DBP (Fig. 1-6, *B*).[39] Finally, when men were stratified by JNC level of SBP and DBP, SBP was associated with greater risk for CHD mortality than DBP in each JNC BP stage.[39]

In fact, when DBP is considered in the context of the SBP level, an inverse association for DBP and CHD risk has been observed. Franklin and associates[40] demonstrated that, at any specified level of SBP, relative risks for CHD decreased with increasing DBP. For example, at an SBP of 150 mm Hg, the estimated hazard ratio for CHD was 1.8 if the DBP was 70 mm Hg, but only approximately 1.3 if the DBP was 95 mm Hg. The higher the SBP level, the steeper the decline in CHD risk with increasing DBP. These data provide some compelling evidence for the importance of PP as a measure of risk, because PP represents the difference between SBP and DBP, and higher risk was observed in this study when the PP widened.[40] PP will be discussed in greater detail below.

The increased risks associated with SBP are clear. When one also appreciates that systolic hypertension out of proportion to diastolic elevation is by far the most common form of hypertension, as discussed previously, it becomes clear that the PAR for CVD conferred by SBP vastly outweighs that for DBP. Finally, lack of control to goal BP in the community appears to be overwhelmingly because of lack of SBP control to <140 mm Hg.[31,41,42] As shown in Table 1-5, among hypertensive participants attending examinations at the FHS in the 1990s, 29.0% were controlled to the overall goal of BP <140/90 mm Hg. Within this poor overall prevalence of control to goal BP, 82.9% of hypertensive individuals had DBP <90 mm Hg, whereas only 32.7% were controlled to SBP <140 mm Hg. Similar findings were observed in the NHANES III cohort.[31]

Cross-sectional predictors of lack of SBP control (and lack of overall control to goal) in the FHS include older age, presence of electrocardiographic LVH, and obesity.[41] In national samples, significant cross-sectional predictors of lack of BP control among those aware of their hypertension include age ≥65 years, male sex, and no visits to a physician in the preceding 12 months.[42] Age

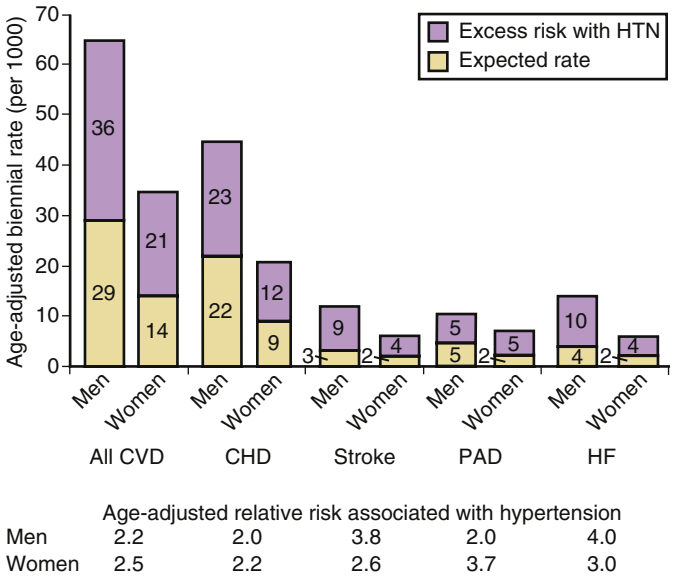

FIGURE 1-4 Age-adjusted biennial rates, relative risks, and absolute excess risks associated with hypertension for different cardiovascular endpoints: Framingham Study, 36-year follow-up, persons aged 35-64 years. CHD, coronary heart disease; CVD, cardiovascular disease; HF, heart failure; HTN, hypertension; PAD, peripheral arterial disease.

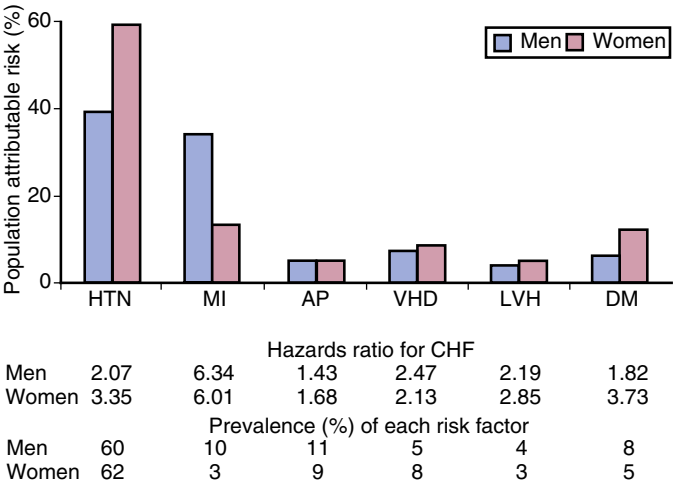

FIGURE 1-5 Hazard ratios for congestive heart failure associated with selected risk factors, prevalence of each risk factor, and population-attributable risk for each factor in congestive heart failure. AP, angina pectoris; DM, diabetes mellitus; HTN, hypertension; LVH, electrocardiographic left ventricular hypertrophy; MI, myocardial infarction; VHD, valvular heart disease. *(Data from Levy D, Larson MG, Vasan RS, et al. The progression from hypertension to congestive heart failure.* JAMA. *1996;275:1557-1562.)*

and the presence of LVH likely represent higher initial SBP before initiation of therapy and longer duration of hypertension, both of which can contribute to greater difficulty in achieving lower BP levels. In addition, it appears likely that clinicians are reluctant to treat older hypertensive individuals to lower BP goals, perhaps as a result of concerns over orthostasis and risk for falls, polypharmacy, or the controversial observation that an increase in CVD events and mortality may occur among the oldest hypertensives when DBP is lowered below 60 or 65 mm Hg (the J-shaped curve phenomenon).[43]

Because of the difficulty in collecting detailed and repetitive data, few studies have examined prospective predictors of initiating

TABLE 1-4 Risks for Cardiovascular Disease Associated with Different Components of Blood Pressure in the Cardiovascular Health Study

		Adjusted Hazard Ratio (95% CI)	
	1 SD	MI	STROKE
SBP	21.4 mm Hg	1.24 (1.15-1.35)	1.34 (1.21-1.47)
DBP	11.2 mm Hg	1.13 (1.04-1.22)	1.29 (1.17-1.42)
Pulse pressure	18.5 mm Hg	1.21 (1.12-1.31)	1.21 (1.10-1.34)

DBP, diastolic blood pressure; MI, myocardial infarction; SBP, systolic blood pressure; SD, standard deviation.
Data from Psaty BM, Furberg CD, Kuller LH, et al. Association between blood pressure level and the risk of myocardial infarction, stroke, and total mortality. *Arch Intern Med.* 2001;161:1183-1192.

antihypertensive therapy or achieving BP control. Among 1103 hypertensive FHS participants who were untreated at a baseline examination between 1987 and 1999, 350 (31.7%) subjects were receiving therapy at a follow-up examination 4 years later, including 25.7% of subjects with stage 1 and 51.2% of those with stage ≥2 hypertension at baseline. Multivariate predictors of initiation of therapy included higher SBP and DBP, prevalent and interim CVD, and presence of LVH. The presence of other CV risk factors did not predict initiation of treatment, indicating that global risk may not, at that time, have been considered in decisions to initiate therapy.[44] Among 2475 hypertensive participants who were uncontrolled (treated or untreated) at baseline, 988 (39.9%) were controlled at follow-up. Prevalent CVD and interim initiation of therapy predicted control; older age and higher baseline SBP predicted lack of control in this prospective analysis.[44] Thus achievement of SBP control remains a major obstacle to achieving better rates of BP control and lowering risks for adverse events in the population.

Risk Across the Spectrum of Blood Pressure and the Importance of Stage 1 Hypertension

As noted previously, increasing BP is associated with increasing risks for CVD, beginning at levels well within the so-called "normal" range. The Prospective Studies Collaboration, a pooling study of approximately 1 million men and women in a number of large epidemiologic cohorts, and including data on more than 56,000 decedents, demonstrated that risks for CVD death increase steadily beginning at least at levels as low as an SBP of 115 mm Hg and DBP of 75 mm Hg. When considered in isolation, for each 20 mm Hg increase in SBP and each 10 mm Hg increase in DBP, there is approximately a doubling of risk for stroke death and ischemic heart disease death for both men and women.[32]

Similarly, the large data set of more than 347,000 men aged 35 to 57 years screened for the MRFIT provides a precise estimate of incremental CVD risk beginning at lower BPs. The data from the MRFIT screenees, shown in Figure 1-7, *A*, confirm a continuous, graded influence of SBP on multivariable-adjusted relative risk for CHD mortality beginning at BP levels well below 140 mm Hg.[45] Men with SBP of 150 to 159 mm Hg have over three times the risk and men with SBP >180 mm Hg have nearly six times the risk of men with SBP <100 mm Hg. These data also make an important point about BP levels in the population at which the majority of CVD events occur. In Figure 1-7, *B*, the numbers above each bar indicate the number of men in that stratum of SBP at baseline. Taking into account the number of men in each stratum and the expected rates of CHD death, the CHD death rates observed in the MRFIT screenee cohort indicate excess CHD deaths occurring at the rates indicated by the line in Figure 1-7, *C*. The proportion of excess CHD deaths by SBP stratum is indicated in Figure 1-7, *D*. As shown, nearly two thirds of excess CHD deaths occurred in men with SBP between 130 and 159 mm Hg, relatively "mild" levels of elevated BP.

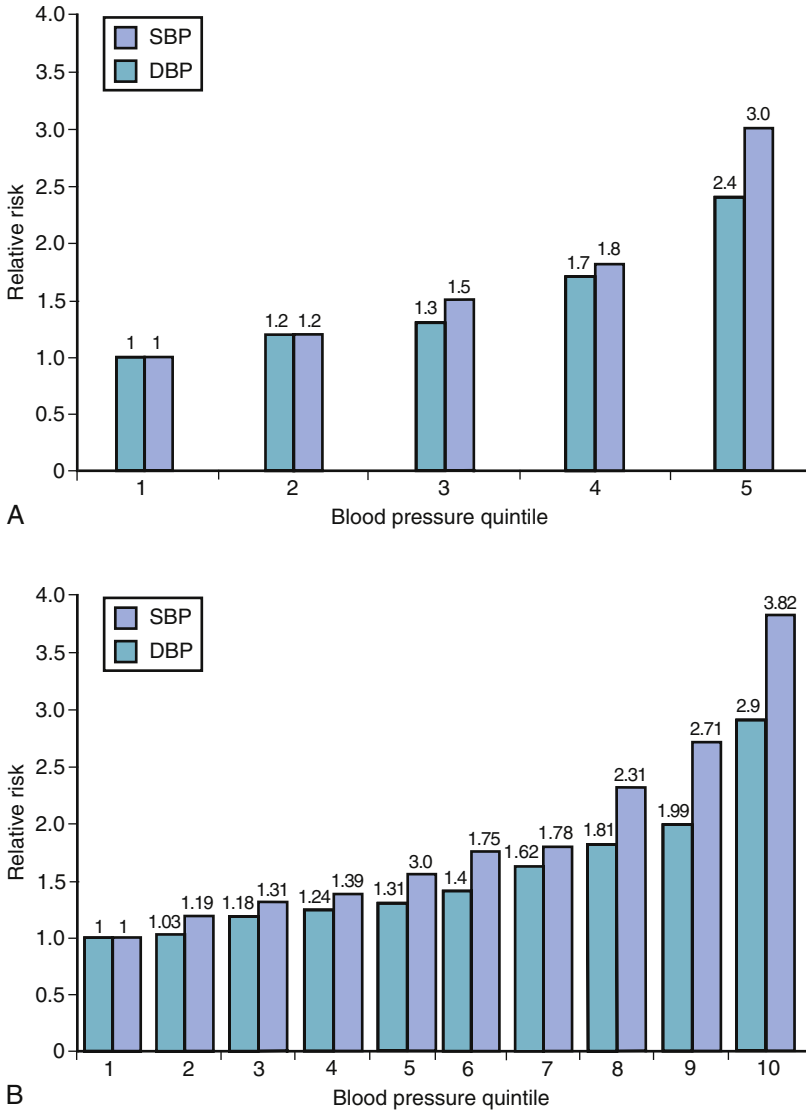

FIGURE 1-6 Relative risks for coronary heart disease mortality among men screened for the Multiple Risk Factor Intervention Trial, by quintiles (**A**) or deciles (**B**) of systolic blood pressure (SBP) and diastolic blood pressure (DBP).

TABLE 1-5 Rates of Control to SBP <140 mm Hg or DBP <90 mm Hg, among 1944 Hypertensive Framingham Heart Study participants, 1990-1995.

	SBP <140 MM HG (%)	SBP ≥140 MM HG (%)	TOTAL (%)
DBP <90 mm Hg	29.0	53.9	82.9
DBP ≥90 mm Hg	3.7	13.4	17.1
Total	32.7	67.3	100

DBP, diastolic blood pressure; SBP, systolic blood pressure.
Data from Lloyd-Jones DM, Evans JC, Larson MG, et al. Differential control of systolic and diastolic blood pressure: factors associated with lack of blood pressure control in the community. *Hypertension*. 2000;36:594-599.

Data from the FHS also indicate that the risk associated with BPs in the range of 130 to 139 mm Hg systolic or 85 to 89 mm Hg diastolic are substantial, despite the fact that these levels are not classified as "hypertension." These levels of BP are associated with significantly elevated multivariable-adjusted relative risks for CVD of 2.5 in women and 1.6 in men.[46] Likewise, individuals with SBP of 120 to 139 mm Hg or DBP of 80 to 89 mm Hg have a high likelihood of progressing to definite hypertension over the next 4 years, especially if they are age 65 or older.[47]

Pulse Pressure and Risks for Cardiovascular Disease

"Pulse pressure" is defined as the systolic minus the diastolic BP. In recent years there has been intense interest in PP as a risk factor for CVD. However, various investigators have struggled with how best to "anchor" the PP. For example, a patient with a BP of 120/60 has the same PP (60 mm Hg) as a patient with a BP of 150/90, although the latter patient is clearly at higher risk for adverse events. Different investigators have anchored the PP to the DBP, the mean arterial pressure, and the SBP. As discussed previously, Franklin and associates[40] demonstrated that increasing PP was associated with marked increases in hazard of CHD for subjects with the same SBP. Chae and associates[48] also found that PP was an independent predictor of HF in an elderly cohort, even after adjustment for mean arterial pressure, prevalent CHD, and other HF risk factors. In another study, Haider and colleagues[49] observed that SBP and PP conferred similar risk for HF. However, other studies have found that SBP confers greater risk than PP, when SBP and PP are considered separately or as covariates in the same multivariable model.[37] The aforementioned Prospective Studies Collaboration, which pooled data from 61 large epidemiologic studies and approximately 1 million men and women, found that the best measure of BP for prediction of CVD events was the mean of SBP and DBP, which predicted it better than SBP or DBP alone, and much better than the PP.[32] The recommendation of

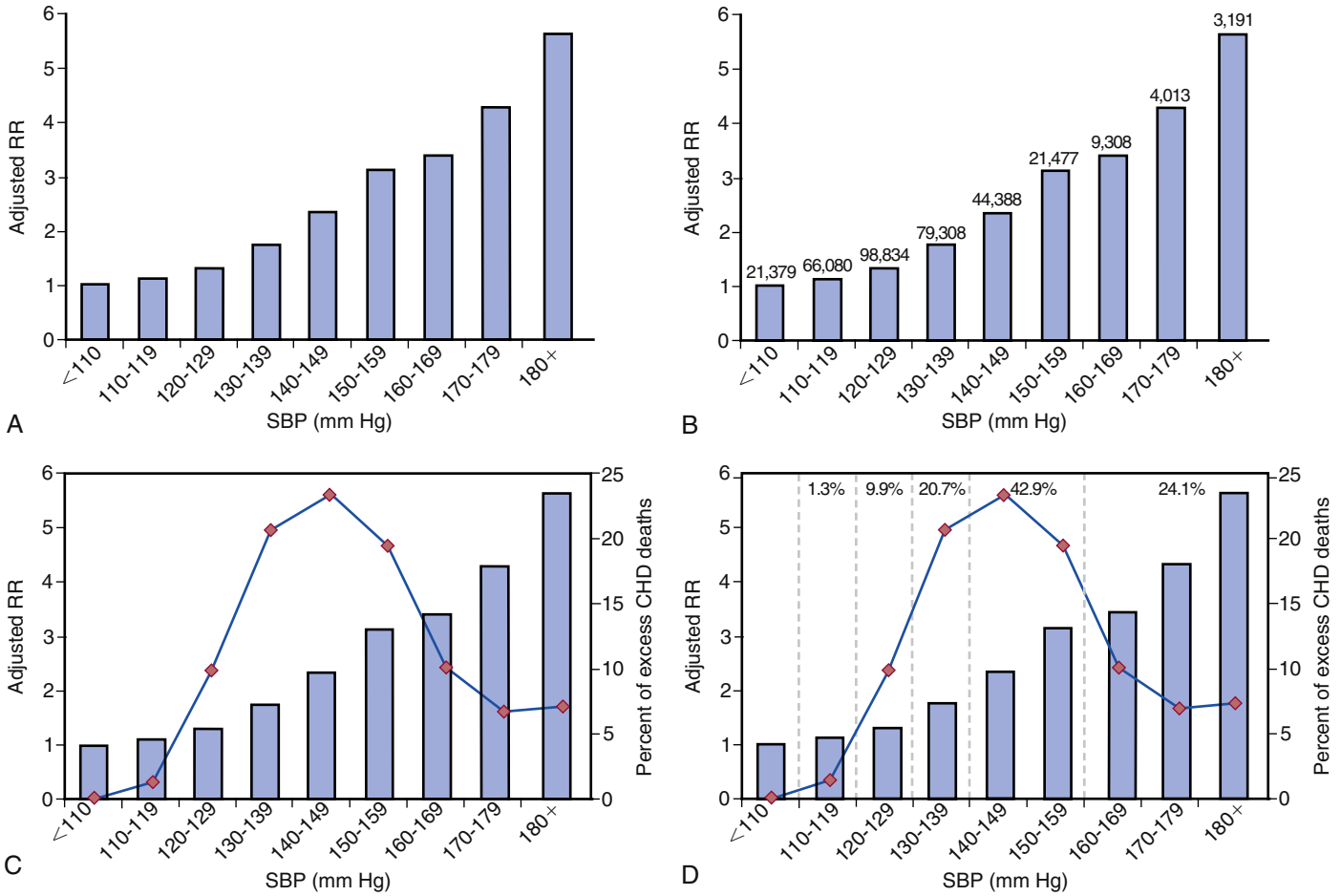

FIGURE 1-7 Relative risks (RRs) for coronary heart disease (CHD) mortality among screenees for the Multiple Risk Factor Intervention Trial by level of systolic blood pressure (**A**) with number of men in each stratum of SBP (**B**), distribution of excess CHD deaths by SBP stratum (**C**), and distribution of excess CHD deaths by JNC stage (**D**).

JNC 7 was that clinical focus should remain on the SBP in determining need for therapy and achieving goal BP.[1]

Mosley and colleagues[50] compared the predictive utility of PP and other BP measures for diverse CVD outcomes (including hospitalizations and mortality from stroke, MI, and HF) using long-term follow-up data from the Chicago Heart Association Detection Project in Industry. Baseline BP measures were assessed for predictive utility for fatal and nonfatal events over 33 years. Among 36,314 participants, who were a mean age of 39 years, 43.4% were women. In univariate analyses, hazard ratios for stroke death per 1 SD of PP, SBP, and DBP, respectively, were 1.49, 1.75, and 1.71. Likelihood ratios, Bayes' information criteria values, and areas under receiver-operating characteristic curves all indicated better predictive utility for SBP and DBP compared with PP. Results for CHD or HF death, and stroke, MI, or HF hospitalization outcomes were similar. PP had weaker predictive utility at all ages, but particularly for those under 50 years of age. Overall then, in this large cohort study, PP had predictive utility for cardiovascular events that was inferior to SBP or DBP. These findings tend to support the approach of current guidelines in the use of SBP and DBP to assess risk and the need for treatment.[50]

Renal Disease

Hypertension is also a major and increasingly important risk factor for renal disease. According to the U.S. Renal Data System, there were 116,000 cases of incident end-stage renal disease (ESRD) in 2009. The rate of ESRD owing to diabetes has remained fairly stable at 154 per 1 million population since 2000, whereas the rate of ESRD as a result of hypertension has increased 8.7% since 2000, to 101 per 1 million population per year.[51] However, these numbers may substantially underestimate the contribution of BP to the increasing incidence of renal disease, because these data provide only a single diagnostic cause, and hypertension is present in the vast majority of those with DM. African Americans have approximately four times the risk as whites of developing ESRD, in part because of their significantly higher prevalence of hypertension.[8] In addition to its contribution to ESRD, elevated BP also occurs in and exacerbates milder forms of chronic kidney disease and worsens proteinuria.

Competing Outcomes with Hypertension

Individuals with hypertension are at risk for multiple potential outcomes simultaneously, including non-CVD death, CHD, stroke, HF, and other causes of CVD death. Traditional survival analysis methods typically only evaluate each of these outcomes independently, without understanding their joint probabilities of occurring. A recent analysis used novel methodology to explore these competing risks among all FHS subjects examined after 1977 who had new-onset hypertension and were initially free of CVD. There were 645 men and 702 women with new-onset hypertension (mean age 57 years). Compared with matched nonhypertensive controls, subjects with new-onset hypertension were significantly more likely to experience a CVD event first rather than non-CVD death. Among new-onset hypertensives, the 12-year competing cumulative incidence of any CVD endpoint as a first event in men was 24.7%, compared with 9.8% for non-CVD death (hazard ratio, 2.53; 95% CI, 1.83-3.50); in women, the competing incidences were 16.0% versus 10.1%, respectively (hazard ratio, 1.58; CI, 1.13-2.20). The most common first major CVD events among those with new-onset hypertension were CHD death or non-fatal MI (8.2%) in men and stroke (5.2%) in women. Type and incidence of first CV events varied by

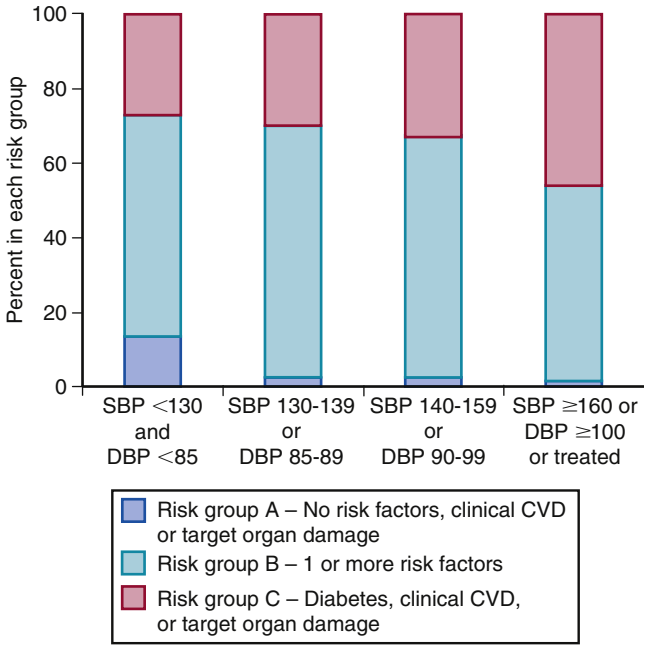

FIGURE 1-8 Cross-classification of risk groups and blood pressure stages among 4962 Framingham Heart Study subjects. *(Data from Lloyd-Jones DM, Evans JC, Larson MG, et al. Cross-classification of JNC VI blood pressure stages and risk groups in the Framingham Heart Study.* Arch Intern Med. *1999;159:2206-2212.)*

age, sex, and severity of hypertension at onset, with stroke predominating among older men and women at all ages with new-onset hypertension.[52] These results represent a novel approach to understanding the complications of hypertension and could help target therapies for patients with new-onset hypertension to optimize prevention strategies. For example, an older individual (>60 years) with new-onset hypertension is at greatest risk for stroke as a first event; BP lowering would likely be of paramount importance to prevent this. However, a younger man with new-onset hypertension is most likely to have a major CHD event first, so aspirin and statin therapy, in addition to BP lowering, might be emphasized.

Risk Factor Clustering

As anticipated by the JNC VI panel, hypertension occurs in isolation very infrequently. Data from 4962 FHS subjects examined in the 1990s were used to assess the cross-classification of JNC VI BP stages and risk groups (Fig. 1-8) in a middle-aged and older community-based population.[53] In this study, higher BP stages were associated with higher mean number of risk factors and higher rates of clinical CVD and/or target organ damage. Overall, among those with high-normal BP or hypertension, only 2.4% had no associated risk factors, whereas 59.3% had at least one associated risk factor, and 38.2% had target organ damage, clinical CVD, or DM.[53]

The current epidemic of obesity among Western societies has led to a greater understanding of the phenomenon of risk factor clustering, and of the pathophysiologic links between hypertension, obesity, DM, and CVD risk. The cluster of risk factors including central obesity, atherogenic dyslipidemia (with low HDL-cholesterol, high triglycerides, and small, dense LDL-cholesterol particles), impaired glucose metabolism, vascular inflammation, proatherogenic milieu, and elevated BP has been termed the "metabolic syndrome (MS)." Visceral adiposity and insulin resistance appear to play central roles in the development of MS, and elevated BP is a key diagnostic feature.[54] In some ethnicities, such as African Americans, elevated BP is the most common criterion leading to diagnosis of the MS. Hypertension confers increased risk for CVD in the absence of risk factors, but absolute risk increases dramatically when other risk factors are present, as shown in Figure 1-3.

TABLE 1-6 Awareness, Treatment, and Control of Hypertension by Age Group in the United States*

AGE (YEARS)	PREVALENCE (%)	TREATMENT (%)	CONTROL (%)
40 to 64	35.6	68.9	48.4
≥65	69.7	78.7	45.7

*National Health and Nutrition Examination Surveys, 2005-2008.

Hypertension in Older Individuals

The elderly are among the fastest growing segments of the U.S. population,[55] and they also have the greatest prevalence of hypertension.[4,5,8,9,13] As shown in Figure 1-2, the percentage of individuals with hypertension exceeds 50% in those over age 60 and is approximately 75% in those over age 75.[5] Despite multiple trials demonstrating the benefits of BP-lowering among older hypertensive individuals, available data suggest that rates of treatment and control in older individuals are suboptimal, but improving.* In NHANES 2005-2008, 78.7% of hypertensive adults aged 65 years and older were treated, but only 45.7% were controlled to goal BP.[4] Nonetheless, this represents an improvement compared with 1999-2000, when control rates were only 27.4% in older Americans.[7] Compared with hypertensives in the 40- to 59-year-old age group, this represents similar rates of treatment and control, as shown in Table 1-6. However, studies from national surveillance data are often limited to adults younger than age 75 years.[1,6,15] Data are sparse regarding current patterns of treatment and control of hypertension among individuals 80 years of age and older.

Some data from the FHS are available that specifically compare the risks associated with hypertension among the oldest age groups compared with younger individuals. Relative risks for CVD over 6 years associated with increasing BP stage did not decline with advancing age, and absolute risks increased markedly. Among participants ≥80 years of age, major CVD events occurred in 9.5% of the normal BP (referent) group, 19.8% of the prehypertensive group (hazard ratio 1.9; 95% CI, 0.9-3.9), 20.3% of the stage 1 hypertensive group (HR, 1.8; 95% CI, 0.8-3.7), and 24.7% of the stage 2 or treated hypertensive group (HR, 2.4; 95% CI, 1.2-4.6).[56] Whereas the absolute risk for CHD increases steadily with increasing age, the risk for HF and atrial fibrillation increases dramatically among older compared with younger hypertensives.[57,58]

Hypertension occurs in the absence of other CVD risk factors only rarely in older persons, and it is often accompanied by a clustering of other risk factors.[59,60] The prevalence of three or more coexisting risk factors is four times higher among hypertensive than among normotensive older individuals.[61]

Conclusions

Hypertension is the most prevalent major risk factor for CVD and renal disease. Risk factors for development of hypertension are well understood, and numerous dietary and personal habits, as well as societal issues, must be addressed if we are to lower population levels of BP and to control individual patients' BPs, particularly SBP. Major public health and clinical efforts are needed to improve prevention of hypertension, especially through better control of weight. Newer research that offers better understanding of the genetic underpinnings of hypertension as well as important gene–environment interactions may help to point the way for novel means of prevention. Although the benefits of antihypertensive therapy are substantial, too few patients achieve optimal BP reduction and therefore do not realize the potential reductions in risk for CVD and renal disease. More widespread treatment and control to goal levels are needed, particularly among older hypertensives, who are at the highest risk for the consequences of hypertension.

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