CLINICAL HYPERTENSION

Fourth Edition

Norman M. Kaplan

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Accurate indications, adverse reactions, and dosage schedules for drugs are provided in this book, but it is possible that they may change. The reader is urged to review the package information data of the manufacture of the medications mentioned.

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Preface to the Fourth Edition

Almost 15 years ago, in putting together the first edition of *Clinical Hypertension*, I wrote: "There is a need for a clinically oriented, up-to-date book on hypertension that focuses all of the significant advances made during the last ten years into a practical, rational approach toward the management of patients. I hope this book will serve that need." The favorable reception accorded the first three editions indicates that this book has met at least part of this need.

It has only been a little over four years since the third edition, but the rapidly progressing increase in research and clinical work in the field demands a frequent update. Once again, almost every page has been revised, using the same general aims:

- to give most attention to the most common problems. Primary (essential) hypertension, unlike the scanty attention given in many texts, takes up almost half of the book.
- to cover every form of hypertension. For those mentioned only briefly, references are provided.
- to include the latest data, even if available only in abstract form.
- to provide enough pathophysiology to base clinical judgment on sound reason.
- to attempt to be objective and to clearly identify biases. Although my views may be counter to those of others, I have tried to give reasonable attention to those with whom I disagree. I am aware that I may be wrong.

Once gain I am pleased that Dr. Ellin Lieberman, Head of Pediatric Nephrology at the Children's Hospital of Los Angeles, has contributed a chapter on hypertension in children and adolescents. Many others have helped. Portions of the text have been reviewed by colleagues at the Medical School, including Drs. Domingo Gonzalez, Harold Helderman, David Hyman, Roderick Meese, and C. V. S. Ram. I am particularly indebted to Dr. William Neal for his imaginative editing. I have been fortunate in being in an academic setting wherein such endeavors are nurtured, much to the credit of our chief, Dr. Donald W. Seldin. I have been greatly helped by the staff of the Medical Illustration department, and by my secretaries, Susan Beaubien and Sharon Washington. And lastly, the forebearance of my wife Audrey can only be acknowledged by the promise that I will not do it again—at least for another four years.

The time and energy required to write a medical book almost single-handedly have made the endeavor increasingly rare and perhaps foolhardly. But I believe the reader benefits from having a single overall perspective, systematically presented, with little redundancy but considerable cross-reference. To divide the task between multiple co-authors may provide greater depth in certain areas but almost certainly will leave some areas uncovered and others rehashed unevenly.

As I went through this revision, I was as much surprised at the need for changes in what was in the third edition as in the amount of totally new knowledge that had to be added. Examples of the changes are: a totally different approach toward the workup for renovascular hypertension; a redefinition of the level of blood pressure used as a basis for instituting therapy; a change in the recommendations for the initial drug to be chosen.

Consider just a few of the new items: atrial natriuretic hormone, sleep apnea, alcohol-induced hypertension, calcium antagonists. The list of additions and corrections could go on for pages. I can only suggest that copies of the third edition be kept as testaments of what was known in 1982. If I'm still around and capable, putting together the fifth edition should be just as exciting and demanding as working on the fourth.

Contents

1

Hypertension in the Population At Large

Hypertension, in the U.S., is now the leading indication both for office visits to physicians (Lawrence and McLemore, 1983) and for the use of prescription drugs (Baum et al, 1985). These leading positions reflect the tremendous increase in the number of people with hypertension who have been identified and brought under active treatment over the past 20 years. This increase has occurred throughout the world but probably nowhere to the degree as in the U.S.

However, for many, here and elsewhere, the risks of unrecognized and untreated hypertension persist. High blood pressure is one of the major risk factors for premature death and disability because of the large number of people afflicted and the consequences of uncontrolled hypertension. The main burden of illness associated with hypertension arises not from the relatively few with severe disease, but from the masses of people with pressures that are only minimally elevated.

However, there are risks of therapy, some of which have only surfaced in the last few years as more and more of the larger population of patients with mild hypertension have been given antihypertensive drug therapy. In the rush to identify and treat all with high blood pressure, there is a need for caution not to falsely label and inappropriately treat many millions of people.

In this first chapter, the overall problems of hypertension for the population at large will be considered. I will attempt to define the disease, quantitate its prevalence and risks, classify types, and describe the current status of its detection and control. The next chapter will consider the individual patient, covering the measurement of the blood pressure, the management of its variability, and guidelines for evaluation of the types, consequences, and risks of hypertension.

A 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 blood pressure to be considered abnormal. Sir George Pickering for many years challenged the wisdom of that debate and decried the search for an arbitrary dividing line between normal and high blood pressure. In 1972 he restated his

argument that "there is no dividing line. The relationship between arterial pressure and mortality is quantitative; the higher the pressure, the worse the prognosis." He saw "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 in dealing with precise criteria, even if they are basically arbitrary. To consider a blood pressure of 138/88 as normal and one of 140/90 as high is obviously arbitrary, but medical practice requires the setting of criteria. Those criteria are required in order to decide upon the need for workup and therapy. They should be established on some rational basis, and that basis must include the risks of disability and death that are associated with various levels of blood pressure as well as the ability to reduce those risks by lowering the blood pressure. 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, since action, i.e., making the diagnosis of hypertension at any level of blood pressure, involves risks and costs as well as benefits, and inaction may provide benefits (Table 1.1). Therefore, I have proposed that the conceptual definition of hypertension be "that level of blood pressure at which the benefits (minus the risks and costs) of action exceed the risks and costs (minus the benefits) of inaction" (Kaplan, 1983).

Most of the elements of this conceptual definition are fairly obvious, although some—such as interference with life style and risks from biochemical side effects of therapy—may not be so obvious and will be analyzed further in this and later chapters. Let us turn first to the issue of the risks of premature cardiovascular disease, since they have been widely taken as the prime, if not the only, basis for deciding the level of blood pressure that is to be called abnormal.

Risks of Inaction: The Risks of Elevated Blood Pressure

The risks of elevated blood pressure have been determined largely from large scale epidemiological surveys.

The Framingham Study

In this monumental study, begun in 1948, observations have been made every 2 years upon 5200 men and women aged 30 to 62 at entry (Kannel et al, 1984; Castelli, 1984). The data relating blood pressure to cardiovascular morbidity and mortality document a number of important points.

—The morbidity and mortality from coronary disease rise progressively with systolic (SBP) and diastolic blood pressure (DBP), more so in men than in women (Fig. 1.1)

—The risks apply to the incidence of virtually all of the major types of cardiovascular disease (Fig. 1.2).

—The risks from an elevated blood pressure are independent of those from other known cardiovascular risk factors.

The Pooling Project

The data from the Framingham men have been combined with those from four other

Table 1.1. Factors Involved in the Conceptual Definition of Hypertension

	Action	Inaction
Benefits	Reduce strokes, heart failure, renal damage	Maintain nonpatient role
	Decrease mortality from heart attacks (?)	Less interference with life style
	Prevent progression of hypertension	
	Diagnose other family members	
Risk/cost	Assume role of patient	Increase risk of premature cardiovascular disease
	Interfere with life style	
	Add risks from biochemical side effects of therapy	Fail to diagnose other family members
	Add costs of health care	

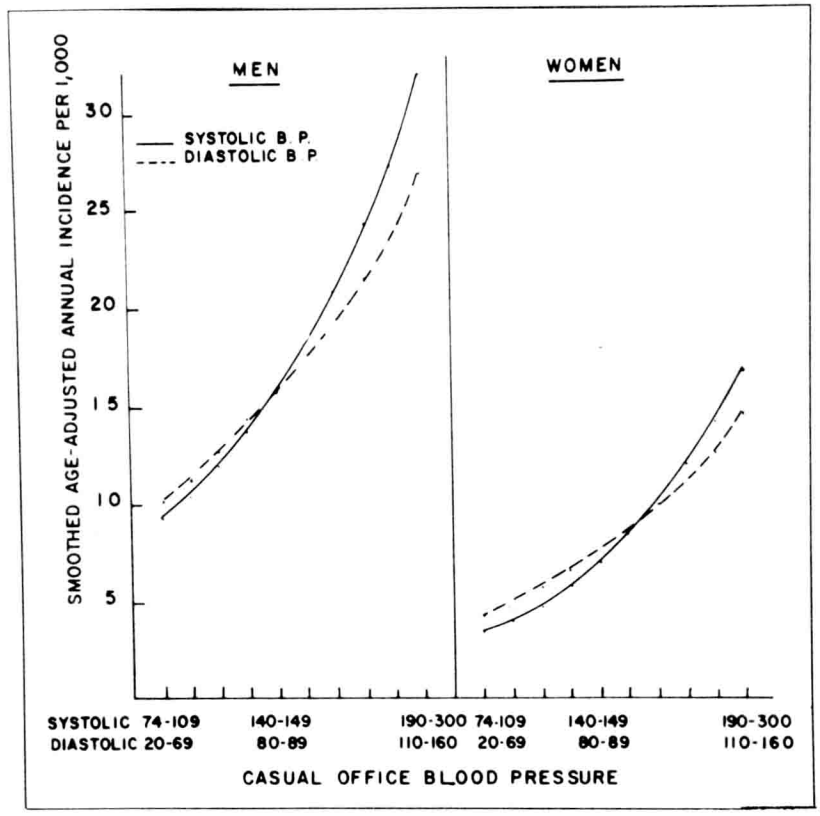

Figure 1.1. The incidence of coronary heart disease according to systolic vs diastolic blood pressure in men and women aged 45 to 74 in the Framingham study over a 20-year follow-up. (From Castelli WP: *Am J Med* 76:4, 1984.)

prospective analyses to examine the risks for major coronary disease. Overall, more than 7000 white men aged 40 to 59 with no clinical evidence of heart disease were followed for 10 years by investigators in five locations in the U.S. Since data from these separate studies were considered comparable, they have been pooled (Pooling Project Research Group, 1978). They show a doubling of the rate of major coronary events over an 8.6-year interval among those men whose initial diastolic blood pressure levels were above 95 mm Hg, a level which put them in the upper 20% of the entire cohort (Table 1.2). Significant increases in relative risk were observed at even lower levels of diastolic blood pressure, when compared to the experience of those with diastolics below 80 (Quintiles 1 and 2).

Actuarial Data

Additional evidence for the risk related to hypertension comes from the 1979 Build and Blood Pressure Study (Society of Actuaries, 1980) (Fig. 1.3). Mortality increases with each increment of both systolic and diastolic blood pressures, more strikingly in men than women, but almost doubled in both when the diastolic pressures are as minimally elevated as 100 mm Hg. Most of these deaths result from coronary artery disease.

These actuarial data may be faulted because they are derived from a population largely white and upper-middle class, with only one or a few blood pressures having been taken, usually at a single visit. However, the size of the data base—4.5 million people followed for up to 20 years—demands that these findings be considered.

Other Epidemiologic Data

Since the data from the three previous studies were derived primarily from white middle-class Americans, the findings from other populations are worth examining. Similar relations between blood pressure

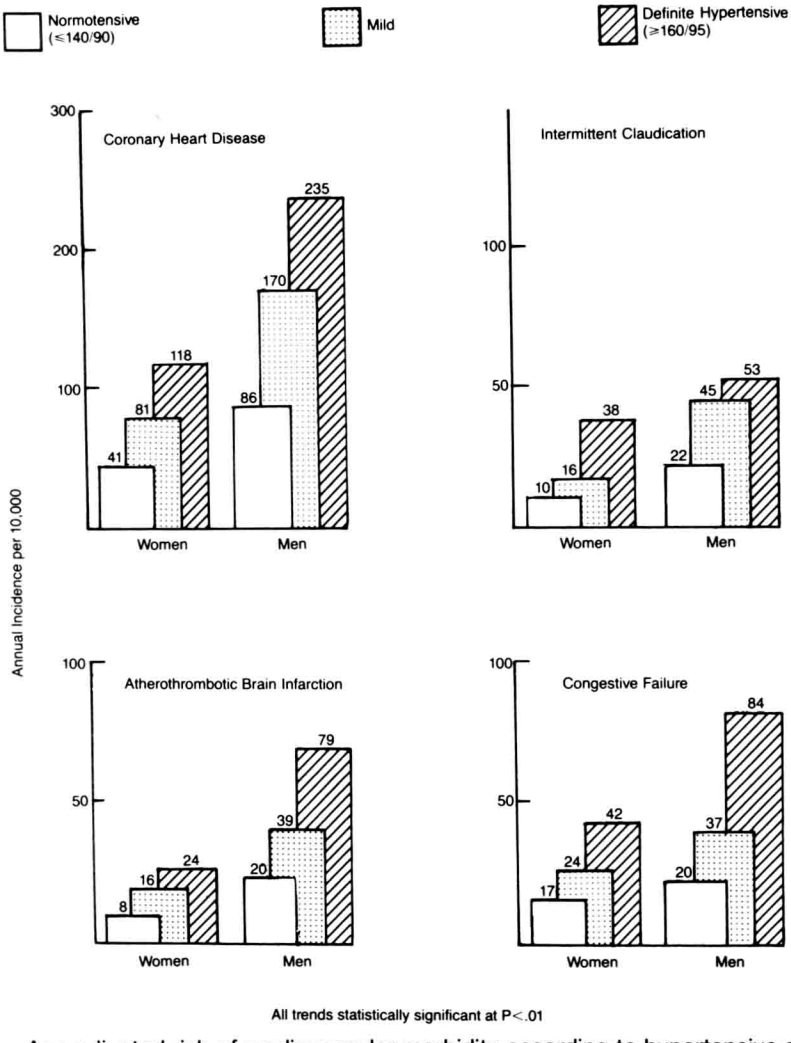

Figure 1.2. Age-adjusted risk of cardiovascular morbidity according to hypertensive status at each biennial examination over 26-year follow-up of the men and women aged 35 to 84 in the Framingham cohort. (From Kannel WB, Doyle JT, Ostfeld AM, et al: Original resources for primary prevention of atherosclerotic diseases. *Circulation* 70:157A, 1984 and by permission of the American Heart Association, Inc.)

and both morbidity and mortality have been observed in black men and women in Evans County, Georgia (Deubner et al, 1975), Swedish men born in 1913 (Svardsudd and Tibblin, 1979), young Canadian pilots (Rabkin et al., 1978), and the general population in South Wales (Miall and Chinn, 1974).

One discrepant report came from a 13-year follow-up of 1065 rural Jamaicans (Ashcroft and Desai, 1978). Overall mortality was increased only at pressures above 180 mm Hg systolic or 110 diastolic, with no association observed with lower levels of blood pressure. This difference may reflect a lower overall incidence of atherosclerotic disease in this population.

Gender and Risk

Women tolerate hypertension better than men: morbidity and mortality rates from any level of hypertension are higher in men (Lerner and Kannel, 1986). It takes higher pressures to hurt women, but when their pressures are high, they suffer. This is clearly demonstrated in the Framingham Study (Fig. 1.2) and in the actuarial data (Fig. 1.3). Nonetheless, the lower rates of coronary dis-

Table 1.2. Risk (8.6-Year) for Major Coronary Events in 7054 White Men by Diastolic Blood Pressure at Entry[a]

Diastolic BP at Entry[b]	Adjusted Rate of Major Coronary Events per 1000	Relative Risk	Absolute Excess Risk Per 1000
Below 80 (Quintiles 1 and 2)	66.0	1.0	
80–87 (Quintile 3)	100.6	1.52	34.6
88–95 (Quintile 4)	109.4	1.66	43.4
Above 95 (Quintile 5)	143.3	2.17	77.3

[a] Data reprinted with permission from The Pooling Project Research Group: Relationship of blood pressure, serum cholesterol, smoking habit. Relative weight and ECG abnormalities to incidence of major coronary events: Final Report of the Pooling Project. *J Chronic Dis* 31:201, 1978 and by permission of the American Heart Association, Inc.

[b] The blood pressure ranges varied slightly for various 5-year age groups: 40 to 44, 45 to 49, etc.

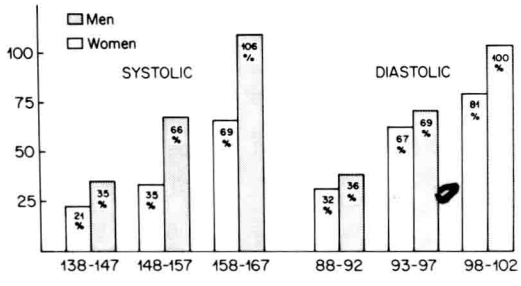

Figure 1.3. Excess mortality observed over 20 years by initial systolic and diastolic blood pressures among 4.5 million men and women who obtained life insurance. (From Society of Actuaries and Association of Life Insurance Medical Directors of America: *Blood Pressure Study,* 1979. Society of Actuaries, 1980.)

ease at all levels of either systolic or diastolic blood pressure among women aged 45 to 74 followed for 20 years in the Framingham study (Fig. 1.1) suggest that somewhat higher levels could be used to define hypertension among women.

Race and Risk

Blacks tend to have higher levels of blood pressure and suffer more overall mortality at all levels (Fig. 1.4) (Neaton et al, 1984). The data in Figure 1.4 were obtained during the 5-year Multiple Risk Factor Intervention

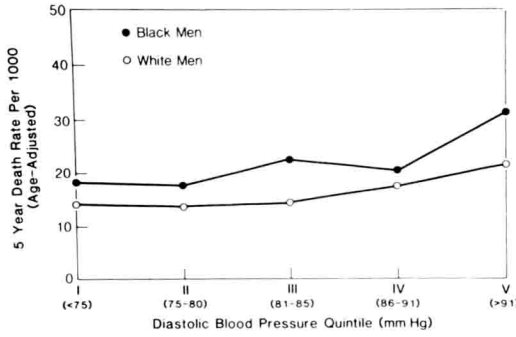

Figure 1.4. Five-year age-adjusted total mortality rate per 1,000 by diastolic blood levels among the 23,490 black men and the 325,384 white men screened in the Multiple Risk Factor Intervention Trial. (From Neaton JD, Kuller LH, Wentworth D, et al: *Am Heart J* 108:759, 1984.)

Trial (MRFIT) involving over 23,000 black men and 325,000 white men. These data portray the results of an interesting racial difference: black men with DBP above 90 had lower mortality rates than white men from coronary heart disease but higher mortality from cerebrovascular disease. The greater risk for stroke and either a lower or a no more than equal risk for heart attack among black hypertensives has long been noted, although South Carolina black men have been found also to have a higher rate of sudden death (Keil et al, 1984).

The greater risk of hypertension among blacks suggests that more attention be paid to even lower levels of hypertension among them, but there seems little reason to use different criteria for the diagnosis of hypertension in blacks than in whites.

Other races differ in their relative risk from hypertension in both the frequency and type of cardiovascular complications. These in turn may largely reflect differences in diet and life style (Stamler and Liu, 1983).

The Risk from Elevated Blood Pressure in the Elderly

The number of people over age 65 is rapidly increasing: in 50 years, one of every five people in the United States will be over 65 (Kirkendall and Hammond, 1980). Blood pressure, particularly the systolic, tends to increase progressively with age (Fig. 1.5), and the elderly with hypertension have a greater risk of dying from cardiovascular disease.

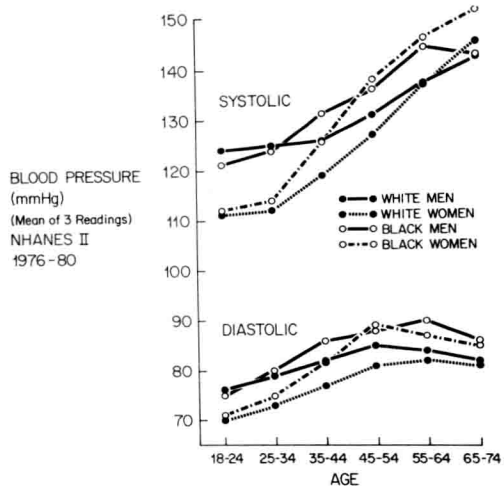

Figure 1.5. The mean systolic and diastolic blood pressures for white and black men and women in various age groups in the 1976–80 National Health and Nutrition Examination Survey. (From Rowland M, Roberts J: *NCHS Advance Data,* No. 84, *Vital and Health Statistics of the National Center for Health Statistics,* October 8, 1982.)

Diastolic Elevations. With advancing age, diastolic blood pressures above 90 mm Hg are associated with a progressively increased risk of cardiovascular events (Table 1.3). Data from the VA Cooperative Study (1972) portray the danger: among men with diastolic pressures between 90 and 114 mm Hg, 62.8% of those 60 years or older developed a major cardiovascular complication during an average 5 years on placebo.

Systolic Elevations. As many as one-third of people over age 65 have isolated elevations in systolic blood pressure, defined as a diastolic below 90 and a systolic above 140 mm Hg. The Framingham data show that the systolic blood pressure is more of a determinant of risk than is the diastolic and that this relation holds true among the elderly as well (Harris et al, 1985) (Fig. 1.6). In the Hypertension Detection and Follow-up Program, 8-year all-cause mortality was more than twice higher among those with isolated systolic hypertension (SBP > 160, DBP < 90) than among those with SBP < 160 (Curb et al, 1985b). Each millimeter increase in SBP was associated with about a 1% increase in 8-year mortality. The high pressures generated during systole put an immediate, direct burden on the heart and the resistance arterioles, so that all forms of cardiovascular disease are logically more frequent. The risk for stroke is particularly ominous (Table 1.4).

Table 1.3. Risk of Cardiovascular Events According to Diastolic Blood Pressure in Men and Women 45 to 74 (Framingham Heart Study: 18-Year Follow-up)[a]

Age	Average Annual Incidence per 1000 Population					
	Men			Women		
	<90	90–109	≥110	<90	90–109	≥110
45–54	9.5	17.7	33.6	3.0	5.9	13.6
55–64	18.0	37.7	62.2	10.2	15.6	39.4
65–74	24.2	42.9	55.6	17.2	32.4	54.5

[a] From 1984 Report of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure: *Arch Intern Med* 144:1045–1047, May 1984.

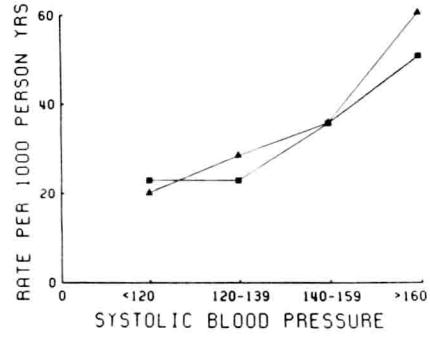

Figure 1.6. Relationship between systolic blood pressure (mm Hg) and the rate per 1000 person-years for the development of cardiovascular disease after age 65 in the Framingham population, based upon either single systolic blood pressure at age 65 (■) or average systolic blood pressure prior to age 65 (▲). (From Harris T, Cook EF, Kannel W, et al: Blood pressure experience and risk of cardiovascular disease in the elderly. *Hypertension* 7:118, 1985 and by permission of the American Heart Association, Inc.)

As people become very old, into their 70s and 80s, hypertension may become less and less of a risk factor, presumably because those most susceptible to the cardiovascular risks of hypertension will already have died. Unlike what has been seen in people below age 65, 2-year mortality rates were lower in those aged 85 or more with high blood pressure (Rajala et al, 1983) (Fig. 1.7). As expressed by J.R.A. Mitchell (1983), "whereas in the younger groups who have figured in

Table 1.4. Risk of Stroke over 24 Years of Follow-up in Framingham Heart Study (Men and Women Aged 50 to 79 with Diastolic Blood Pressure below 95 mm Hg)[a]

Systolic BP	Men		Women	
	Population at Risk (Person Years)	Age-adjusted Rate/ 1000 in 2 Years	Population at Risk (Person Years)	Age-adjusted Rate/1000 in 2 Years
Below 140	6735	5.3	7827	3.8
140–159	1816	7.4	2894	6.6
Above 160	544	21.0	1295	9.6

[a] Data from Kannel WB, Wolf PA, McGee DL, et al: *JAMA* 245:1225–1229, March 27, 1981.

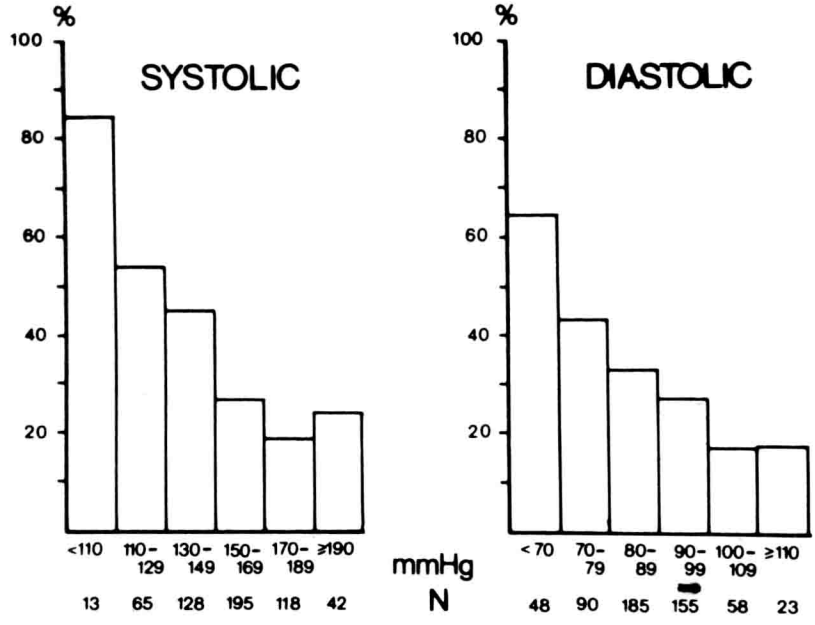

Figure 1.7. All cause mortality over the 2 years after systolic and diastolic (4th phase) blood pressures were measured in 559 people 85 years old or more living in Tampere, Finland. (From Rajala S, Haavisto M, Heikinheimo R, et al: *Lancet* 2:520, 1983.)

large-scale longitudinal studies, such as Framingham and the Pooling Project, high blood pressure is indeed a pointer to what is about to happen (stroke, heart failure, and myocardial infarction), in the very elderly low pressure may be a monument to cardiovascular problems which have already happened."

Nonetheless, hypertension remains a risk for those whose age is between 65 and 85. In two such populations followed for 9 and 10 years, respectively, high blood pressure had predictive value for all cause mortality in one (Barrett-Connor et al, 1984) and cardiovascular morbidity in the other (Agner, 1983).

Relative vs Absolute Risk

In most of the data presented to this point, the risks related to elevated blood pressure have been presented in relation to those found with lower levels of blood pressure, in a relative manner. This way of looking at risk may tend to exaggerate its degree.

For example, the life insurance actuarial data (Fig. 1.3) show that men with an initial DBP of 88 to 92 mm Hg had a mortality rate over the ensuing 20 years of 36% over that of the normotensive population. Since the approximate 20-year mortality rate for normotensive men is 20%, that translates into an increase of 7.2%, not an inconse-

quential increase but not the additional 36% on top of the 20% rate, as some have assumed.

Similarly, the Pooling Project data (Table 1.2) show a 52% increase in the relative risk for coronary disease over an 8.6-year interval for white men with initial DBP in the 80 to 87 mm Hg range, as compared to that for those with DBP below 80. That 52% increase is derived by taking the increased rate of actual coronary events, 100.6 per 1000 vs 66 per 1000, and dividing the difference (34.6) by the rate for those with the lower DBP (66). The 52% higher relative risk, then, reflects an actual 34.6 per 1000, or 3.5% higher, absolute excess risk. The importance of this excess risk should not be ignored by use of the smaller absolute risk numbers, but caution is needed in applying epidemiological statistics to clinical medicine.

Fortunately, the Framingham data provide an easy way to assess the actual risk for every patient above age 35. As we shall see in the next chapter, that risk is unevenly distributed and closely related to the degree of concomitant risk factors.

For now, however, the problem seems well defined: for the population at large, risk clearly increases with every increment in blood pressure; for the entire population, levels of blood pressure that are accompanied by significantly increased risks should be called "high." However, for individual patients, the absolute risk from slightly elevated blood pressure may be quite small. Therefore, more than just the level of blood pressure should be used in the determination of risk and, even more importantly, in the decision to diagnose or treat the person for hypertension.

It should be noted that most of the evidence for the risk of elevated blood pressure reviewed until now comes from the U.S. A great deal more is available from multiple populations around the world (Keys et al, 1984). Suffice it to say that, with the previously noted possible exception of the very old, morbidity and mortality—mostly related to cardiovascular disease—increase progressively with each increment in blood pressure. In some populations, such as in Australia (MacMahon and Leeder, 1984), hypertension may be even more of a risk for premature cardiovascular disease than in the United States.

Benefits of Action: Reducing Cardiovascular Disease

Let us now turn to the second major factor listed in Table 1.1 as being involved in a conceptual definition of hypertension, the level at which it is possible to show benefit from the use of available means of lowering the blood pressure. 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 as hypertensive if nothing is to be done to lower the blood pressure.

Natural vs Induced Blood Pressure

Before proceeding, one caveat is in order. As we have noted, the lower the blood pressure, the less cardiovascular disease seen in the general population that is not on antihypertensive therapy. However, that fact cannot be used as evidence in support of the benefits of therapy. A blood pressure that is low naturally may offer a degree of protection that is not provided by a similarly low blood pressure resulting from antihypertensive therapy.

The available evidence supports that view: patients under antihypertensive drug treatment do continue to have a higher morbidity and mortality rate than untreated people with similar levels of blood pressure. This has been shown in analyses of populations in England (Bulpitt, 1982), Australia (Doyle, 1982), Hawaii (Yano et al, 1983), and Framingham (Kannel et al, 1985). More will be said about the Australian experience in Chapter 5. The data from Hawaii involved a 10-year follow-up of 7610 Japanese men, aged 45 to 68 at baseline. Those who were receiving antihypertensive therapy at baseline had a higher mortality from cardiovascular diseases overall, coronary heart disease, and stroke, as compared to untreated men whose blood pressures were comparable (Fig. 1.8). The authors conclude that "after adjustment of age, blood pressure and nine other risk factors in multivariate logistic analysis, antihypertensive medication remained significant as a risk factor for CVD, CHA and stroke" (Yano et al, 1983).

The Framingham data, now available only in abstract form, report a 2-fold increased risk of sudden death over 30 years "among people receiving antihypertensive

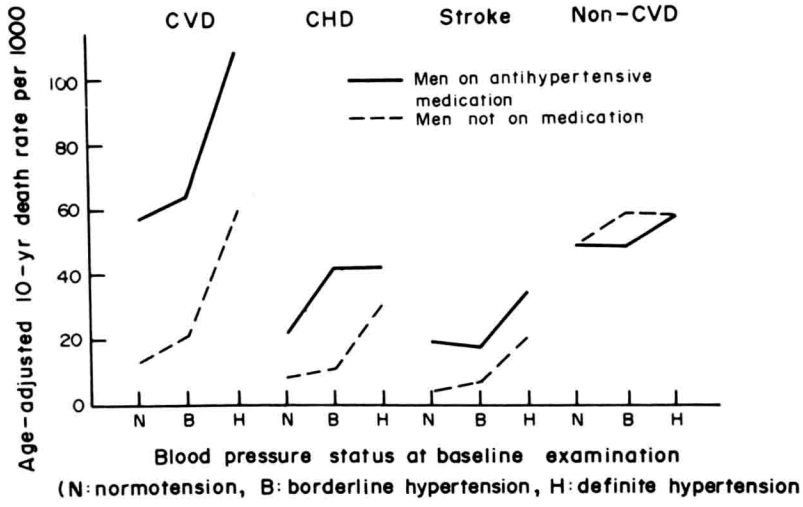

Figure 1.8. Age-adjusted 10-year mortality rates according to baseline blood pressure status and use of antihypertensive medication. (Reprinted with permission from Yano K, McGee D, Reed DM: The impact of elevated blood pressure upon 10-year mortality among Japanese men in Hawaii: The Honolulu Heart Program. *J Chron Dis* 36(8):569–579, 1983, Copyright 1983, Pergamon Press.)

drug treatment and this escalated risk was not accounted for by higher pressures" (Kannel et al, 1985). On the other hand, another analysis of the Framingham study showed a decrease in the 8-year incidence of coronary heart disease among subjects with initial systolic blood pressure of 180 mm Hg or higher who were treated for more than 2 successive years (Shea et al, 1985). No such protection, but no adverse effects either, was shown by treatment among those with less hypertension.

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 the blood pressure with drugs. They simply indicate that the protection provided may only be partial, perhaps because of only partial reduction of the blood pressure; perhaps because of dangers inherent in the drugs; perhaps because of irreversible damage already done by the hypertension; perhaps because of underlying features, either causal or coincidental to the hypertension. Whatever their explanation, these data do document a difference between natural and induced levels of blood pressure.

The Rationale for Reduction of Elevated Blood Pressure

Despite these disquieting data, there is considerable evidence, experimental, epidemiological, and clinical, for benefits from reduction of elevated blood pressure (Table 1.5). Only the last point, the reduction of cardiovascular disease, can be quantitated in a manner that will provide evidence as to the level of blood pressure wherein benefit can be shown from the use of available means to lower the blood pressure. It is that level which can be used as part of the operational definition of hypertension.

In the past 15 years, there have been 8 controlled therapeutic trials which have included patients with diastolic blood pressure levels as low as 90 or 95 mm Hg (Table 1.6). Detailed analyses of these trials will be provided in Chapter 5. For now, it is enough to say that there is disagreement as to whether they have shown protection against cardiovascular diseases for patients with DBP below 95 or even 100 mm Hg. On the one hand, some believe the data validate the need for drug therapy for those with DBP above 90 mm Hg (Gifford et al., 1983). On the other hand, some believe they do not validate the need for drug therapy, even for those with DBP as high as 100 mm Hg (Oliver, 1984). The English, in general, remain more conservative than Americans, advocating therapy only if the DBP is above 100 mm Hg (Sleight, 1985).

The differences are highlighted in recent reports of three expert committees: The Canadian Hypertension Society (1984) recommends that "antihypertensive treatment

Table 1.5. The Rationale for Reduction of Elevated Blood Pressure

1. The frequency of cardiovascular disease and death is directly related to the height of the blood pressure.
2. The blood pressure rises most in those whose pressures are already high.
3. In man, vascular damage is less where the blood pressure is lower: beneath a coarctation, beyond a renovascular stenosis, and in the pulmonary circulation.
4. Experimentally, lowering the blood pressure protects the vascular system.
5. Antihypertensive therapy reduces cardiovascular disease and death.

Table 1.6. Controlled Trials of Therapy for Mild Hypertension

	No. of Patients	DBP	Design	
			Control	Active
VA (1970)	170	90–104	Placebo	Step-care
USPHS (1977)[a]	389	90–104	Placebo	Step-care
HDFP (1979)	7825	90–104	Referred care	Step-care
Australian (1980)	3427	95–109	Placebo	Step-care
Oslo (1980)[b]	785	90–109	No therapy	Step-care
MRFIT (1982)	8012	90–114	Usual care	Step-care
MRC (1985)	17354	95–109	Placebo	Diuretic or β-blocker
European (1985)[c]	840	90–119	Placebo	Diuretic + triamterene

[a] Smith (1977).
[b] Helgeland (1980).
[c] Amery et al (1985).

should be initiated among all mildly hypertensive patients with diastolic pressures consistently at or above 100 mm Hg"; the World Health Organization and International Society of Hypertension (1983) recommend treatment for diastolic pressures above 95 mm Hg; the Third Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (1984) recommends treatment for those with a diastolic blood pressure above 95 mm Hg but adds that "Data from HDFP suggest that if the diastolic blood pressure remains above 90 mm Hg, despite nonpharmacologic therapy, antihypertensive drugs should be started."

As a compromise—and likely as the consensus—a diastolic pressure of 95 mm Hg seems to be the level wherein therapy has been shown to provide protection. That level may then be used in the operational definition of hypertension.

As a separate but related issue, the protection shown in the various therapeutic trials has been against stroke, heart failure, and renal damage. Little if any protection has been shown against the major cardiovascular risk from hypertension, coronary disease, an issue which will be discussed further in Chapter 5.

Prevention of Progression of Hypertension

One of the other benefits of action listed in Table 1.1 is to prevent progression of hypertension. The evidence for that benefit is strong, as shown in the results of the four therapeutic trials that followed half of their patients while they were on placebo (Table 1.7). From 10 to 17% of these patients had progression of hypertension beyond their respective thresholds, whereas fewer than 1% of the treated half did so.

Additional Risks and Costs of Action

The decision to label and treat a person for hypertension at any given level of blood pressure entails assumption of the role of a patient, interferences with life style, risks from biochemical side effects of therapy, and financial costs (Table 1.1).

The Assumption of the Role of a Patient

The mere labeling of a person as "hypertensive" may provoke ill effects. This should come as no surprise considering the common lay name for hypertension—"the silent killer." After review of the literature on the effects of labeling, these conclusions were

Table 1.7. Progression of Hypertension in Placebo-Controlled Trials of the Treatment of Hypertension

	VA	USPHS[a]	Australian	Oslo[b]	MRC
No. of patients	380	389	3427	785	17354
Initial level of DBP (mm Hg)	90–114	90–115	95–109	90–109	95–109
Threshold level of DBP (mm Hg)	125	130	110	110	110
Progression beyond threshold: no. of patients (%)					
On placebo	20 (10%)	24 (12%)	198 (12%)	65 (17%)	1011 (11.7%)
On treatment	0	0	4 (0.2%)	1 (0.3%)	76 (0.9%)

[a] Smith, 1970.
[b] Helgeland, 1980.

made (Macdonald et al, 1984):

—Labeling by itself, without treatment, may be harmful
—Absenteeism from work because of illness and psychological distress are increased more among aware hypertensives than among either normotensives or unaware hypertensives
—People who are labeled but who receive appropriate counseling and care and who are compliant to therapy usually do not have increased absenteeism or psychological distress

Two studies published after the review of Macdonald et al (1984) further document the problem. In one, a series of interviews were given to three groups of actively employed, relatively healthy 40- to 64-year-old men and women—50 newly diagnosed and untreated hypertensives, 50 previously diagnosed and treated hypertensives, and 50 age- and sex-matched normotensive controls (Milne et al, 1985). Both hypertensive groups displayed significantly lower indices of health and the ability to participate in enjoyable activities and higher indices of symptoms, absenteeism from work, and worry about health. In the other study, 230 hypertensive Canadian steelworkers, 5 years after they were identified, were found to earn an average of $1093 less than did a matched group of normotensives despite similar incomes in the year prior to screening (Johnston et al, 1984). The lesser income was not entirely related either to their higher rate of absenteeism or to any other obvious differences between the two groups.

Interferences with the Quality of Life

One-third of the 3844 patients who were begun on antihypertensive medications for the Hypertension Detection and Follow-up Program developed side effects which resulted in discontinuation of their drug treatment (Curb et al, 1985a). These side effects were recognized by detailed surveillance procedures.

Table 1.8. Estimates of the Effects of Antihypertensive Therapy on Quality of Life

	Physician (%)	Patient (%)	Relatives (%)
Improvement	100	48	1
No change		43	
Worse		9	99

Data from Jachuck SJ, Brierley H, Jachuck S, et al: *J R Coll GP* 32:103, 1982.

In ordinary practice, neither physicians nor patients may be so aware of side effects which, nonetheless, may impair the quality of life of those who take drugs. A survey was performed on 75 consecutive patients from an English group practice who had hypertension controlled by the usual antihypertensive drugs, including diuretics, β-blockers, and methyldopa (Jachuck et al, 1982). A series of questions about the quality of life was asked of the patients, their physicians, and their closest relatives (Table 1.8). Whereas most of the patients responded that they were improved or no different after therapy, all of the physicians stated that the patients were improved. However, 99% of the patient's closest relatives said the patients were worse after therapy. The symptoms that they described in the patients included loss of memory (33%), more irritability (45%), depression (46%), more hypochondria (55%), and decreased sexual interest (64%).

This study, though small in scope and uncontrolled, suggests that the treatment of hypertension may often interfere with patients' enjoyment of life in ways of which

neither they nor their physicians are aware. Beyond these effects of drugs, the various nonpharmacological therapies that are often advocated may interfere further. Though none should suffer from a moderate reduction in calories and sodium intake, these restrictions may be perceived as unpleasant intrusions.

Risks from Biochemical Side Effects of Therapy

These risks are less likely to be perceived by the patient than the interferences with life style, but they may actually be hazardous. A great deal more about them will be considered in Chapters 5 and 6. For now, mention will be made of only two: diuretic-induced hypokalemia that develops in about one-third of patients (Kaplan, 1984) and elevations in serum cholesterol or triglycerides which may accompany the use of either diuretics or β-blockers (Weinberger, 1985).

An Overview of Risks and Benefits

We have now examined some of the issues involved in determining the level of blood pressure that poses enough risks to mandate the diagnosis of hypertension and to call for the use of appropriate therapy, despite the potential risks that such therapy entails. Another analysis of the issue of risk factor intervention by Dr. Allan S. 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. Particular 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 that 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.
>
> The example of mild hypertension may be further developed. It is widely acknowledged that, with successively higher blood pressure levels, the risk of complications increases gradually rather than abruptly. Therefore, the reasons to intervene should be viewed as gradually more compelling as blood pressure rises, rather than suddenly compelling at a specific level such as 90 mm Hg. Guttmacher et al (1981) argue persuasively that selection of a cutoff for critically elevated blood pressure reflects a value judgment about the point at which a risk is thought to be serious enough to warrant treatment. Each decision must be individualized, depending on the patient's aversion to risk, perception of the intrusiveness of medical care in his life, tolerance for discomfort or untoward drug effects, etc. When the medical data base contains considerable uncertainty, as it does for mild hypertension, the risk-benefit calculation is even more difficult (From Brett AS: *Am J Med* 76:557, 1984.)

OPERATIONAL DEFINITIONS OF HYPERTENSION

Now that the issues of risk and benefit have been examined, operational definitions of hypertension can be offered.

The WHO Criteria

A short time ago, in 1978, an expert committee of the World Health Organization (WHO Expert Committee Report, 1980) considered the evidence and recommended these criteria:

—Normotension: systolic $\leq$ 140 and diastolic $\leq$ 90 mm Hg
—Borderline: systolic 141 to 159 and diastolic 91 to 94 mm Hg
—Hypertension: systolic $\geq$ 160 and/or diastolic $\geq$ 95 mm Hg

Since then, the increasing awareness of increased risk with blood pressures in the "borderline" category (Fig. 1.2) has caused a reassessment of these criteria.

Third Joint National Committee (JNC III) Criteria

On the basis of these data, the Third Joint National Committee on the Detection, Evaluation and Treatment of High Blood Pressure (1984) recommended that hypertension be diagnosed, in people aged 18 years or