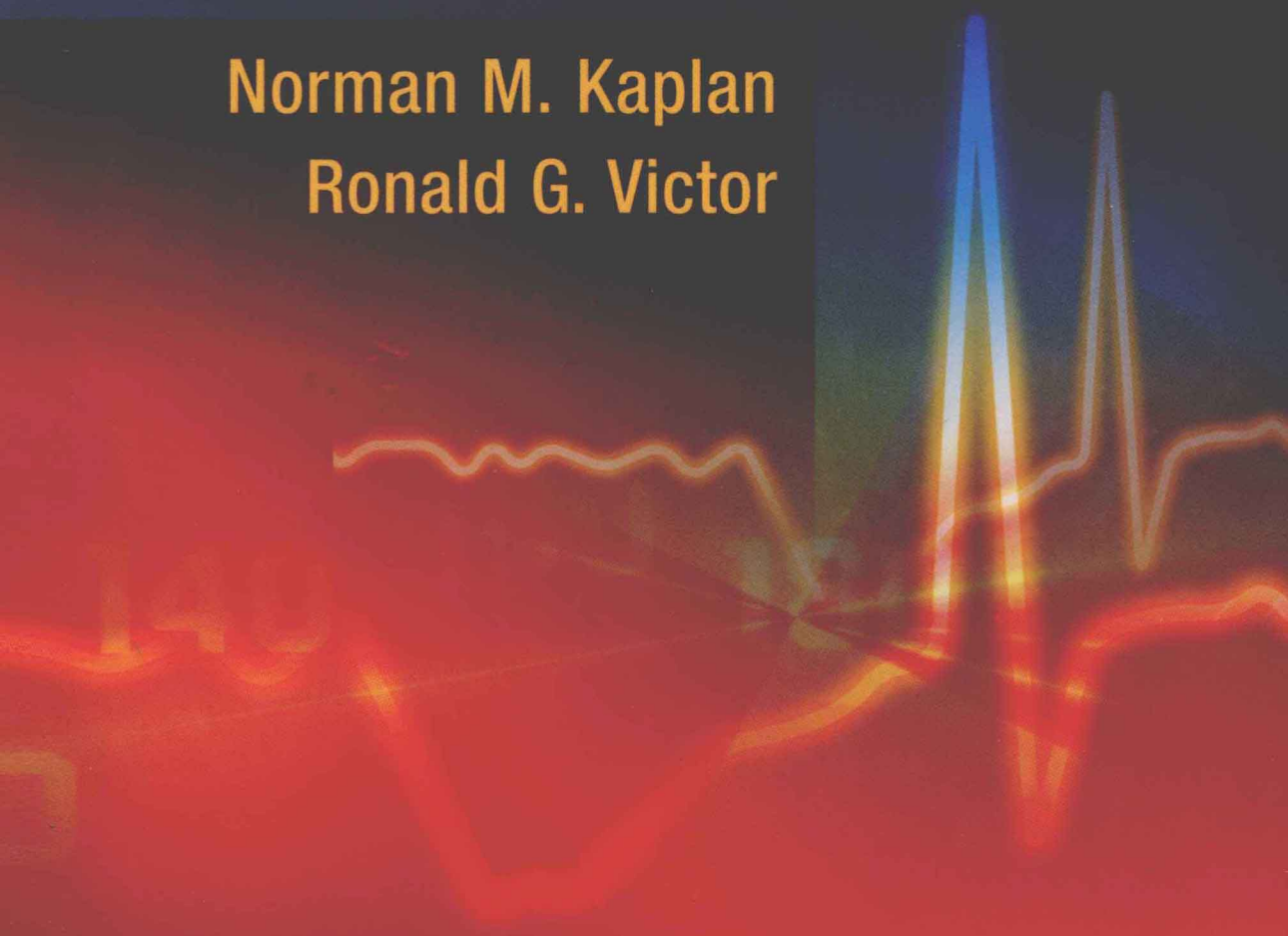
TENTH EDITION

KAPLAN'S Clinical Hypertension

Norman M. Kaplan
Ronald G. Victor



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Kaplan's Clinical Hypertension

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To those such as
Goldblatt and Grollman,
Braun-Menéndez and Page,
Lever and Pickering,
Mancia, Brenner, and Laragh,
Julius, Hansson, and Freis,
and the many others, whose work has made it
possible for us to put
together what we hope will be a useful book on
clinical hypertension

PREFACE TO THE TENTH EDITION

Hypertension is increasingly being diagnosed worldwide, in developed and undeveloped societies, as populations become fatter and older. The literature on hypertension keeps pace with the increased prevalence of the disease. The ability required of a simple author to digest and organize this tremendous body of information into a relatively short book that is both current and inclusive has become almost impossible. Fortunately, Dr. Ronald Victor has been willing and able to join as a coauthor. After 10 years of close contact at the University of Texas Southwestern Medical School, I know him to be a clearheaded and open-minded clinician, teacher, and researcher. Despite his move to smoggy Los Angeles, he brings a fresh perspective that adds greatly to this book.

As noted in the previous edition, I am amazed at the tremendous amount of hypertension-related literature published over the past 4 years. A considerable amount of significant new information is included in this edition, presented in a manner that I hope enables the reader to grasp its significance and place it in perspective. Almost every page has been revised, using the same goals:

- Give more attention to the common problems; primary hypertension takes up almost half.
- Cover every form of hypertension at least briefly, providing references for those seeking more information. Additional coverage is provided on some topics that have recently assumed importance.
- Include the latest data, even if available only in abstract form.
- Provide enough pathophysiology to permit sound clinical judgment.
- Be objective and clearly identify biases, although my views may differ from those of others.

I have tried to give reasonable attention to those with whom I disagree.

Dr. Joseph T. Flynn, Professor of Pediatrics, Division of Nephrology, Seattle Children's Hospital, Seattle, Washington has contributed a chapter on hypertension in children and adolescents. I have been fortunate in being in an academic setting wherein such endeavors are nurtured and wish to thank all who have been responsible for establishing this environment and all of our colleagues who have helped us through the years.

Norman M. Kaplan, MD
Ronald G. Victor, MD

CONTENTS

CHAPTER 1

Hypertension in the Population at Large

Hypertension provides both despair and hope: despair because it is quantitatively the largest risk factor for cardiovascular diseases (CVD), it is growing in prevalence, and it is poorly controlled virtually everywhere; and hope because prevention is possible (though rarely achieved) and treatment can effectively control almost all patients, resulting in marked reductions in stroke and heart attack.

Although most of this book addresses hypertension in the United States and other developed countries, it should be noted that CVDs are the leading cause of death worldwide, more so in the economically developed countries, but also in the developing world. As Lawes et al. (2008) note: "Overall about 80% of the attributable burden (of hypertension) occurs in low-income and middle-income economies."

In turn, hypertension is, overall, the major contributor to the risks for CVDs. When the total global impact of known risk factors on the overall burden of disease is calculated, 54% of stroke and 47% of ischemic heart disease (IHD) are attributable to hypertension (Lawes et al., 2008). Of all the potentially modifiable risk factors for myocardial infarction in 52 countries, hypertension is exceeded only by smoking (Danaei et al., 2009).

The second contributor to our current despair is the growing prevalence of hypertension as seen in the ongoing survey of a representative sample of the U.S. population (Cutler et al., 2008; Lloyd-Jones et al., 2009). According to their analysis, the prevalence of hypertension in the United States has increased from 24.4% in 1990 to 28.9% in 2004. This increased prevalence primarily is a consequence of the population becoming older and more obese.

The striking impact of aging was seen among participants in the Framingham Heart Study: Among those who remained normotensive at either age 55 or 65 (providing two cohorts) over a 20-year follow-up, hypertension developed in almost 90% of those who were now aged 75 or 85 (Vasan et al., 2002).

The impact of aging and the accompanying increased prevalence of hypertension on both stroke and IHD mortality has been clearly portrayed in a meta-analysis of data from almost one million adults in 61 prospective studies by the Prospective Studies Collaboration (Lewington et al., 2002). As seen in Figure 1-1, the absolute risk for IHD mortality was increased at least twofold at every higher decade of age, with similar lines of progression for both systolic and diastolic pressure in every decade.

At the same time as populations are growing older, obesity has become epidemic in the United States (Hedley et al., 2004) and is rapidly increasing wherever urbanization is occurring (Yusuf et al., 2001). With weight gain, blood pressure (BP) usually increases and the increased prevalence of overweight is likely responsible for the significant increase in the BP of children and adolescents in the United States over the past 12 years (Ostchega et al., 2009).

The third contributor to our current despair is the inadequate control of hypertension virtually everywhere. According to similar surveys performed in the 1990s, with control defined at the 140/90 mm Hg threshold, control has been achieved in 29% of hypertensives in the United States, 17% in Canada, but in fewer than 10% in five European countries (England, Germany, Italy, Spain, and Sweden) (Wolf-Maier et al., 2004). Some improvement in the U.S. control rate has subsequently been found but the percentage has reached only 45% (Lloyd-Jones et al., 2009) (Table 1-1), whereas better control rates are reported from Canada (Mohan & Campbell, 2008), Cuba (Ordunez-Garcia et al., 2006), Denmark

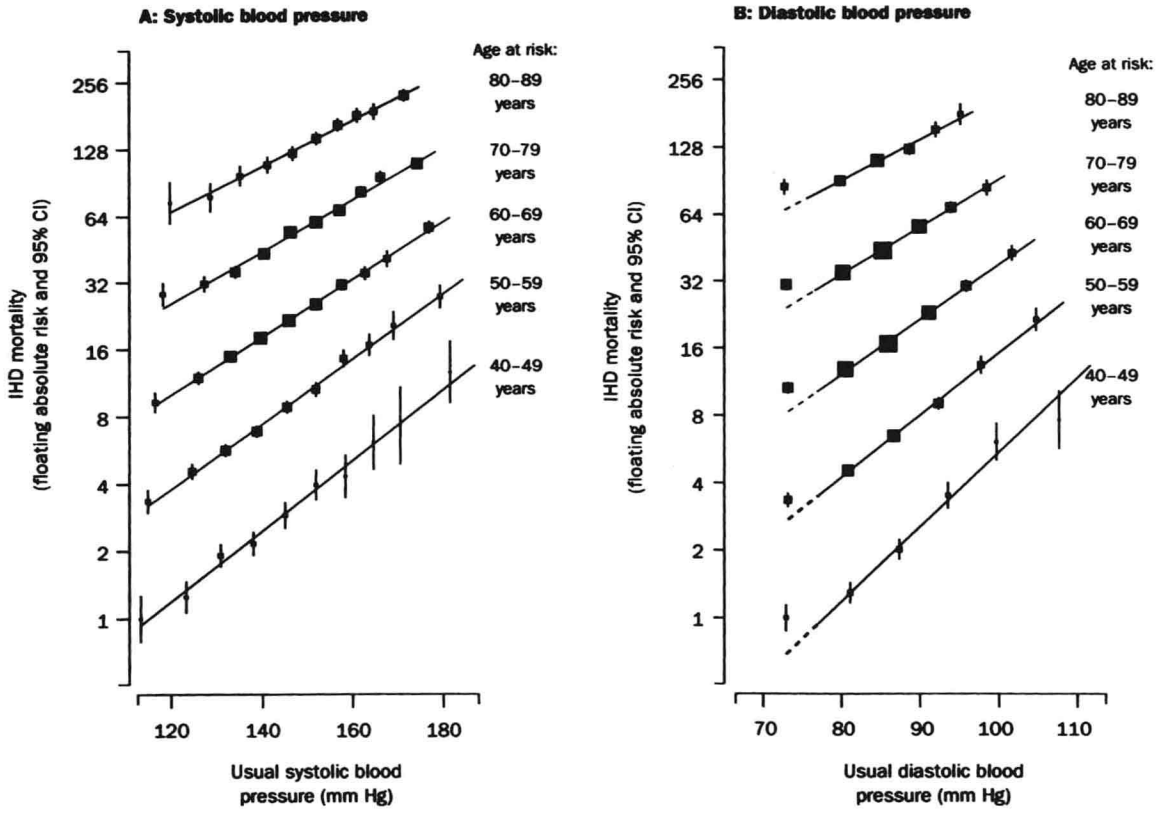


FIGURE 1-1 Ischemic heart disease (IHD) mortality rate in each decade of age plotted for the usual systolic **(left)** and diastolic **(right)** BPs at the start of that decade. Data from almost one million adults in 61 prospective studies. (Modified from Lewington S, Clarke R, Qizilbash N, et al. Age-specific relevance of usual blood pressure to vascular mortality: A meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002;360:1903–1913.)

(Kronborg et al., 2009), and England (Falaschetti et al., 2009). As expected, even lower rates of control have been reported from less developed countries such as China (Dorjgochoo et al., 2009). Moreover, in the United States, control rates among the most commonly afflicted, the elderly, are significantly lower: only 29% of women 70 to 79 years of age are controlled (Lloyd-Jones et al., 2009). Furthermore, the relatively lower control rates among Hispanics and African Americans compared to whites remain unchanged (McWilliams et al., 2009). And of even greater concern, even when hypertensives are treated

TABLE 1.1 Trends in Awareness, Treatment, and Control of High Blood Pressure in U.S. Adults (Over Age 20) 1976–2004

	National Health and Nutrition Examination Survey (%)				
	1976–1980	1988–1991	1991–1994	2000–2004	2005–2006
Awareness	51	73	68	70	79
Treatment	31	55	54	59	61
Control	10	29	27	34	45

Percentage of adults aged 18 to 74 years with SBP of 140 mm Hg or greater, with DBP of 90 mm Hg or greater, or taking antihypertensive medication.

Adapted from Lloyd-Jones D, Adams R, Carnethon M, et al. Heart disease and stroke statistics-2009 update: A report from the American Heart Association statistics committee and stroke statistics subcommittee. *Circulation* 2009;119:e21–e181.

down to an optimal level, below 120/80 mm Hg, they continue to suffer a greater risk of stroke than normotensives with similar optimal BP levels (Asayama et al., 2009).

Despite all of these problems, there is hope, starting with impressive evidence of decreased mortality from CVDs, at least in the United States (Parikh et al., 2009) and England (Unal et al., 2004). However, as well as can be ascertained, control of hypertension has played only a relatively small role in the decreased mortality from coronary disease in the United States (Ford et al., 2007).

Nonetheless, there is also hope relative to hypertension. Primary prevention has been found to be possible (Whelton et al., 2002) but continues to be rarely achieved (Kotseva et al., 2009). Moreover, the rising number of the obese seriously questions the ability to implement the necessary lifestyle changes in today's world of faster foods and slower physical activity. Therefore, controlled trials of primary prevention of hypertension using antihypertensive drugs have begun (Julius et al., 2006).

On the other hand, the ability to provide protection against stroke and heart attack by antihypertensive therapy in those who have hypertension has been overwhelmingly documented (Blood Pressure Trialists, 2008). There is no longer any argument as to the benefits of lowering BP, though uncertainty persists as to the most cost-effective way to achieve the lower BP. Meanwhile, the unraveling of the human genome has given rise to the hope that gene manipulation or transfer can prevent hypertension. As of now, that hope seems extremely unlikely beyond the very small number of patients with monogenetic defects that have been discovered.

All in all, hope about hypertension seems overshadowed by despair. However, health care providers must, by nature, be optimistic, and there is an inherent value in considering the despairs about hypertension to be a challenge rather than an acceptance of defeat. As portrayed by Nolte and McKee (2008), the most realistic way to measure the health of nations is to analyze the mortality that is amenable to health care. By this criterion, the United States ranks 19th among the 19 developed countries analyzed. This sobering fact can be looked upon as a failure of the vastly wasteful, disorganized U.S. health care system. We prefer to look upon this poor rating as a challenge: current health care is inadequate, including, obviously, the management of hypertension, but the potential to improve has never been greater (Shih et al., 2008).

This book summarizes and analyses the works of thousands of clinicians and investigators worldwide who have advanced our knowledge about the mechanisms behind hypertension and who have provided increasingly effective therapies for its control. Despite their continued efforts, however, hypertension will almost certainly not ever be conquered totally, because it is one of those diseases that, in the words of a *Lancet* editorialist (Anonymous, 1993):

> ...afflict us from middle age onwards [that] might simply represent "unfavorable" genes that have accumulated to express themselves in the second half of our lives. This could never be corrected by any evolutionary pressure, since such pressures act only on the first half of our lives: once we have reproduced, it does not greatly matter that we grow "sans teeth, sans eyes, sans taste, sans everything."

In this chapter, the overall problems of hypertension for the population at large are considered. We define the disease, quantify its prevalence and consequences, classify its types, and describe the current status of detection and control. In the remainder of the book, these generalities will be amplified into practical ways to evaluate and treat hypertension in its various presentations.

CONCEPTUAL DEFINITION OF HYPERTENSION

Although it has been more than 100 years since Mahomed clearly differentiated hypertension from Bright's renal disease, authorities still debate the level of BP that is considered abnormal (Task Force, 2007). Sir George Pickering challenged the wisdom of that debate and decried the search for an arbitrary dividing line between normal and high BP. In 1972, he restated his argument: "There is no dividing line. The relationship between arterial pressure and mortality is quantitative; the higher the pressure, the worse the prognosis." He viewed arterial pressure "as a quantity and the consequence numerically related to the size of that quantity" (Pickering, 1972).

However, as Pickering realized, physicians feel more secure when dealing with precise criteria, even if the criteria are basically arbitrary. To consider a BP of 138/88 mm Hg as normal and one of 140/90 mm Hg as high is obviously arbitrary, but medical practice requires that some criteria be used to determine the need for workup and therapy. The criteria should be established on some rational basis that includes the

risks of disability and death associated with various levels of BP as well as the ability to reduce those risks by lowering the BP. As stated by Rose (1980): "The operational definition of hypertension is the level at which the benefits... of action exceed those of inaction."

Even this definition should be broadened, because action (i.e., making the diagnosis of hypertension at any level of BP) involves risks and costs as well as benefits, and inaction may provide benefits. These are summarized in Table 1-2. Therefore, the conceptual definition of hypertension should be that level of BP at which the benefits (minus the risks and costs) of action exceed the risks and costs (minus the benefits) of inaction.

Most elements of this conceptual definition are fairly obvious, although some, such as interference with lifestyle and risks from biochemical side effects of therapy, may not be. Let us turn first to the major consequence of inaction, the increased incidence of premature CVD, because that is the prime, if not the sole, basis for determining the level of BP that is considered abnormal and is called *hypertension*.

Risks of Inaction: Increased Risk of CVD

The risks of elevated BP have been determined from large-scale epidemiologic surveys. The Prospective Studies Collaboration (Lewington et al., 2002) obtained data on each of 958,074 participants in 61 prospective observational studies of BP and mortality. Over a mean time of 12 years, there were 11,960 deaths attributed to stroke, 32,283 attributed to IHD, 10,092 attributed to other vascular causes, and 60,797 attributed to nonvascular causes. Mortality during each decade of age at death was related to the estimated usual BP at the start of that decade. The relation between usual systolic and diastolic BP and the absolute risk for IHD mortality is shown in Figure 1-1. From ages 40 to 89, each increase of 20 mm Hg systolic BP or 10 mm Hg diastolic BP is associated with a twofold increase in mortality rates from IHD and more than a twofold increase in stroke mortality. These proportional differences in vascular mortality are about half as great in the 80 to 89 decade as it is in the 40 to 49 decade, but the annual absolute increases in risk are considerably greater in the elderly. As is evident from the straight lines in Figure 1-1, there is no evidence of a threshold wherein BP is not directly related to risk down to as low as 115/75 mm Hg.

As the authors conclude: "Not only do the present analyses confirm that there is a continuous relationship with risk throughout the normal range of usual blood pressure, but they demonstrate that within this range the usual blood pressure is even more strongly related to vascular mortality than had previously been supposed." They conclude that a 10 mm Hg higher than usual systolic BP or 5 mm Hg higher than usual diastolic BP would, in the long term, be associated with about a 40% higher risk of death from stroke and about a 30% higher risk of death from IHD.

These data clearly incriminate levels of BP below the level usually considered as indicative of

TABLE 1.2 Factors Involved in the Conceptual Definition of Hypertension

Action	Benefits	Risks and Costs
Action	Reduce risk of CVD, debility, and death	Assume psychological burdens of "the hypertensive patient" Interfere with QOL
	Decrease monetary costs of catastrophic events	Require changes in lifestyle Add risks and side effects from therapy Add monetary costs of health care
Inaction	Preserve "nonpatient" role	
	Maintain current lifestyle and QOL	Increase risk of CVD, debility, and death
	Avoid risks and side effects of therapy	Increase monetary costs of catastrophic events
	Avoid monetary costs of health care	

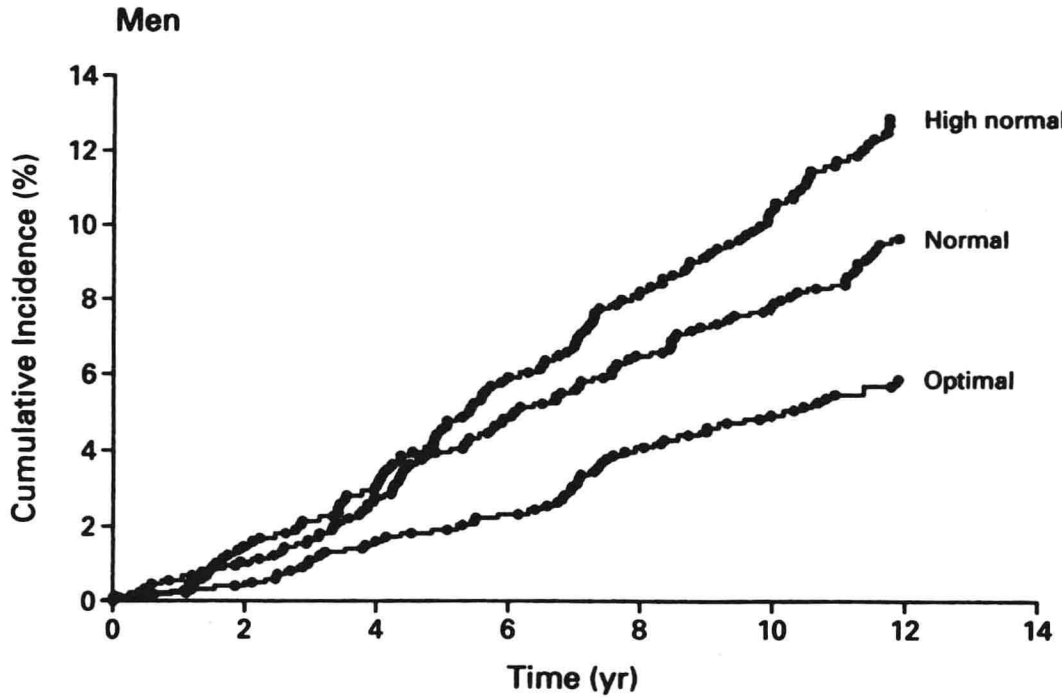
hypertension, i.e., 140/90 mm Hg or higher. Data from the closely observed participants in the Framingham Heart Study confirm the increased risks of CVD with BP levels previously defined as *normal* (120 to 129/80 to 84 mm Hg) or *high-normal* (130 to 139/85 to 89 mm Hg) compared to those with *optimal* BP (<120/80 mm Hg) (Vasan et al., 2001) (Fig. 1-2). The data of Lewington et al. (2002) and Vasan et al. (2001) are the basis of a new classification of BP levels, as will be described later in this chapter.

A similar relation between the levels of BP and CVDs has been seen in 15 Asian Pacific countries, although the association is even stronger for stroke and somewhat less for coronary disease than seen in the western world (Martiniuk et al., 2007). Some of these differences in risk and BP levels can be explained by obvious factors such as socioeconomic differences and variable access to health care (Victor et al., 2008; Wilper et al., 2008).

Beyond the essential contribution of BP per se to cardiovascular risk, a number of other associations may influence the relationship.

Gender and Risk

Although some studies of women have shown that they tolerate hypertension better than do men and have lower coronary mortality rates with any level of hypertension (Barrett-Connor, 1997), the Prospective Studies Collaboration found the age-specific associations of IHD mortality with BP to be slightly greater for women than for men and concluded that "for vascular mortality as a whole, sex is of little relevance" (Lewington et al., 2002). In the United States, women have a higher prevalence



No. at Risk							
Optimal	1005	995	973	962	934	892	454
Normal	1059	1039	1012	982	952	892	520
High normal	903	879	857	819	795	726	441

FIGURE 1-2 The cumulative incidence of cardiovascular events in men enrolled in the Framingham Heart Study with initial BPs classified as optimal (below 120/80 mm Hg), normal (120 to 129/80 to 84 mm Hg), or high-normal (130 to 139/85 to 89 mm Hg) over a 12-year follow-up. (Modified from Vasan RS, Larson MG, Leip EP, et al. Impact of high-normal blood pressure on the risk of cardiovascular disease. *N Engl J Med* 2001;345:1291–1297.)

of uncontrolled hypertension than men (Ezzati et al., 2008).

Race and Risk

As shown in Figure 1-3, U.S. blacks tend to have higher rates of hypertension than do nonblacks (Lloyd-Jones et al., 2009), and overall hypertension-related mortality rates are higher among blacks (Hertz et al., 2005). In the Multiple Risk Factor Intervention Trial, which involved more than 23,000 black men and 325,000 white men who were followed up for 10 years, an interesting racial difference was confirmed: the mortality rate for coronary heart disease (CHD) was lower in black men with a diastolic pressure exceeding 90 mm Hg than in white men (relative risk, 0.84), but the mortality rate for cerebrovascular disease was higher (relative risk, 2.0) (Neaton et al., 1989).

The greater risk of hypertension among blacks suggests that more attention must be given to even lower levels of hypertension among this group, but there seems little reason to use different criteria to diagnose hypertension in blacks than in whites. The special features of hypertension in blacks are discussed in more detail in Chapter 4.

The relative risk of hypertension differs among other racial groups as well. In particular, hypertension rates in U.S. Hispanics of Mexican origin are lower than those in whites (Cutler et al., 2008). In keeping with their higher prevalence for obesity and diabetes, U.S. Hispanics have lower rates of control of hypertension than do whites or blacks (Lloyd-Jones et al., 2009).

Age and Risk: The Elderly

The number of people older than 65 years is rapidly increasing and, in fewer than 30 years, one of every five people in the United States will be over age 65. Systolic BP rises progressively with age (Lloyd-Jones et al., 2009) (Fig. 1-4), and elderly people with hypertension are at greater risk for CVD (Wong et al., 2007).

Pulse Pressure

As seen in Figure 1-5, systolic levels rise progressively with age, whereas diastolic levels typically start to fall beyond age 50 (Burt et al., 1995). Both of these changes reflect increased aortic stiffness and pulse-wave velocity with a more rapid return of the reflected pressure waves, as are described in more detail in Chapter 3. It therefore comes as no surprise that the progressively widening of pulse pressure is a prognosticator of cardiovascular risk, as both the widening pulse pressure and most of the risk come from the same pathology—atherosclerosis and arteriosclerosis (Thomas et al., 2008).

Isolated Systolic Hypertension

As expected from Figure 1-5, most hypertension after age 50 is isolated systolic hypertension (ISH), with a diastolic BP of less than 90 mm Hg. In an analysis based on the National Health and Nutrition Examination Survey (NHANES) III data, Franklin et al. (2001a) found that ISH was the diagnosis in 65% of all cases of uncontrolled hypertension seen in the entire population and in 80% of patients older

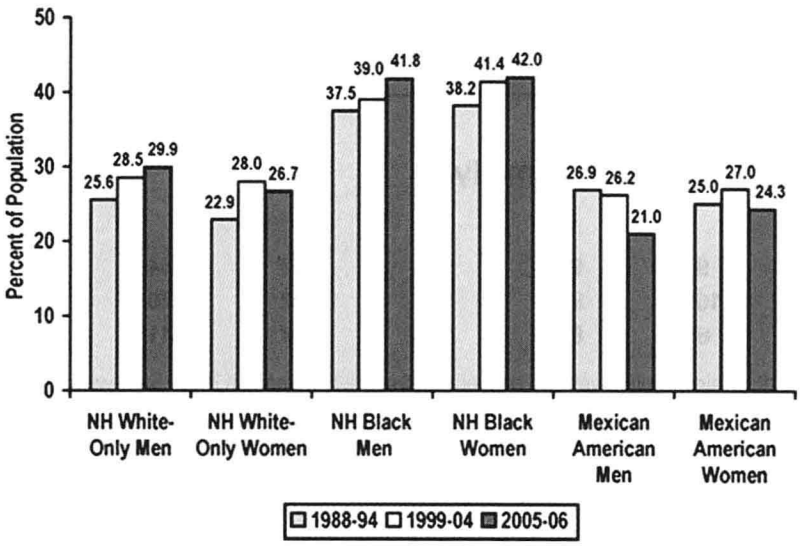


FIGURE 1-3 Age-adjusted prevalence trends for HBP in adults more than 20 years of age by race/ethnicity, sex, and surveys (NHANES: 1988 to 1994, 1999 to 2004, and 2005 to 2006). (From Lloyd-Jones D, Adams R, Carnethon M, et al. Heart disease and stroke statistics-2009 update: A report from the American Heart Association statistics committee and stroke statistics subcommittee. *Circulation* 2009;119:e21–e181, with permission.)

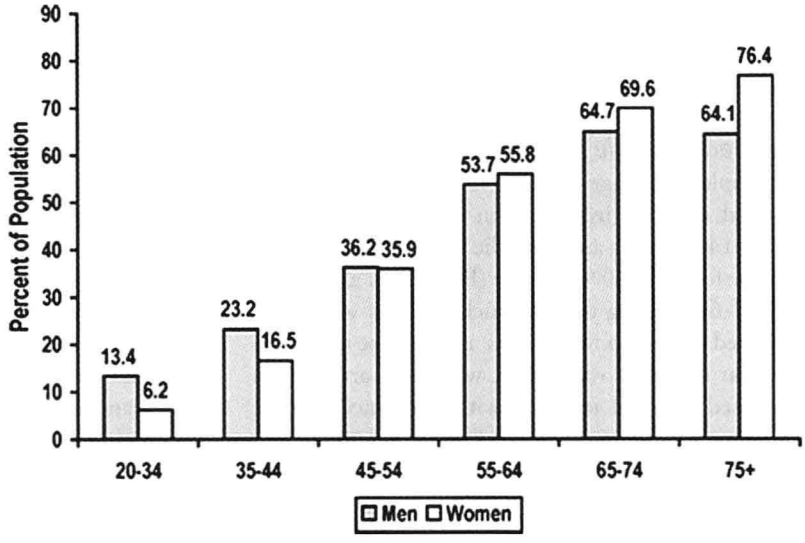


FIGURE 1-4 Prevalence of HBP in adults more than 20 years by age and sex (NHANES: 2005 to 2006). Adapted from NCHS and NHLBI. Hypertension is defined as SBP ≥ 140 mm Hg or DBP ≥ 90 mm Hg, taking antihypertensive medication, or being told twice by a physician or other professional that one has hypertension. (From Lloyd-Jones D, Adams R, Carnethon M, et al. Heart disease and stroke statistics-2009 update: A report from the American Heart Association statistics committee and stroke statistics subcommittee. *Circulation* 2009;119:e21–e181, with permission.)

than 50. It should be noted that, unlike some reports that define ISH as a systolic BP of 160 mm Hg or greater, Franklin et al. (2001a) appropriately used 140 mm Hg or higher.

ISH is associated with increased morbidity and mortality from coronary disease and stroke in patients as old as 94 years (Lloyd-Jones et al., 2005). However, as older patients develop CVD and cardiac pump function deteriorates, systolic levels often fall and a U-shaped curve of cardiovascular mortality becomes obvious: Mortality increases both in those with systolic BP of less than 120 mm Hg and in those with

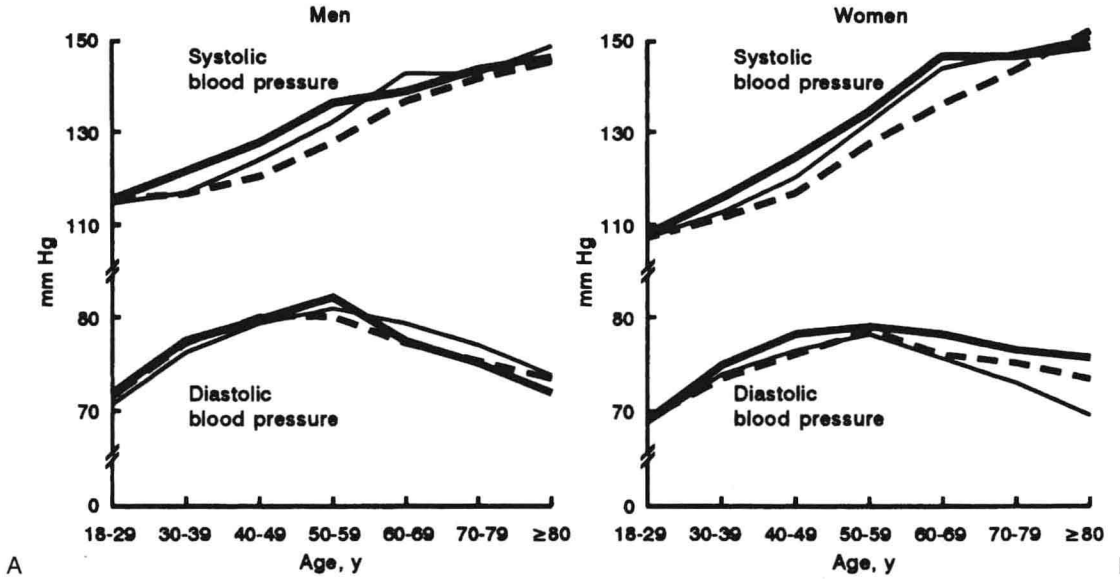


FIGURE 1-5 Mean systolic and diastolic BPs by age and race or ethnicity for men and women in the U.S. population 18 years of age or older. *Thick solid line*, non-Hispanic blacks; *dashed line*, non-Hispanic whites; *thin solid line*, Mexican Americans. Data from the NHANES III survey. (Modified from Burt VL, Whelton P, Roccella EJ, et al. Prevalence of hypertension in the U.S. adult population. Results from the Third National Health and Nutrition Examination Survey, 1988–1991. *Hypertension* 1995;25:305–313.)

systolic BP of more than 140 mm Hg. Similarly, mortality is higher in those 85 years of age or older if their systolic BP is lower than 140 mm Hg or their diastolic BP is lower than 70 mm Hg, both indicative of poor overall health (van Bemmel et al., 2006).

Isolated Diastolic Hypertension

In people under age 45, ISH is exceedingly rare but isolated diastolic hypertension (IDH), i.e., systolic below 140 mm Hg and diastolic 90 mm Hg or higher, may be found in 20% or more (Franklin et al., 2001a) (Fig. 1-6). Among the 346 such patients with IDH followed up for up to 32 years, no increase in cardiovascular mortality was found, whereas mortality was increased 2.7-fold in those with combined systolic and diastolic elevations (Strandberg et al., 2002).

Relative Versus Absolute Risk

The risks of elevated BP are often presented as relative to risks found with lower levels of BP. This way of looking at risk tends to exaggerate its degree, as is described in Chapter 5 where the benefits of therapy and the decision to treat are discussed. For now, a single example should suffice. As seen in Figure 1-7, when the associations among various levels of BP to the risk of having a stroke were examined in a total of 450,000 patients followed up for 5 to 30 years, there was a clear increase in stroke risk with increasing levels of diastolic BP (Prospective Studies Collaboration, 1995). In *relative* terms, the increase in risk was much greater in the younger group (<45 years), going from 0.2 to 1.9, which is almost a 10-fold increase in relative risk compared to the less than twofold increase in the older group (10.0 to 18.4). But, it is obvious that the *absolute* risk is much greater in the elderly, with 8.4% (18.4 – 10.0) more having a stroke with the higher diastolic BP while only 1.7% (1.9 – 0.2) more of the younger were afflicted. The importance of this increased risk in the young with higher BP should not be ignored, but the use of the smaller change in absolute risk rather than the larger change in relative risk seems more appropriate when applying epidemiologic statistics to individual patients.

The distinction between the risks for the population and for the individual is important. For the population at large, risk clearly increases with every increment in BP, and levels of BP that are accompanied by significantly increased risks should be called *high*. As Stamler et al. (1993) note: "Among persons aged 35 years or more, most have BP above optimal (<120/<80 mm Hg); hence, they are at increased CVD risk, i.e., the BP problem involves most of the population, not only the substantial minority with clinical hypertension." However, for individual patients, the absolute risk from slightly elevated BP may be quite small. Therefore, more than just the level of BP should be used to determine risk and, even more importantly, to determine the need to institute therapy (Jackson, 2009). This issue is covered in detail in Chapter 5.

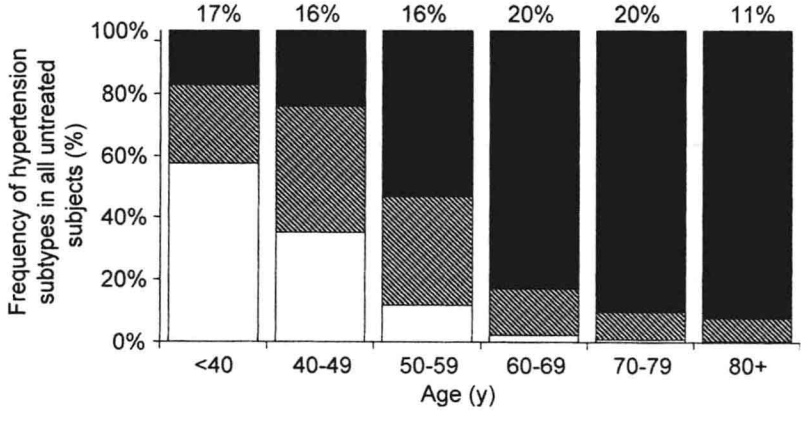


FIGURE 1-6 Frequency distribution of untreated hypertensive individuals by age and hypertension subtype. Numbers at the top of the bars represent the overall percentage distribution of all subtypes of untreated hypertension in that age group. Black bar = ISH (SBP 140 mm Hg and DBP ≥ 90 mm Hg); lined bar = SDH (SBP 140 mm Hg ≥ 90 mm Hg); open bar = IDH (SBP ≥ 140 mm Hg and DBP ≥ 90 mm Hg). (Reproduced from Franklin SS, Jacobs MJ, Wong ND, et al. Predominance of isolated systolic hypertension among middle-aged and elderly U.S. hypertensives. *Hypertension* 2001a;37: 869–874, with permission.)

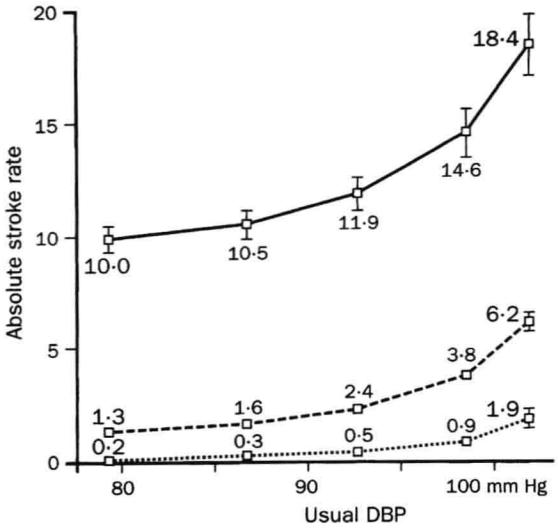


FIGURE 1-7 The absolute risks for stroke by age and usual diastolic BP in 45 prospective observational studies involving 450,000 individuals with 5 to 30 years of follow-up during which 13,397 participants had a stroke. *Dotted line*, less than 45 years old; *dashed line*, 45 to 65 years old; *solid line*, ≥65 years old. (Modified from Prospective Studies Collaboration. Cholesterol, diastolic blood pressure, and stroke: 13,000 strokes in 450,000 people in 45 prospective cohorts. *Lancet* 1995;346:1647–1653.)

Benefits of Action: Decreased Risk of CVD

We now turn to the major benefit listed in Table 1-2 that is involved in a conceptual definition of hypertension, the level at which it is possible to show the benefit of reducing CVD by lowering the BP. Inclusion of this factor is predicated on the assumption that it is of no benefit—and, as we shall see, is potentially harmful—to label a person hypertensive if nothing will be done to lower the BP.

Natural Versus Treatment-Induced BP

Before proceeding, one caveat is in order. As noted earlier, less CVD is seen in people with low BP, who are not receiving antihypertensive therapy. However, that fact cannot be used as evidence to support the benefits of therapy, because naturally low BP may offer a degree of protection not provided by a similarly low BP resulting from antihypertensive therapy (Asayama et al., 2009).

The available evidence supports that view: Morbidity and mortality rates, particularly those of coronary disease, continue to be higher in many patients at relatively low risk who are undergoing antihypertensive drug treatment than in untreated people with similar levels of BP. This has been shown for coronary disease in follow-up studies of multiple populations (Andersson et al., 1998; Clausen & Jensen, 1992; Thürmer et al., 1994) and in Japanese for strokes (Asayama et al., 2009). This issue, too, will be covered in more detail in Chapter 5, but one piece of the evidence will be acknowledged here.

An analysis of all-cause and cardiovascular mortality observed in seven randomized trials of middle-aged patients with diastolic BP from 90 to 114 mm Hg showed a reduction in mortality in the treated half in those trials wherein the population was at fairly high risk, as defined by an all-cause mortality rate of greater than 6 per 1,000 person-years in the untreated population (Hoes et al., 1995). However, in those studies involving patients who started at a lower degree of risk, those who were treated had *higher* mortality rates than were seen in the untreated groups.

These disquieting data should not be taken as evidence against the use of antihypertensive drug therapy. They do not, in any way, deny that protection against cardiovascular complications can be achieved by successful reduction of BP with drugs in patients at risk. They simply indicate that the protection may not be universal or uniform for one or more reasons, including the following: (i) only a partial reduction of BP may be achieved; (ii) irreversible hypertensive damage may be present; (iii) other risk factors that accompany hypertension may not be improved; and (iv) there are dangers inherent to the use of some drugs, in particular the high doses of diuretics used in the earlier trials covered by Hoes et al. (1995). Whatever the explanation, these data document a difference between the natural and the induced levels of BP.

In contrast to these data, considerable experimental, epidemiologic, and clinical evidences indicate that reducing elevated BP is beneficial, particularly in high-risk patients (Blood Pressure Trialists, 2008).

Rationale for Reducing Elevated BP

Table 1-3 presents the rationale for lowering elevated BP. The reduction in CVD and death (listed last in the table) has been measured to determine the BP level at which a benefit is derived from antihypertensive therapy. That level can be used as part of the operational definition of hypertension.

During the past 40 years, controlled therapeutic trials have included patients with diastolic BP levels

TABLE 1.3 Rationale for the Reduction of Elevated BP

1. Morbidity and mortality as a result of CVDs are directly related to the level of BP
2. BP rises most in those whose pressures are already high
3. In humans, there is less vascular damage where the BP is lower: beneath a coarctation, beyond a renovascular stenosis, and in the pulmonary circulation
4. In animal experiments, lowering the BP has been shown to protect the vascular system
5. Antihypertensive therapy reduces CVD and death

as low as 90 mm Hg. Detailed analyses of these trials are presented in Chapter 5. For now, it is enough to say that there is no question that protection against CVD has been documented for reduction of diastolic BP levels that start at or above 95 mm Hg, but there is continued disagreement about whether protection has been shown for those whose diastolic BP starts at or above 90 mm Hg who are otherwise at low risk. Similarly, protection for the elderly with ISH has been documented with a systolic BP ≥ 160 mm Hg or higher, but there are no data for the large elderly population between 140 and 160 mm Hg. Therefore, expert committees have disagreed about the minimum level of BP at which drug treatment should begin.

In particular, the British guidelines (Williams et al., 2004) are more conservative than those from the United States (Chobanian et al., 2003). Whereas the U.S. guidelines recommend drug therapy for all with sustained BP above 140/90 mm Hg, the British use 160/100 mm Hg as the level mandating drug therapy with the decision to be individualized for those with levels of 140 to 159/90 to 99 mm Hg.

These disagreements have highlighted the need to consider more than the level of BP in making that decision. As will be noted in Chapter 5, the consideration of other risk factors, target organ damage, and symptomatic CVD allows a more rational decision to be made about whom to treat.

Prevention of Progression of Hypertension

Another benefit of action is the prevention of progression of hypertension, which should be looked on as a surrogate for reducing the risk of CVD. Evidence of that benefit is strong, based on data from multiple, randomized, placebo-controlled clinical trials. In such trials, the number of patients whose hypertension progressed from their initially less severe degree to more severe hypertension, defined as BP greater than 200/110 mm Hg, increased from only 95 of 13,389 patients on active treatment to 1,493 of 13,342 patients on placebo (Moser & Hebert, 1996).

Risks and Costs of Action

The decision to label a person hypertensive and begin treatment involves assumption of the role of a patient, changes in lifestyle, possible interference with the quality of life (QOL), risks from biochemical side effects of therapy, and financial costs. As will be emphasized in the next chapter, the diagnosis should not be based on one or only a few readings since there is often an initial white-coat effect which frequently dissipates after a few weeks, particularly when readings are taken out of the office.

Assumption of the Role of a Patient and Worsening QOL

Merely labeling a person hypertensive may cause negative effects as well as enough sympathetic nervous system activity to change hemodynamic measurements (Rostrup et al., 1991). People who know they are hypertensive may have considerable anxiety over the diagnosis of "the silent killer" and experience multiple symptoms as a consequence (Kaplan, 1997). The adverse effects of labeling were identified in an analysis of health-related QOL measures in hypertensives who participated in the 2001–2004 NHANES (Hayes et al., 2008). Those who knew they were hypertensive had significantly poorer QOL measures than did those who were hypertensive with similar levels of BP but were unaware of their condition. QOL measures did not differ by the status of hypertension control. Fortunately, hypertensive people who receive appropriate counseling and comply with modern-day therapy usually have no impairment and may have improvements in overall QOL measures (Degl'Innocenti et al., 2004; Grimm et al., 1997).

Risks from Biochemical Side Effects of Therapy

Biochemical risks are less likely to be perceived by the patient than the interferences with QOL, but they may actually be more hazardous. These risks are discussed in detail in Chapter 7. For now, only two will be mentioned: Hypokalemia, which develops in 5% to 20% of diuretic-treated patients, and elevations in

blood triglyceride and glucose levels, which may accompany the use of β-blockers.

Overview of Risks and Benefits

Obviously, many issues are involved in determining the level of BP that poses enough risk to mandate the diagnosis of hypertension and to call for therapy, despite the potential risks that appropriate therapy entails. An analysis of issues relating to risk factor intervention by Brett (1984) clearly defines the problem:

> Risk factor intervention is usually undertaken in the hope of long-term gain in survival or quality of life. Unfortunately, there are sometimes trade-offs (such as inconvenience, expense, or side effects), and something immediate must be sacrificed. This tension between benefits and liabilities is not necessarily resolved by appealing to statements of medical fact, and it is highlighted by the fact that many persons at risk are asymptomatic. Particularly when proposing drug therapy, the physician cannot make an asymptomatic person feel any better, but might make him feel worse, since most drugs have some incidence of adverse effects. But how should side effects be quantitated on a balance sheet of net drug benefit? If a successful antihypertensive drug causes impotence in a patient, how many months or years of potentially increased survival make the side effect acceptable? There is obviously no dogmatic answer; accordingly, global statements such as "all patients with asymptomatic mild hypertension should be treated" are inappropriate, even if treatment were clearly shown to lower morbidity or mortality rates.

On the other hand, as noted in Figures 1-1 and 1-2, the risks related to BP are directly related to the level, progressively increasing with every increment of BP. Therefore, the argument has been made that, with currently available antihypertensive drugs, which have few, if any, side effects, therapy should be provided even at BP levels lower than 140/90 mm Hg to prevent both the progression of BP and target organ damages that occur at "high-normal" levels (Julius, 2000). Dr. Julius and coworkers have conducted a controlled trial of placebo versus active drug therapy in such patients to prove the principle that drug therapy can prevent or at least delay progression (Julius et al., 2006).

An even more audacious approach toward the prevention of cardiovascular consequences of hypertension has been proposed by the English epidemiologists Wald and Law (2003) and Law et al. (2009). They recommend a "Polypill" composed of low doses of a statin, a diuretic, an ACEI, a β-blocker, folic acid (subsequently deleted), and aspirin to be given to all people from age 55 on and everyone with existing CVD, regardless of pretreatment levels of cholesterol or BP. Wald and Law concluded that the use of the Polypill in this manner would reduce IHD events by 88% and stroke by 80%, with one third of people benefiting and gaining an average 11 years of life free from IHD or stroke. They estimated side effects in 8% to 15% of people, depending on the exact formulation. In their more recent analysis, the use of their currently devised Polypill would provide a 46% reduction in CHD and a 62% reduction in stroke (Law et al., 2009).

The ability to reduce CVD in developing societies depends, in large part, on the costs of therapy (Lim et al., 2007). A polypill with generic components would meet this need. A pilot trial with such a polypill has been performed (Indian Polycap Study, 2009).The risk reductions from the observed effects of the Polycap were estimated to be a 62% reduction in CHD and 48% reduction in strokes. These effects were seen after only 12 weeks; greater benefits might be seen over a longer duration of therapy. Therapy with the Polycap was discontinued by 16% and a variety of side effects were seen in 3% to 9% of the subjects.

Both the investigators and a commentator (Cannon, 2009) call for additional, larger scale trials with hard end-points. Cannon (2009) predicts that it may be possible to "vastly broaden the number of patients who might benefit from drugs that have been proven in multiple trials to reduce cardiovascular disease and mortality." The adoption of such an inexpensive therapy will have to overcome numerous obstacles, not the least of which would be the billions of dollars that the pharmaceutical companies with patent-protected antihypertensive drugs will use to persuade the public, the FDA, and Congress that this shall not come to pass.

OPERATIONAL DEFINITIONS OF HYPERTENSION

Seventh Joint National Committee Criteria

In recognition of the data shown in Figures 1-1 and 1-2, the Seventh Joint National Committee report