

TENTH EDITION

# 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

**H**ypertension 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

# C O N T E N T S

*Dedication* iii

*Preface to the Tenth Edition* iv

<b>1</b>	Hypertension in the Population at Large	1
<b>2</b>	Measurement of Blood Pressure	20
<b>3</b>	Primary Hypertension: Pathogenesis	42
<b>4</b>	Primary Hypertension: Natural History and Evaluation	108
<b>5</b>	Treatment of Hypertension: Why, When, How Far	141
<b>6</b>	Treatment of Hypertension: Lifestyle Modifications	168
<b>7</b>	Treatment of Hypertension: Drug Therapy	192
<b>8</b>	Hypertensive Crises	274
<b>9</b>	Renal Parenchymal Hypertension	288
<b>10</b>	Renovascular Hypertension	319
<b>11</b>	Primary Aldosteronism	339
<b>12</b>	Pheochromocytoma (with a Preface about Incidental Adrenal Masses)	358
<b>13</b>	Hypertension Induced by Cortisol or Deoxycorticosterone	378
<b>14</b>	Other Forms of Identifiable Hypertension	392
<b>15</b>	Hypertension with Pregnancy and the Pill	410
<b>16</b>	Hypertension in Childhood and Adolescence	430

*Appendix: Patient Information* 455

*Index* 457

# Hypertension in the Population at Large

**H**ypertension 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.

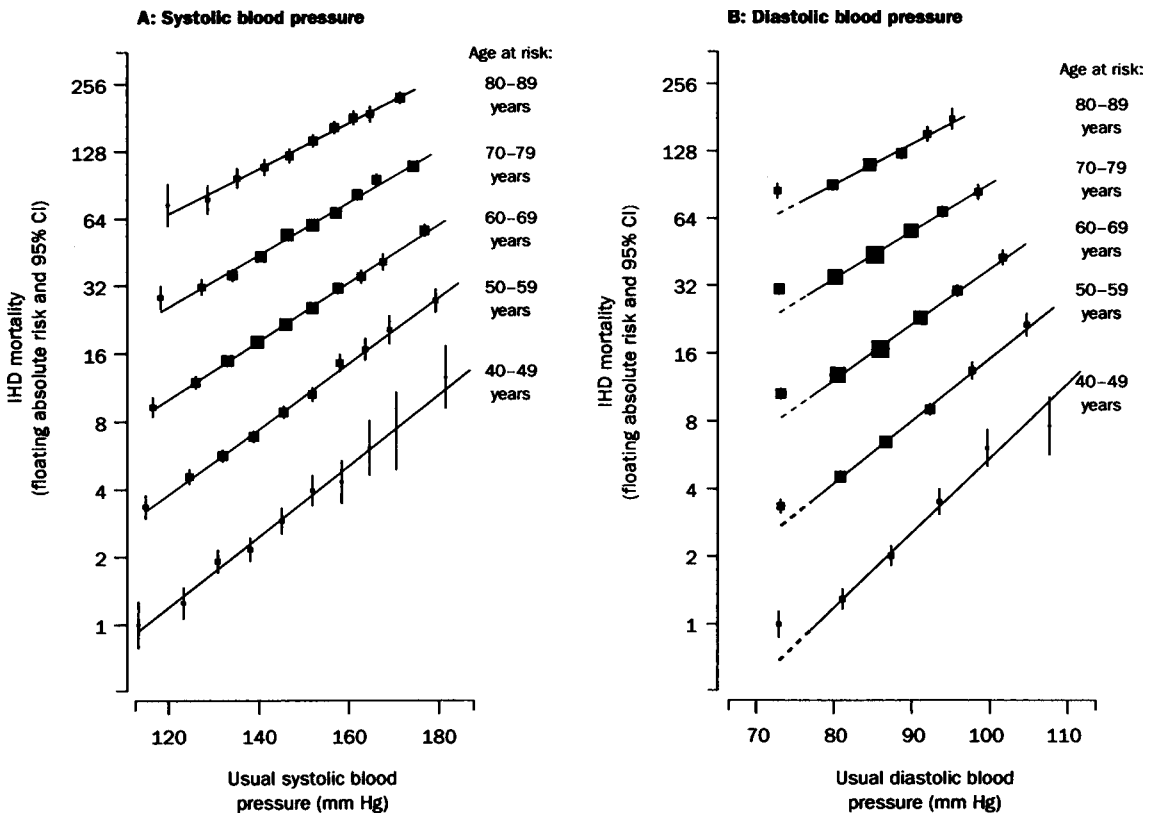
The striking impact of aging was seen among participants in the Framingham Heart Study: Among

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"
	Decrease monetary costs of catastrophic events	Interfere with QOL Require changes in lifestyle Add risks and side effects from therapy Add monetary costs of health care
Inaction	Preserve "nonpatient" role	Increase risk of CVD, debility, and death Increase monetary costs of catastrophic events
	Maintain current lifestyle and QOL	
	Avoid risks and side effects of therapy	
	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.

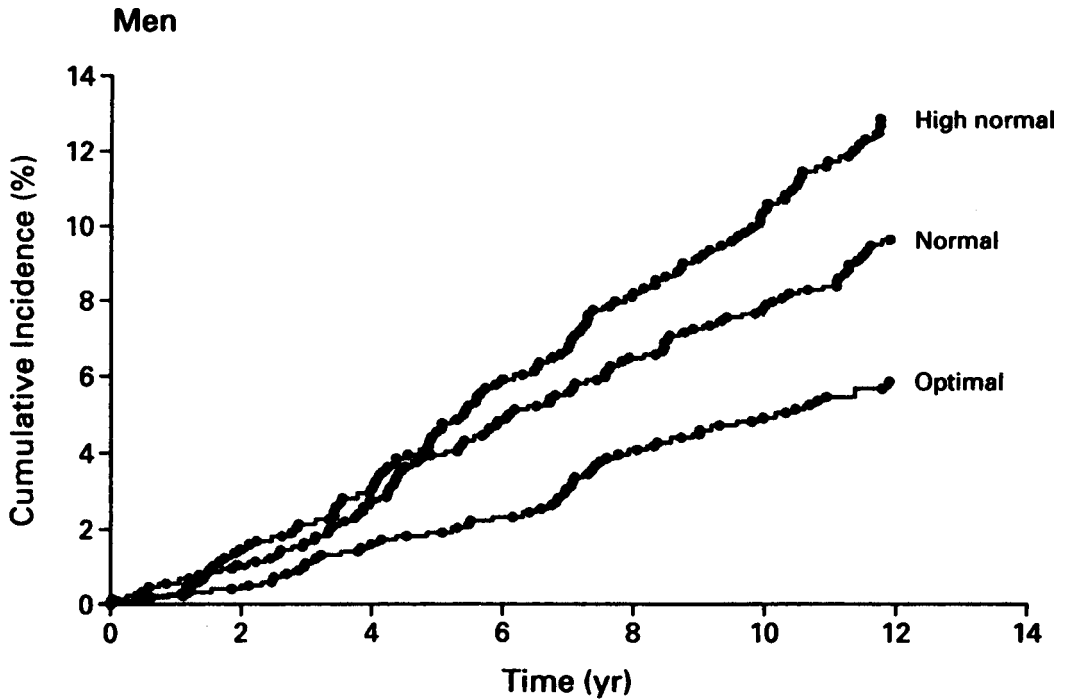
A similar relation between the levels of BP and CVDs has been seen in 15 Asian Pacific countries, although the association is even stronger for stroke and somewhat less for coronary disease than seen in the western world (Martiniuk et al., 2007). Some of these differences in risk and BP levels can be 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

<b>Optimal</b>	<b>1005</b>	<b>995</b>	<b>973</b>	<b>962</b>	<b>934</b>	<b>892</b>	<b>454</b>
<b>Normal</b>	<b>1059</b>	<b>1039</b>	<b>1012</b>	<b>982</b>	<b>952</b>	<b>892</b>	<b>520</b>
<b>High normal</b>	<b>903</b>	<b>879</b>	<b>857</b>	<b>819</b>	<b>795</b>	<b>726</b>	<b>441</b>

**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.)