THE CHOICE OF THERAPY FOR MILD HYPERTENSION

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MEDICINE GRAND ROUNDS

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My thanks to Ellen Rudisill for preparing the protocol and to Marty Burgin for the original artwork.

We have entered into the 1980's. We have learned that pharmacologic control of arterial pressure is essential for patients with diastolic pressure in excess of 90 mm Hg.... And because the lower limit of diastolic pressure elevation recommended for treatment has been reduced from 105 to 90 mm Hg, we now include among the potential beneficiaries of therapy upwards of 54--not 23--million Americans.

(Frohlich ED, 1981)

On the basis of the results of the Hypertension Detection and Follow-up Program (HDFP), the prestigious Joint National Committee recently recommended that, "It is reasonable to reduce blood pressure even in uncomplicated mild hypertension by pharmacologic or nonpharmacologic therapy" and that "The initial goal of antihypertensive therapy is to achieve and maintain diastolic pressure levels at less than 90 mm Hg" (Joint National Committee: *Arch Intern Med* 1980; 140:1280).

Though I have, in the past, been a therapeutic enthusiast for the more active treatment of hypertension, the current attitude taken by more and more authorities seems to be going beyond reasonable boundaries. In this Rounds, the evidence documenting the risks of mild hypertension and the benefits of its treatment will be reviewed. Based upon an objective assessment of the available data, specific recommendations will be made as to the appropriate management of the millions of people with relatively mild hypertension. My conclusions are much more conservative than the views expressed above, perhaps reflecting my advancing age--but, rather more likely, a more careful analysis of what is known about mild hypertension.

I. The Risks for the Public's Health

High blood pressure is quantitatively the largest single risk for premature death 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 severe cases but from the very large number of people with pressures that are only mildly raised.

A. The Number of People Involved

Perhaps the best data now available on the U.S. population comes from the examination of a 17,000 person representative sample in the National Health and Nutrition Survery of 1971-74 (Figure 1). The diagnosis of hypertension is based on a level of 160/95 or higher on single readings taken at mobile examination centers.

A larger sample, numbering almost 160,000, from 14 communities was examined during the early 1970's for the HDFP (Hypertension Detection and Follow-up Program, 1977). These people were picked as representative of the adult population, aged 30 to 69, and were examined at home. The frequency distribution of the average of the second and third readings of the diastolic blood pressure shows that over 20% of the adult population have "mild" hypertension, defined as a diastolic between 90 and 104 mm Hg (Figure 2). Notice that over 10% are between 90 and 95 mm Hg.

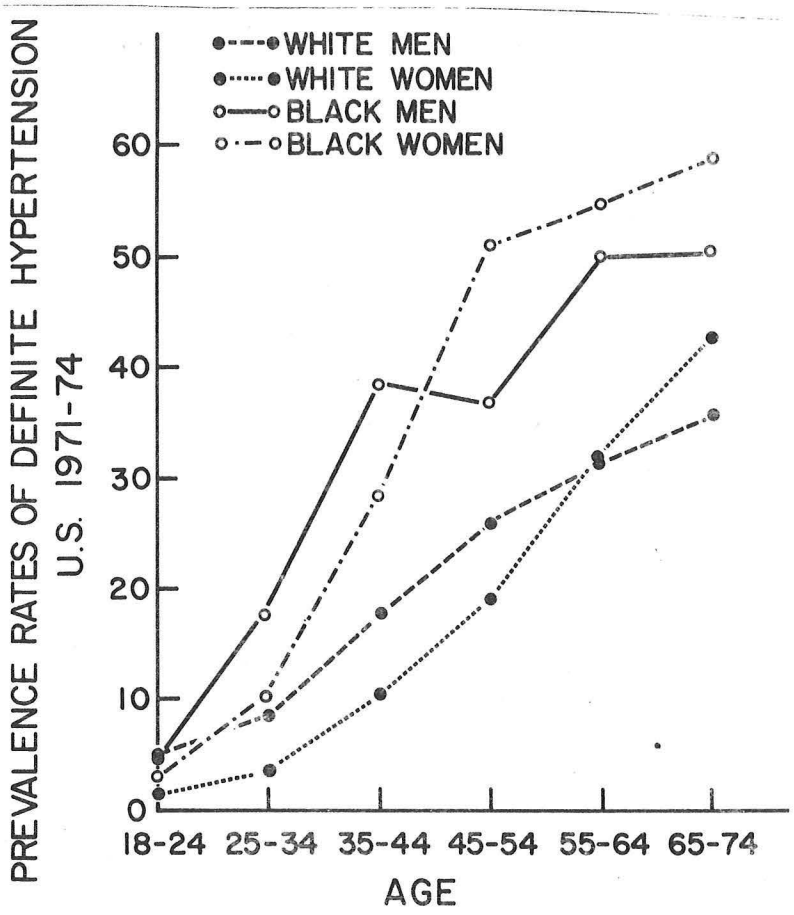
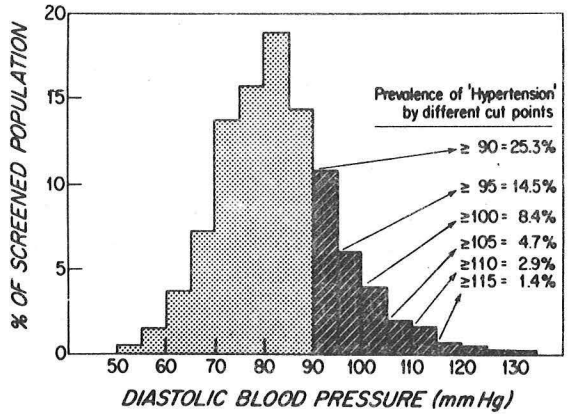


Figure 1

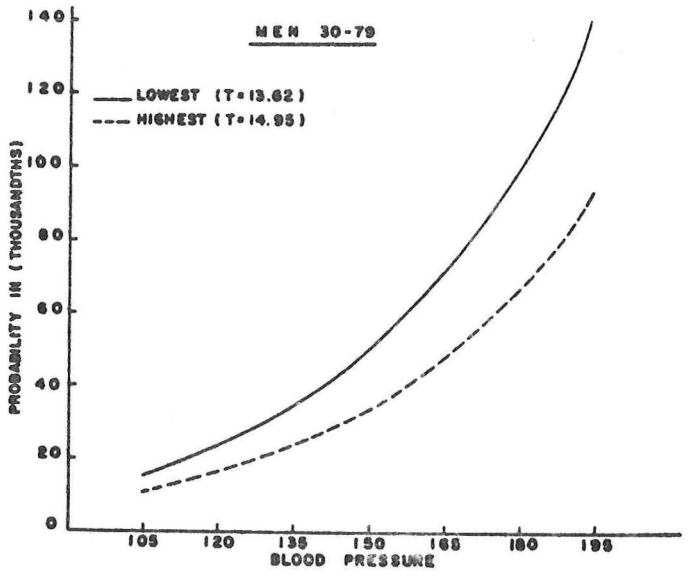


Frequency distribution of diastolic blood pressure at home screen (158, 906 persons; 30–69 years of age). (From "The Hypertension Detection and Follow-up Program." Circulation 40 (5): May 1977 by permission of the American Heart Association, Inc.)

Figure 2

When these patients were re-examined, their pressures were usually lower: among the white males with first screen DBP of 95 to 104, 44% were below 90 on the second screen.

Thus, two variables are involved in the criteria for the diagnosis of hypertension: which level should be used and how many readings should be taken. As we shall see, for most of the data on large populations used to determine the eventual risks associated with various levels of blood pressure, only one set of readings were taken. When such "casual" readings are compared to repeated or more "basal" readings, there is little difference in the association of severity of complications associated with hypertension (Sokolow, 1966; Caldwell, 1978). In the Framingham experience, the probability of cardiovascular risk at various levels of systolic blood pressure was higher using the lowest of 3 readings taken at each exam, but there was a sharp rise with increasing levels of both the lowest and the highest readings (Figure 3). Moreover, comparison of the casual pressures taken every 2 years shows that they are reasonably closely correlated from one exam to the next over 18 years. The best course is to take 3 readings at each exam and average them.



(from: Kannel, 1977)

Figure 3

As to the level to consider high, readings above 140 systolic and 90 diastolic are associated with increased risk, so it seems that for most purposes the diagnosis should be based upon the level of 140/90. This means that about 50 million Americans have hypertension.

B. The Degree of Risk from Mild Hypertension

There are numerous data which are useful in examining the relation between levels of blood pressure and both morbidity and mortality. The largest number of people have been followed for the longest time by life insurance companies, in the Framingham study, and in the Pooling Project, a combination of six prospective studies on 7,054 white men aged 40 to 59

at entry. As useful as they are, all suffer from obvious faults: the life insurance data are taken from single observations of largely upper-middle class whites; the Framingham cohort is also largely white, and since only 5,200 people are included, the number of "events" for various analyses is often limited. Moreover, the blood pressures were single casual readings. In the Pooling Project, only white men were followed, and the lowest of 3 blood pressures taken on the first exam was used.

However, these sources provide important information. The life insurance actuarial data covers 4.5 million people followed for up to 20 years, so by its size alone it demands attention. The biennial exams started in 1948 in Framingham provide over 30 years of the most detailed observations ever performed on a group of people. The Pooling Project carefully followed a large number of men initially free of clinical heart disease for at least 10 years.

1. The Life Insurance Actuarial Data

The 1979 Build and Blood Pressure Study has not yet been published in full. Preliminary data show significantly increased eventual mortality from coronary disease, stroke, and renal insufficiency in both men and women with even minimally elevated pressures (Lew, 1978) (Figure 4). Note the lesser risk for women.

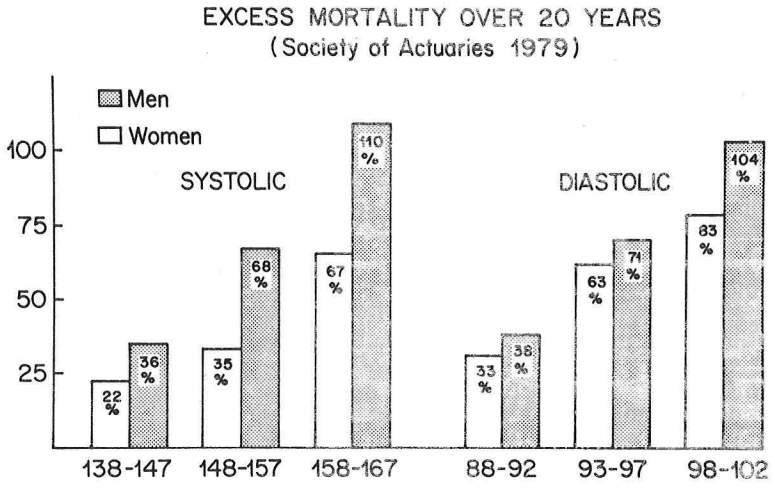


Figure 4. Excess mortality observed over 20 years by initial systolic and diastolic blood pressures among 4.5 million men and women who obtained life insurance.

2. The Framingham Study

Much of the background and findings of this monumental study are provided in a recent book authored by the principal architect, T. R. Dawber (Dawber TR: The Framingham Study, Harvard University Press, Cambridge, Mass., 1980). Of the many other publications, these are particularly useful:

Kannel *et al:* *Am J Cardiol*, 1971
Kannel *et al:* *Am J Cardiol*, 1976
Kannel: *In:* Hypertension. Genest (Ed.), McGraw-Hill, 1977
Kannel: *In:* Preventive Cardiology. Kaplan & Stamler (Eds.), Saunders, in press.

In various surveys, including Framingham, the systolic blood pressure has been found to be a better determinant of risk than the diastolic. For each increment, an increased likelihood of both cardiovascular mortality and morbidity is noted (Figure 5), more for men than for women and more with advancing age.

When the excess risks for various levels of diastolic blood pressure in the Framingham population are multiplied by the number of people with such levels found in the HDFP survey, most of the excess deaths attributable to hypertension are seen to occur in those with "mild" disease--i.e., DBP 90 to 104 (Figure 6).

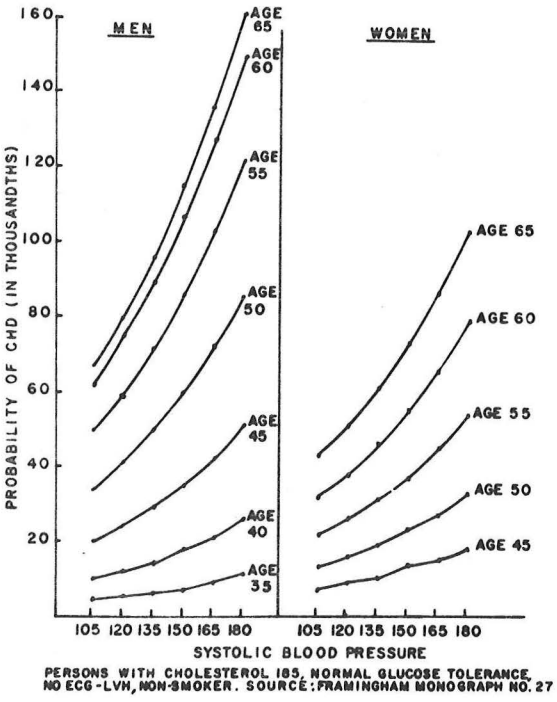


Figure 5. The probablility of developing cardiovascular disease in 8 years in low-risk men and women aged 35 to 65 in Framingham, according to their initial systolic blood pressure (from: Kannel, 1977).

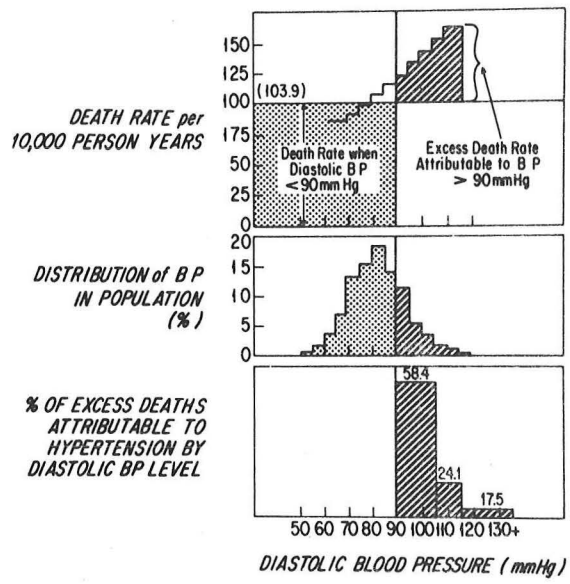


Figure 6. The percentage of excess deaths attributable to hypertension by diastolic blood pressure level (bottom), based upon the death rate observed in Framingham (top) and the distribution of the blood pressure found in the HDFP population (middle) (from: HDFP, 1977).

Yet, the Framingham data provide another view: it is not possible to discriminate on the basis of the blood pressure alone who is going to develop cardiovascular disease and who is not (over the next 18 years) (Figure 7). The mean systolic blood pressure in women 30 to 49 years old who subsequently developed coronary heart disease was 146 mm Hg compared to 130 mm Hg for those who remained free. But most who developed disease are in the range of those who did not.

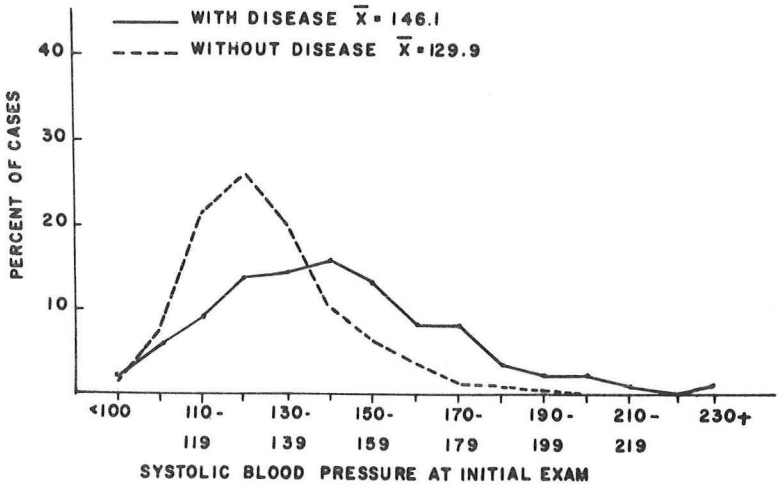


Figure 7. The distribution of systolic blood pressure at initial exam for those women aged 30 to 49 who did not (--- without disease) or who did (—— with disease) subsequently develop coronary heart disease, stroke, CHF, or peripheral vascular disease in the 18 years after entry into the Framingham study (from: Kannel, 1977).

3. The Pooling Project

The number of major coronary events (non-fatal and fatal MI, sudden death) seen among white men aged 40 to 59 with no clinical evidence of heart disease at entry over the next 8.6 years increased significantly at the mid-range of 80 to 87 and doubled with DBP above 95 (Table 1A) (Pooling Project Research Group, 1978.

Notice how much greater the relative risk for coronary disease is among those in the upper 2 quintiles for all 3 major risk factors, a point we will re-examine. (Table 1B).

Considering all of these data, a casual blood pressure above 140/90 is associated with significantly increased risk of cardiovascular disease in large populations of white people (mainly men) followed for 10 to 20 years. When the systolic alone is elevated above 160, the risk for all cardiovascular disease, but particularly for stroke, is increased (Table 2).

TABLE 1A: 8.6 year risk for major coronary events in 7,054 white men by diastolic blood pressure at entry

Diastolic BP at Entry*	Adjusted Rate of Major Coronary Events per 1,000	Relative Risk	Absolute Excess Risk Per 1,000
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

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

[Data from: The Pooling Project: *J Chronic Dis* 1978]

TABLE 1B:

Three major risk factors (serum cholesterol, diastolic pressure, cigarette smoking) and risk of a first major coronary event between ages 40–64, 8,162 white men, pool 5, National Cooperative Pooling Project (final report)

Quintile of level	Number of first events	Risk of an event, age 40–64, per 1,000 men	Relative risk	Absolute excess risk, per 1,000 men	Percent of all excess risk
I	23	57.9	—	—	—
II	66	118.3	2.04	60.4	8.7%
III	107	168.0	2.90	110.1	15.9%
IV	167	241.1	4.16	183.2	26.5%
V	271	395.7	6.83	337.8	48.9%
All	634	221.0	—	—	—

TABLE 2

Risk of stroke over 24 years of follow-up in Framingham, men and women aged 50 to 79 (all subjects with diastolic blood pressure below 95 mm Hg over a 24-year follow-up)

	MEN		WOMEN	
Systolic BP	Population at Risk (Person Years)	Age Adjusted Rate/1000 in 2 Years	Population at Risk (Person Years)	Age Adjusted Rate/1000 in 2 Years
< 140	6,735	5.3	7,827	3.8
140-159	1,816	7.4	2,894	6.6
>160	544	21.0	1,295	9.6

[Data from: Kannel *et al: JAMA* 1981; 245:1225]

II. The Risk for the Individual

Aware of these population data, we need to focus on the individual patient since in all of these studies only a minority of patients with mild hypertension developed cardiovascular disease. Can we pick the ones from the larger group who are most susceptible in order to more aggressively treat them but to leave the others alone?

A. Quantifying the Degree of Risk

In addition to those shown in Table 1 from the Pooling Project, Framingham provides the best data to determine an overall cardiovascular risk profile. The major determinants beyond age and blood pressure are the level of serum cholesterol and the smoking of cigarettes. Glucose intolerance, defined as the presence of overt diabetes or a post-prandial whole blood glucose above 120 mg%, increases risk. (Among 18,403 English men aged 40 to 64 years, the risk of coronary heart disease in the next 7.5 years doubled in the 5% with a blood glucose above 95 mg% 2 hours after a 50 g oral glucose load (Fuller *et al*, 1980).

The presence of LVH on the ECG also increases risk significantly, and it is included in the profile.

The card provided by the Dow Pharmaceutical Company uses 4 measures--the age, systolic blood pressure, cigarette smoking (Yes or No), and serum cholesterol--and applies only to those without glucose intolerance or LVH on the ECG. The coronary Risk Handbook provided by the American Heart Association also takes into account glucose tolerance and LVH on the ECG (Yes or No). Table 3 shows the probability per 1,000 of developing cardiovascular disease in 8 years for a 40-year-old man, based upon all 6 characteristics.

TABLE 3

Probability (per 1000) of developing cardiovascular disease in 8 years according to specified characteristics: 40-year-old men

THE FRAMINGHAM STUDY: 18-YEAR FOLLOW-UP

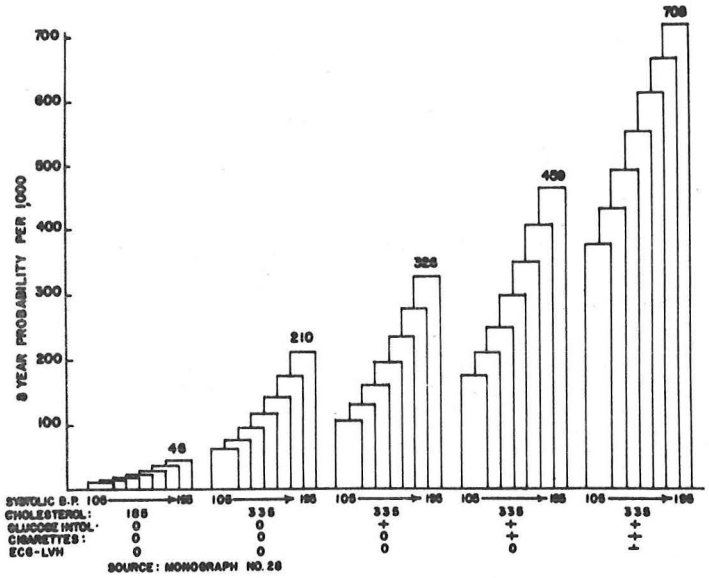
ECG-LVH negative		DOES NOT SMOKE CIGARETTES								SMOKES CIGARETTES							
	SBP:	105	120	135	150	165	180	195		SBP:	105	120	135	150	165	180	195
	CHOL								CHOL								
	185	12	15	19	23	29	37	46	185		20	25	32	40	50	63	78
	210	15	19	24	31	39	48	60	210		27	33	42	53	66	82	101
Glucose	235	20	26	32	40	51	63	79	235		35	44	55	69	85	106	130
intolerance	260	27	34	42	53	66	82	102	260		46	58	72	89	110	135	165
absent	285	35	44	55	69	86	106	131	285		60	75	93	115	141	172	208
	310	46	58	72	90	111	136	167	310		78	97	120	147	179	216	259
	335	61	76	94	116	142	173	210	335		101	125	153	186	225	268	317
	SBP:	105	120	135	150	165	180	195		SBP:	105	120	135	150	165	180	195
	CHOL								CHOL								
	185	21	27	33	42	52	65	81	185		36	45	57	71	88	109	134
	210	28	35	44	55	68	85	105	210		48	60	74	92	114	140	170
Glucose	235	37	46	57	71	89	110	135	235		62	77	96	119	145	177	214
intolerance	260	48	60	75	93	115	141	172	260		81	100	124	152	184	222	266
present	285	63	78	97	119	147	178	216	285		105	129	158	192	231	275	325
	310	82	101	125	153	186	224	267	310		134	164	199	239	285	335	389
	335	106	130	159	193	232	277	326	335		171	207	248	295	346	401	459
ECG-LVH positive																	
	SBP:	105	120	135	150	165	180	195		SBP:	105	120	135	150	165	180	195
	CHOL								CHOL								
	185	33	41	51	64	80	99	122	185		56	70	86	107	132	161	195
	210	43	54	67	83	103	127	156	210		73	90	112	137	168	203	244
Glucose	235	56	70	87	108	133	162	197	235		94	117	143	174	211	253	300
intolerance	260	73	91	113	138	169	204	245	260		122	149	181	219	262	310	362
absent	285	95	117	144	176	212	254	301	285		155	189	227	271	320	373	430
	310	122	150	183	220	264	312	364	310		196	236	281	331	385	442	500
	335	156	190	229	273	322	375	432	335		245	291	341	396	454	512	571
	SBP:	105	120	135	150	165	180	195		SBP:	105	120	135	150	165	180	195
	CHOL								CHOL								
	185	58	73	90	111	137	167	202	185		97	120	147	180	217	259	307
	210	76	94	116	143	174	210	252	210		125	154	187	225	269	317	371
Glucose	235	93	121	148	181	218	261	309	235		160	194	234	278	328	382	439
intolerance	260	125	155	188	227	270	319	372	260		202	242	288	339	393	450	509
present	285	161	195	235	280	330	384	441	285		251	298	349	405	462	521	579
	310	203	244	290	340	395	453	511	310		308	360	416	474	533	591	646
	335	253	300	351	407	464	523	581	335		371	428	486	545	602	657	708

Framingham men aged 40 yrs have an average SBP of 129 mmHg and an average serum cholesterol of 228 mg/100 ml, 70% smoke cigarettes. 0.3% have definite LVH by ECG and 3.3% have glucose intolerance. At these average values the probability of developing cardiovascular disease in 8 years is 41/1000.

B. The Value of Knowing the Individual's Risk Profile

The risk of varying levels of hypertension differs greatly depending upon the absence or presence of the other risk factors (Figure 8). A 40-year-old man with a systolic blood pressure of 195 but none of the other risk factors has a 4.6% probability of developing cardiovascular disease in 8 years. With the same blood pressure but a cholesterol of 335, glucose intolerance, LVH on ECG, and cigarette smoking, the 8-year probability is 70.8%. (The 6 year risks given both in the Handbook and by the calculator are about half as great.)

MEN



WOMEN

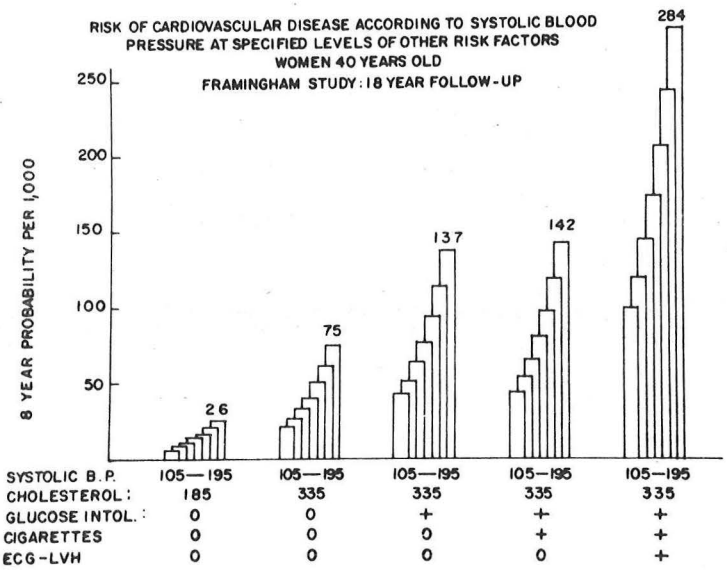


Figure 8. The 8 year risk of cardiovascular disease for 40-year-old men (upper) and women (lower) in Framingham according to progressively higher systolic blood pressure at specified levels of other risk factors. Notice the lower scale for women (from: Kannel, 1977).

The differences are equally impressive when 15 year risk data are examined (Alderman, 1981) (Figure 9). A 35-year-old man at "high risk" with a systolic blood pressure of 195 has an 86% probability of developing cardiovascular disease within 15 years; with the same blood pressure but "low risk," a 15% chance. A "low risk" woman with a systolic of 195 mm Hg has only one-tenth the risk of a "high risk" man with a systolic blood pressure of 135.

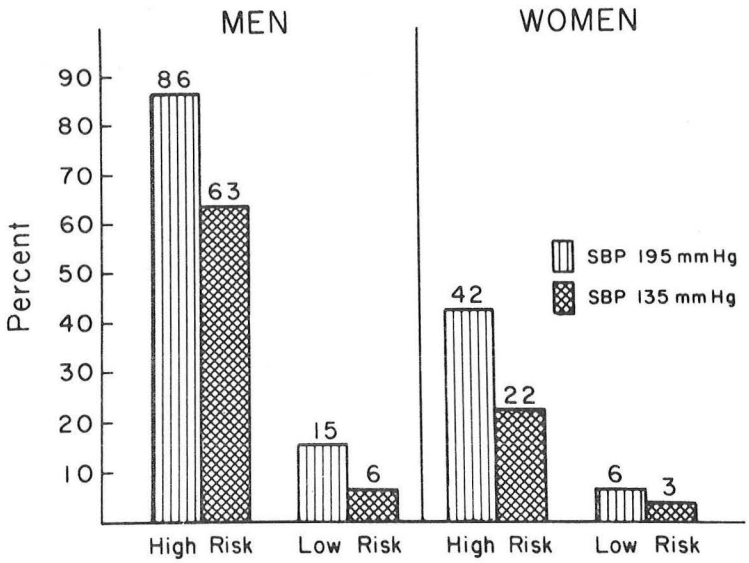


Figure 9. Risk of developing CVD in 15 years for 35-year-old men and women, by SBP level and risk status. High risk = LVH, cigarette smoker, a cholesterol of 310 mg%, and glucose intolerance. Low risk = no LVH, nonsmoker, a cholesterol of 235 mg%, and no glucose intolerance.

When the Framingham population's various risk factors were divided into 5 parts (quintiles), it becomes possible to identify 20% of the asymptomatic population from which 40% of the coronary disease, 81% of the strokes, and 73% of the congestive heart failure will develop (Figure 10).

As seen in Figures 5 and 9, young patients with rather high blood pressure but otherwise at "low risk" have a relatively small likelihood of developing cardiovascular disease over the next 10 to 15 years. Using the Framingham data, possible effects of successful lowering of the blood pressure for both "low risk" and "high risk" men and women at various ages can be calculated. Alderman and Madhavan (1981) have determined the "relative benefit" of lowering the blood pressure for 15 years by taking the number of people who would thereby be saved from developing cardiovascular disease for every 100 treated (Figure 11). For every 100 35-year-old "low risk" women with an initial systolic blood pressure of 195 who are treated to a systolic blood pressure of 135 for 15 years, only 4 would benefit; for every 100 with an initial systolic blood pressure of 165 so treated, only 2 would benefit. For both men and women at "high risk," the proportion of those benefitted is obviously much higher.

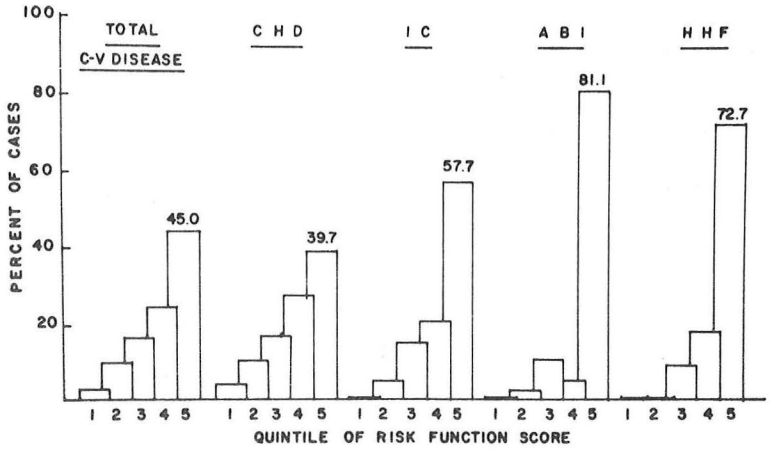


Figure 10. The proportion of cases of cardiovascular diseases: total, CHD (coronary heart disease), IC (intermittent claudication), ABI (atherothrombotic brain infarct), HHF (hypertensive heart failure) developing over 18 years in Framingham men, aged 35 to 74, according to their quintile of risk function, a composite of their overall cardiovascular risk status (divided into 5 parts) at the initial exam. Notice the high percentages of each disease occurring in those in the upper 20% (quintile 5). [From: Kannel, 1977.]

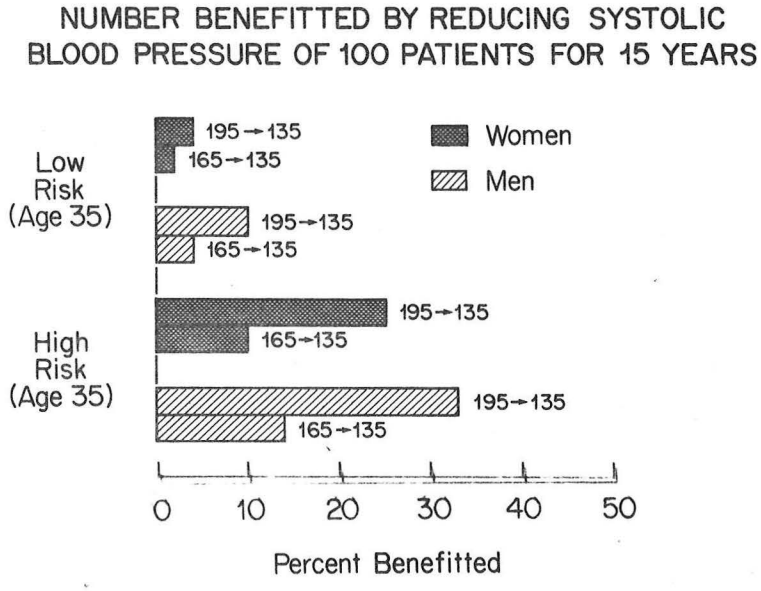


Figure 11. The percentage of low risk and high risk women and men age 35 who would be expected to benefit by reduction of their systolic blood pressure from either 195 to 135 or 165 to 135 over a 15-year period. High risk = LVH, cigarette smoker, a cholesterol of 310 mg%, and glucose intolerance. Low risk = no LVH, nonsmoker, a cholesterol of 235 mg%, and no glucose intolerance. [Derived from: Alderman and Madhavan, 1981.]

This analysis is of interest but depends upon a number of unproved assumptions, including: (1) the ability to successfully lower the blood pressure and keep it at 135 mm Hg for all patients for 15 years, (2) the absence of harm from the means used to lower the blood pressure, and (3) the removal of all risk from hypertension by lowering of the blood pressure (i.e., a treated hypertensive = an untreated normotensive).

We need not depend upon such an analysis since the results of therapeutic trials of mild hypertension are now available.

III. The Effects of Lowering the Blood Pressure

A. An Analysis of Therapeutic Trials

The results of 5 trials of treatment of mild hypertension are now available and a sixth is still under progress in England (MRC). From them, the evidence is absolutely clear: therapy will protect those at risk. But, two caveats should be remembered in considering these data: first, they all cover relatively short intervals in the long natural history of mild hypertension; and, second, all of the pertinent data to determine the individual patient's chances of benefit from therapy are not provided and probably cannot be provided. There are too many variables in the large population of people involved, both in initial risk profile and in responses to therapy.

1. The VA Study (1967,1970,1972)

This, the first controlled study of therapy, was the fuse that set off the current explosive growth in the treatment of hypertension. As good as it was, it had numerous short-comings: only men were included; the blood pressures were determined after 6 days of hospitalization; the number of patients was too small; and the duration of follow-up was too brief to provide conclusive evidence about the potential benefits of therapy for mild hypertension (i.e., DBP 90-104). Fortunately, the initial risk profiles were well described and enough patients had enough additional risks to provide useful information about the relationships between overall risks and the benefits of therapy.

As shown in Figures 12 and 13, those with mild hypertension who entered the VA study with no recognizable cardiovascular disease or below the age of 50 achieved little reduction in their already low rate of cardiovascular disease during the next 3.3 years. On the other hand, those with pre-existing CVD abnormality or age above 50 benefitted significantly.

As Alderman and Madhavan (1981) state, "The VA study confirms the expectation [from the Framingham experience] that cardiovascular disease events, as well as their reduction through chemotherapy, do not follow a chance pattern, but tend to cluster according to the presence or absence of factors other than arterial pressure level. The results demonstrate that the level of blood pressure, certainly in the mild and moderate range, is of only modest prognostic value and of even less value in determining whom to treat."

Figures 12 and 13 from: Alderman & Madhaven, 1981.

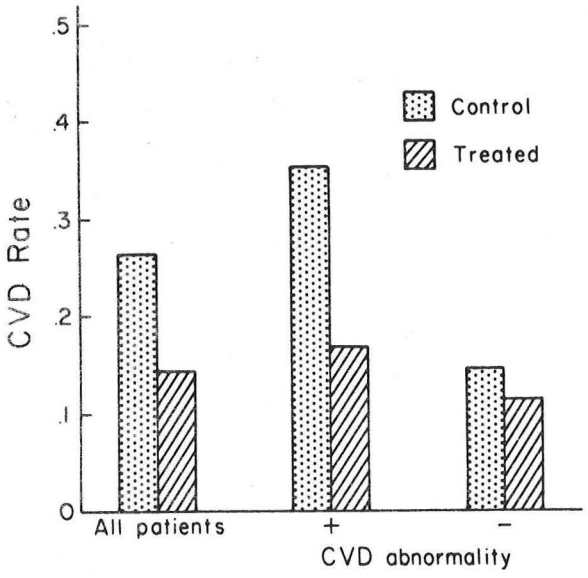


Figure 12. CVD incidence and benefit of therapy in mild hypertension (90-104 mm Hg) by CVD status. (CVD rate estimated by multiple regression technique.)

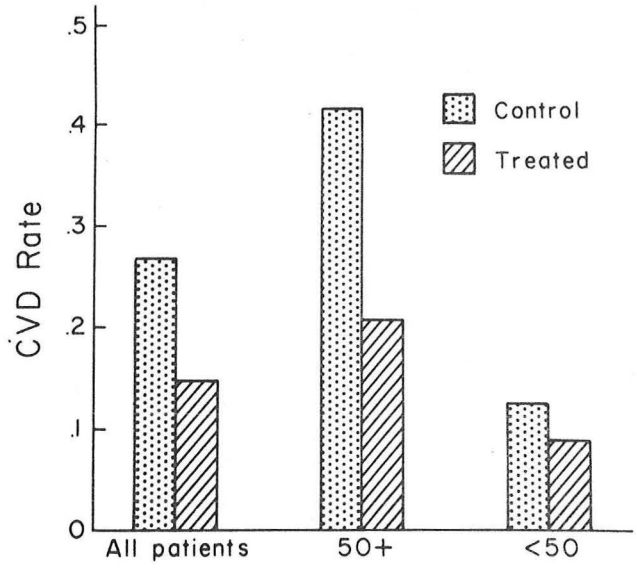


Figure 13. CVD incidence and benefit of therapy in mild hypertension (90-104 mm Hg) by age. (CVD rate estimated by multiple regression technique.)

2. The US Public Health Service Hospital Study (Smith, 1977)

The 389 men and women, ages 21 to 55, enrolled in the USPHS study had milder hypertension (control BP = 148/99) and were free of any other recognizable risk factors. After a follow-up of 7 to 10 years, there was no difference in mortality between the placebo and drug-treated halves (2:2). Similarly, the number of atherosclerotic complications were not reduced, but the number of hypertensive complications were reduced from a rate of 45 per 100 patients to 19 per 100 (Table 4).

TABLE 4

ALL MORBID EVENTS WHILE ON ASSIGNED REGIMEN

	Active			Placebo		
	No.	Rate/ 100 pts.	%	No.	Rate/ 100 pts.	%
Total Patients	193			196		
Total Events	72	37.3	100.0	127	64.8	100.0
Hypertensive	37	19.2	51.4	89	45.4	70.1
CVA	1	0.5	1.4	3	1.5	2.4
ECG Hypervoltage	9	4.7	12.5	24	12.2	18.9
LVH by ECG	14	7.3	19.4	32	16.3	25.2
Cardiomegaly	12	6.2	16.7	20	10.2	15.7
Retinopathy	1	0.5	1.4	8	4.1	6.3
Renal Insufficiency	0	0.0		1	0.5	0.8
Congestive Heart Failure	0	0.0		1	0.5	0.8
Atherosclerotic	35	18.1	48.6	38	19.4	29.9
Myocardial Infarction	9	4.7	12.5	8	4.1	6.3
Death	2	1.0	2.8	2	1.0	1.6
Other CHD	22	11.4	30.6	28	14.3	22.0
Transient Ischemic Attacks	0	0.0		0		
Arterial Insufficiency	2	1.0	2.8	0		
	Treatment Failures					
Total	0			24	12.2	
Asymptomatic	0			11	5.6	
Symptomatic	0			13	6.6	

All morbid events among the patients in the USPHS Trial on mild hypertension (from: Smith, 1977).

3. Hypertension Detection and Follow-up Program (HDFP, 1979)

This study, the largest now completed, was designed to test the value of antihypertensive therapy for all grades of hypertension among a truly representative sample of the population. By its design, it suffers from significant defects:

- -Since all levels of hypertension were included, it was considered inappropriate to have a placebo-treated group. Therefore, half were assigned to Referred Care (RC) from usual sources in the community; the other half were provided Stepped Care (SC) in special centers. More than half of the RC group ended up on active drug therapy (Table 5). Among white women, there was little difference in the number under treatment, and there was no difference in their eventual mortality (Figure 14).
- -The SC group obtained much more intensive, overall medical care. They were seen at least every 4 months; the RC group perhaps once a year. Non-cardiovascular deaths were reduced by 13% in the SC group, so the good results attributed to more intensive antihypertensive therapy and the resultant greater reduction in blood pressure may have been in large part a result of improved overall medical care.
- -There may be serious problems with the mortality data: in those with DBP 90-104 given more intensive therapy, deaths from all coronary heart disease were reduced by 20%; deaths from "acute myocardial infarction" were reduced by 46%; but deaths from "ischemic heart disease" *were increased* by 9%. We await explanation of "ischemic heart disease."

TABLE 5

Hypertension Detection and Follow-up Program (HDFP): Comparison of therapy between the two groups

	ALL PATIENTS		*DBP 90-104*	
	RC	SC	RC	SC
On Treatment				
Year 1	42%	68%	40%	67%
Year 5	58%	78%	54%	75%
BP at Goal				
Year 1	29%	52%	30%	52%
Year 5	44%	65%	43%	64%
Average DBP (mm Hg)				
Entry	101	101	96	96
Year 5	89	84	88	83

RC = Referred Care; SC = Stepped Care
[Data from: *JAMA* 1979; 242, 2562.]

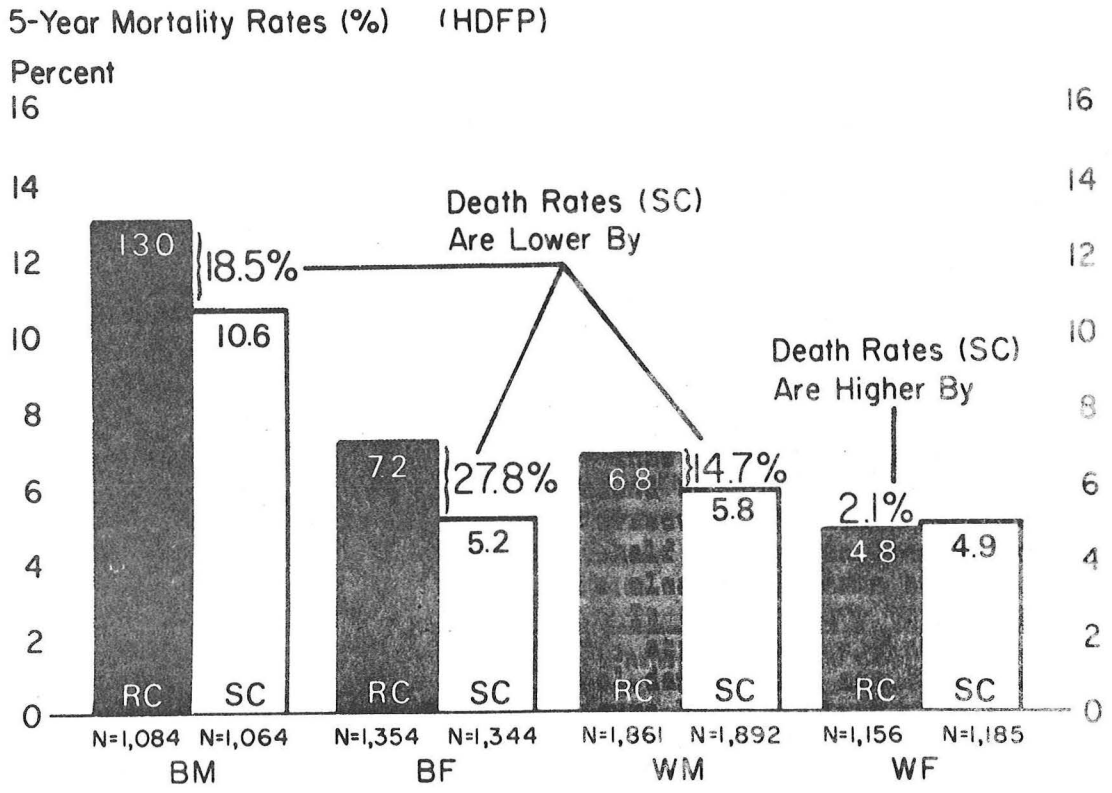


Figure 14. Five-year mortality rates for all causes by sex and race, in %. BM = black male; WM = white male; BF = black female; WF = white female (from: Alderman, 1981).

-The only available data relate to overall mortality. We need data on morbidity, the side effects of therapy, and, for our purposes, the relationships between pre-existing cardiovascular disease (present in about 25% of all subjects) and the protection from subsequent disease and death provided by therapy. Unpublished data indicates a 28.6% decrease in mortality among those with mild hypertension (DBP 90-104 mm Hg) who had no target organ damage at entry into the study.
-The overall proportional benefit ascribed to more active therapy, 16.9% for all patients and 20.3% in the mild group (DBP 90 to 104 mm Hg), looks quite impressive. But, death rates in both groups were quite low and the actual improvement realized in the SC group was rather small. If the number of survivors in the two groups are compared, it was slightly less than 93% in the RC group and slightly more than 94% in the SC group after 5 years. When these figures are translated into the number of patients saved from cardiovascular death, it becomes 8 out of every 1,000 treated for 5 years.

Despite these limitations, much has been made from these results. Dr. Arnold Relman editorialized, "The lesson of the HDFP study is clear. There is benefit to be derived from assiduous treatment of patients with any degree of hypertension. Physicians can no longer assume that mild, asymptomatic hypertension is harmless. The protective effects of antihypertensive drugs may be more striking when hypertension is severe and the risk of cardiovascular events greater, but even patients with diastolic pressures of 90 to 104 mm Hg will be helped by appropriate drug treatment. And, considering the huge number of patients involved, the treatment of mild hypertension may have a greater total impact on cardiovascular morbidity and mortality in our society than anyone ever imagined." [Editorial (Relman): *N Engl J Med* 1980; 302:293]

Dr. Robert Levy, at a press conference, took the 1.42% difference in survival over 4 years between the 2 groups and multiplied that number by the total estimated hypertensive population in the U.S., coming up with a figure of 316,163 fewer deaths over a 4-year interval by more intensive therapy.

4. The Australian Therapeutic Trial in Mild Hypertension (Management Committee, 1980) (Table 6).

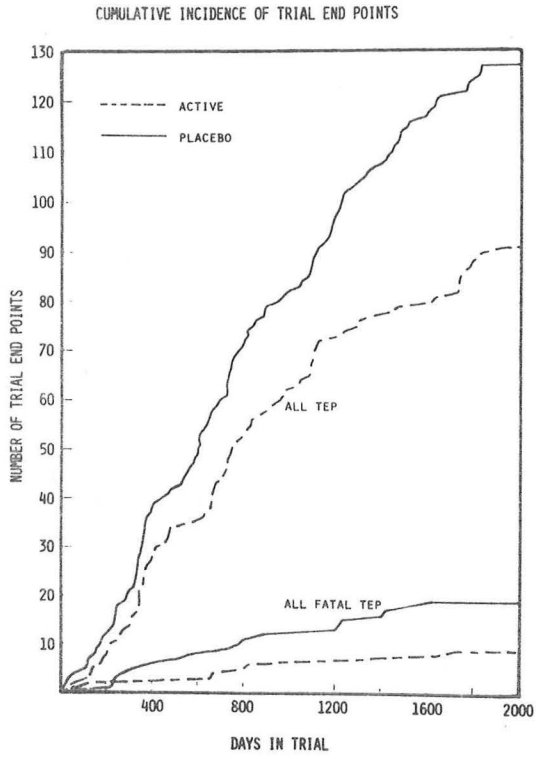
The 3,427 men and women chosen for this trial had a diastolic blood pressure between 95 and 109 mm Hg on the second set of blood pressure readings and were free of clinical evidence of cardiovascular disease. Because they were not considered to be at immediate risk, half were given placebo and the trial was constantly monitored so that, when a clear difference between the two groups appeared, the trial was stopped. It took 3 years to show the 30% difference in trial end points (i.e., death, stroke, MI, angina, CHF, dissecting aneurysm, Grade 3 or 4 retinopathy, renal damage with serum creatinine >2 mg/dl, or hypertensive encephalopathy) (Figure 15).

These results appear to be strong affirmation of the value of active drug therapy for mild hypertension. But a closer look at the Australian data shows that the excess in morbidity among the placebo-treated half was limited to those whose DBP remained above 100 (Figure 16). And, 80% of the entire placebo treated group with initial DBP between 95 and 109 had an end DBP below 100. In fact, for those whose end DBP was below 100, there was *less morbidity* among those *on placebo* than among those on drug therapy as shown in Figure 17, taken from Table 10 of the *Lancet* paper (Table 7).

TABLE 6

A comparison of three trials of therapy for mild hypertension

	Hypertension Detection and Follow-up Program HDFP Stratum I (DBP 90-104)	Australian Therapeutic Trial in Mild Hypertension (DBP 95-109)	The Oslo Study (DBP 90-109)
Number of Patients	7,825	3,427	785
Characteristics:			
Mean age (years)	50.8	50.5	
Per cent male	55	63	
Mean screening BP	152/96	157/100	
Treatment Regimens:			
Control group	Referred to usual sources: 54% on drugs at end of trial	Placebo plus "advice" on diet	No therapy
Active treatment	(1) Chlorthalidone (2) Reserpine, methyldopa, etc. (3) Hydralazine	(1) Chlorthiazide (2) Methyldopa, propranolol, pindolol (3) Hydralazine or clonidine	(1) Hydrochlorothiazide (2) Methyldopa or propranolol
Mean DBP at end of trial (mm Hg fall):			
Control group	87.8 (-8.6)	93.9 (-6.6)	96 (-1)
Active treatment	83.4 (-12.9)	88.3 (-12.2)	86 (-11)
Incidence of end points	(Control:Active)		
Deaths			
Cardiovascular	165:122	13:4	6:7
Non-cardiovascular	122:109	6:5	3:3
Non-fatal cardiovascular events		127:91	28:18



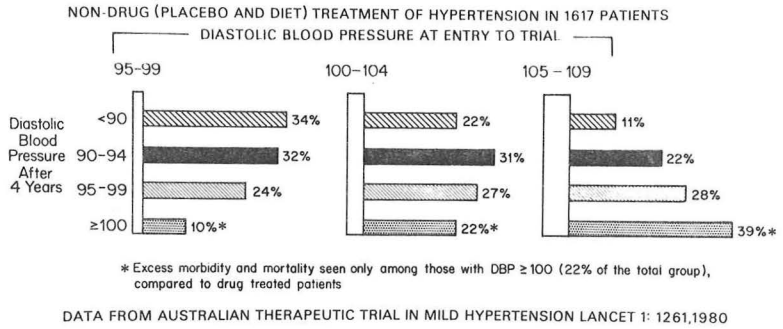


Figure 16. The changes in diastolic blood pressure (DBP) from entry into the Australian Therapeutic Trial until the completion of the study, an average of 4 years, in the 1,617 patients treated without drugs. Note that the majority of those with initial DBP from 95 all the way up to 109 ended with DBP below 100 and that excess complications were noted only in those whose end DBP was above 100.

Figure 15. The results of the Australian Therapeutic Trial in Mild Hypertension showing the cumulative occurrence of total end-points (TEP) and of deaths from all causes in 1,720 subjects of the active (---) and 1,706 of the placebo (——) groups. The differences between the two groups are significant for both TEP and deaths. [From: The Management Committee, 1980]

TABLE 7

TABLE X—TRIAL END-POINT RATES BY AVERAGE DBP ON TRIAL REGIMEN AND ACCORDING TO SCREENING DBP CLASS*

Screening DBP (mm Hg)	95–99				100–104				105–109			
Average DBP (mm Hg)	No. of subjects A	No. of subjects P	Rates† A	Rates† P	No. of subjects A	No. of subjects P	Rates† A	Rates† P	No. of subjects A	No. of subjects P	Rates† A	Rates† P
<90	543	255	12·1	20·5	335	121	17·6	14·7	166	31	12·2	0
90–94	144	244	24·8	15·7	142	174	14·4	17·8	84	64	19·9	12·3
95–99	46	183	69·8	24·6	48	146	38·4	19·3	49	83	58·4	25·4
≥100	23	81	0	46·2	33	122	0	62·2	21	113	131·6	64·6
Total	756	763	15·6	22·3	558	563	17·5	24·5	320	291	20·7	30·5

*This table does not include 176 subjects who did not have any blood-pressure readings after starting trial regimen.
†Rates per 1000 person-years.

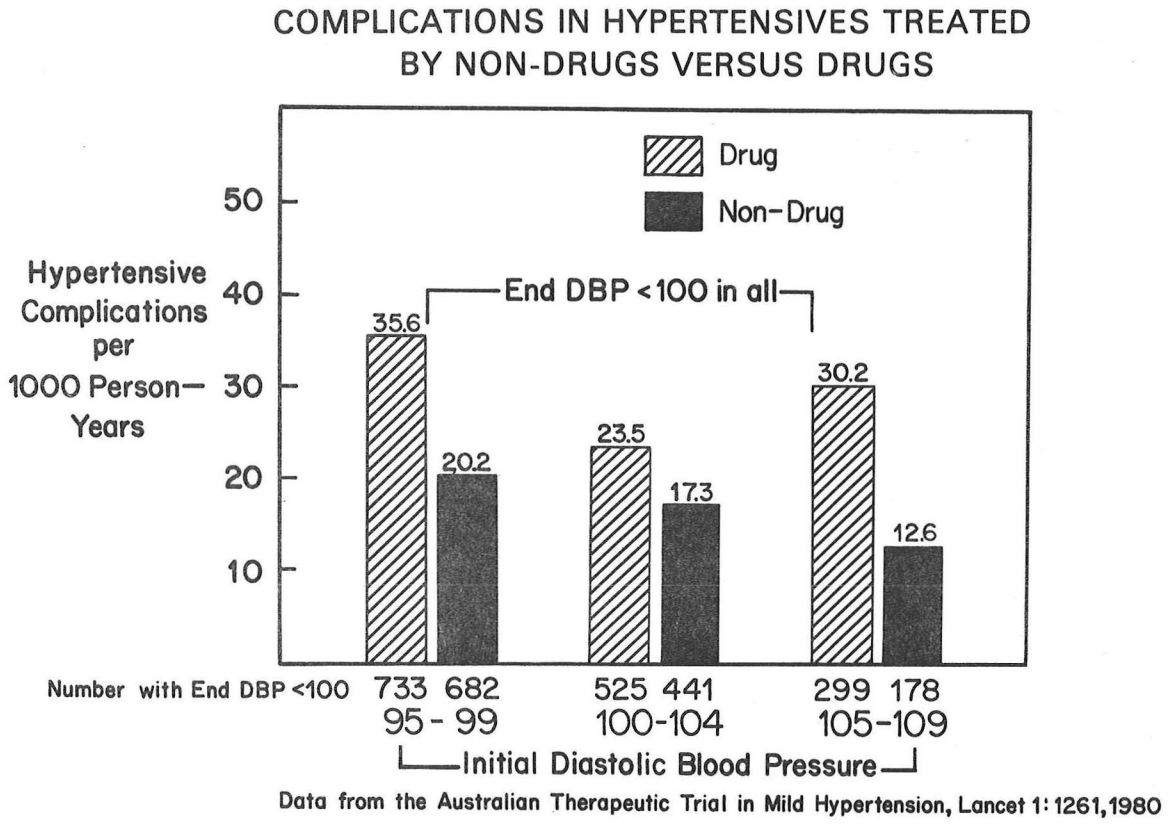


Figure 17. The cardiovascular complications per 1,000 person years among those not receiving drugs (non-drug) and those receiving drugs during the Australian Therapeutic Trial. Note that, for those who achieved an end DBP below 100, regardless of the initial DBP range, the complication rates were lower in those not on drugs. More of those from each initial DBP group on drugs achieved an end DBP below 100 (composed from: The Management Committee, 1980, Table 10).

In a personal communication, Dr. Ralph Reader, director of the Australian Trial, indicates that these data are misleading since the duration of exposure to risk and numbers of subjects varied widely between the two groups. However, what is in Table 10, despite differences in the numbers of patients between the drug and non-drug treated groups, cannot be so easily swept away. In a personal communication from one of the principal investigators of the Australian Trial, Dr. Austin Doyle, it was noted that there were no apparent differences between the two groups in weight loss or smoking cessation which might explain why the placebo treated group with end DBP below 100 had fewer cardiovascular complications. We are left with one conclusion: uncomplicated patients whose DBP stay below 100 may be better off if they are not on drug therapy. As we shall see, both diuretics and beta-blockers may have adverse effects on plasma lipids, adding to one cardiovascular risk while reducing another.

A less ominous explanation is that the drug treated patients, who *ended up* at the same final DBP as the placebo treated group, *started* with higher pressures--a logical assumption since their blood pressures fell more than did the placebo treated group. Therefore, their hypertension may have been biologically more aggressive, inducing more underlying pathology that would lead to more clinical disease despite effective lowering of the blood pressure. We have no proof for this latter explanation since all patients were initially free of obvious cardiovascular disease, and the two groups were identical in all features known to predispose to later morbidity.

Another important piece of their data should be recognized: of those 3,931 with an average diastolic blood pressure of 95 mm Hg (based on two readings taken at two screening exams), 12.8% had a fall in their pressure to below 95 mm Hg before the tablets were dispensed, and they "never again reached the [95 mm Hg DBP] threshold to qualify them to start tablets." Thus, we immediately see reinforcement of the need for multiple readings in those with minimally elevated pressures to ensure that they are really hypertensive.

5. The Oslo Trial (Helgeland, 1980) (Table 6)

The results of the Oslo Trial provide further evidence that drug therapy for mild hypertension may *not* provide protection from cardiovascular events *if the DBP remains below 100*. This trial was similar to the Australian one in that it included only uncomplicated patients free of target organ damage with DBP below 110 and randomly divided them into non-therapy and drug therapy groups. It differed in being smaller in size and involving only men--all of whom were below 50 years of age.

For those with an initial DBP below 100, there was no difference in either mortality or cardiovascular events between the non-treated and drug-treated groups. However, among those with an initial DBP above 100, the incidence of cardiovascular disease was 16.4% in those not treated and only 7.6% in those given drug therapy. This difference in cardiovascular morbidity among those with an initial DBP above 100 was accompanied by a 10 mm Hg lower DBP in the drug-treated group.

B. The Prevention of Progression

Both the Australian and the Oslo trials strongly document the relative (short-term) benignity of DBP below 100 and the relative danger of DBP above 100. Most of the trouble occurred in those whose DBP *started and stayed* above 100. Recall that most of the Australian patients on placebo who started with DBP between 95 and 109 ended with a DBP below 100. According to the figures in the paper from Oslo, about half of their non-treated group had a fall in DBP during the first 3 years. Such falls in blood pressure in the absence of drug therapy could represent the gradual relief from initial stress-induced elevations in pressure or the effect of non-drug therapies. Thus, it seems prudent not to treat with drugs those who have no obvious cardiovascular disease with a DBP that starts below 110 and comes down and stays below 100. Those with any elevation in blood pressure should be encouraged to lose weight, if obese, and to restrict dietary sodium to a level below 100 mEq per day (Ram, 1981).

One point must be remembered, however, if the DBP of 100 is to be used as the decision point for active drug treatment: the patients not actively treated--10% in the VA study, 12% in the USPHS study and the Australian trial, and 17% in the Oslo trial--had a progression of their DBP within 3 to 5 years to above 110, wherein danger is clear and active therapy mandatory (Table 8). Thus, those not treated with drugs must be watched as carefully as those who are--probably every 6 months to ensure that their DBP remains below 100 while they are encouraged to keep slim, to stay in good shape, and to follow a diet modestly restricted in sodium.

TABLE 8

Progression of hypertension in placebo-treated patients with initially mild hypertension

	VA	USPHS	AUSTRALIAN	OSLO
Number of Patients	194	196	1,706	379
Initial level of DBP (mm Hg)	90-114	90-115	95-109	90-109
Threshold level of DBP (mm Hg)	125	130	110	110
Percent with progression beyond threshold	10%	12%	12%	17%

Beyond protection from progression of the degree of hypertension, active drug therapy may actually reverse the functional and structural changes that are responsible for the underlying pathophysiology. When systemic hemodynamics were restudied in 13 patients with essential hypertension after 1 year of good control of the blood pressure (and 4 weeks after stopping diuretics, 1 week after stopping other drugs), the initially high peripheral resistance had become normal in all but one (Jennings, 1980) (Figure 18).

The change was not permanent: within 1 to 4 months off therapy, the blood pressure rose back to pretreatment levels in 12 of the 13 patients.

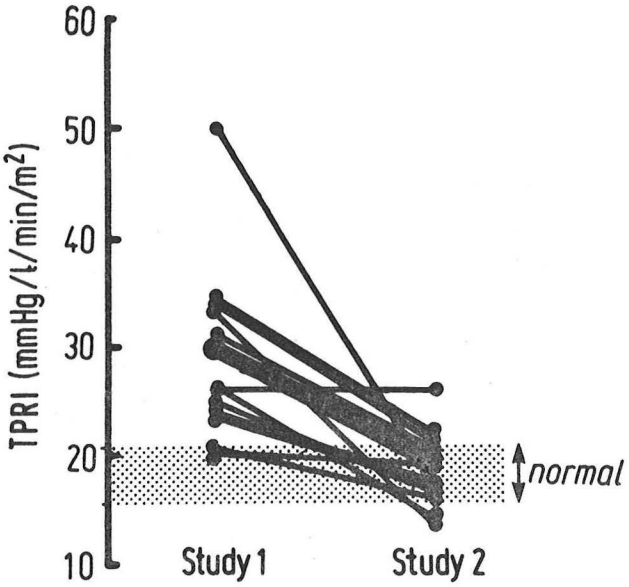


Figure 18. Total peripheral resistance index (TPRI) after autonomic block in study 1 and study 2, compared with the findings in another group of normotensive subjects described by Korner *et al* (from: Jennings, 1980).

C. The Costs of Therapy

The benefits of therapy noted in the 5 therapeutic trials were achieved at great financial cost under circumstances which may not apply to the usual practice of medicine--certainly not in the clinics at Parkland and likely not in the private sector as well. Beyond the problems of keeping individual patients on therapy, there are societal considerations as well. Is it worth the costs to achieve the benefits for the majority of patients with hypertension?

Weinstein and Stason have written a book and excerpted their major conclusions in an article (1977) that explores the financial costs that must be borne to treat hypertension in men and women at varying ages with differing degrees of success. Their data are expressed as the net dollar cost per year of increased "quality-adjusted" life expectancy--the "quality adjustment" adding time for the prevention of disability and subtracting time for the production of side effects. As shown in Table 9, they used the Framingham data to determine the increases in life expectancy that would follow the lowering of diastolic blood pressure from 110 mm Hg to 90 mm Hg at different ages in women and men.

Based upon certain assumptions (e.g., the average cost of treatment each year is $200), they come up with some rather startling conclusions: it costs (In 1976 dollars) $13,000 to add a year of life expectancy to a man aged 50 with a pretreatment diastolic blood pressure of 100; for a woman aged 20 with a pretreatment DBP of 100, it would cost $40,000 to add a year of life expectancy.

Looking at 40-year-old men and women with varying pretreatment DBP, it is obvious that the cost of adding a year of life expectancy is less the higher the pretreatment level and the lower the level that is reached by therapy (Figure 19).

TABLE 9

Increase in life expectancy and quality-adjusted life expectancy according to age and sex*

AGE (Yrs.)	LIFE EXPECTANCY (Yrs.)	INCREASE IN QUALITY-ADJUSTED LIFE EXPECTANCY (Yrs.)
Women:		
20	53.2	5.4
30	43.9	4.8
40	34.8	4.0
50	26.4	3.1
60	18.5	2.6
Men:		
20	46.5	8.2
30	38.2	5.9
40	29.7	4.0
50	21.7	2.6
60	14.5	1.5

*Estimates are for a reduction in diastolic blood pressure from 110 mm Hg to 90 mm Hg.
[Data from: Weinstein and Stason, *N Engl J Med*, 1977.]

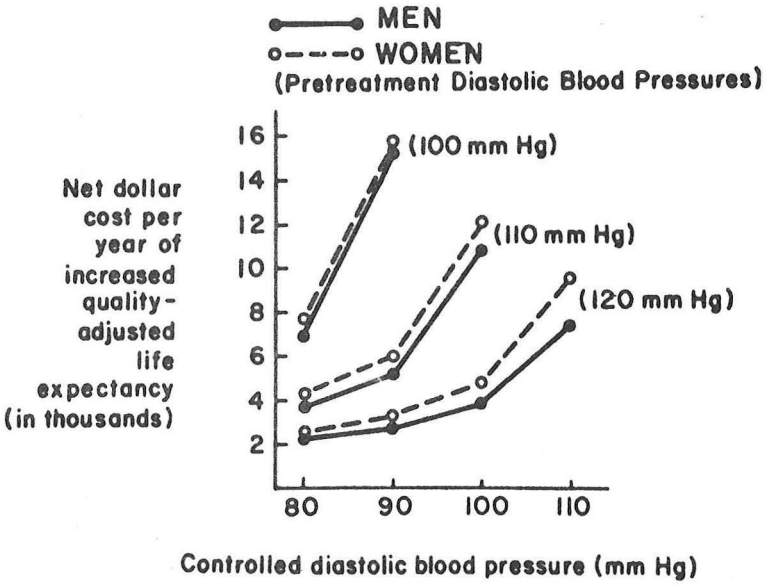


Figure 19. Cost effectiveness for varying pretreatment and controlled levels of diastolic blood pressures. Results are for 40-year-old men and women. The analysis assumes age-varying partial benefit, full adherence to medical regimens and discounting at 5 per cent per year (from: Weinstein and Stason, 1977).

As interesting as this analysis is, it is largely irrelevant to the care provided by individual practitioners for individual patients. We rarely consider the financial costs or the expected benefits when applying therapies that have been proved to be even marginally effective. But, as the costs of health care continue to rise, maybe we will have to. The British do not provide ready access to kidney dialysis to all patients deemed in need of this therapy because of cost constraints.

IV. The Choice of Initial Drug Therapy

A. Deciding Upon the Need for Drug Therapy

The preceding material attempts to document the need for a more conservative approach toward active drug therapy for the majority of hypertensives. Quoting Michael Alderman (1980):

> *The common practice of treating persons on the basis of their blood pressure alone is to ignore the heterogeneity of mild hypertension. This approach substitutes a standardized universally applicable chemotherapeutic recipe for individual clinical judgment based on the comprehensive assessment of each patient. Experience in mild hypertension trials suggests that the level of pressure is about as specific a guide to course, outcome and need for therapy as is temperature. Both these vital signs, although useful clinically as well as epidemiologically, neither describe etiology, predict a course nor justify, by themselves, the institution of lifelong therapy for any individual patient. By analogy, persons with tuberculosis have fever, but hyperpyrexia does not always signify the need for antituberculosis therapy.*

I believe the following guidelines are appropriate in deciding upon the institution of therapy, once having confirmed the presence of hypertension by multiple readings:

1. Patients with DBP above 110 or with DBP above 100 with accompanying target organ damage or other cardiovascular risks should be treated immediately with drugs.
2. Patients with DBP below 110 without obvious cardiovascular disease or other risk factors should be encouraged to follow good health habits for 6 months while being closely followed.
3. If the DBP remains below 100, they should be left off drugs and followed at least every 6 months.
4. If the DBP stays above or goes above 100, they should be treated with appropriate antihypertensive drugs.

This approach runs counter to what most authorities are now saying and what most American practitioners are now doing. When a survey was done in 1978 of 64 hypertension clinics and offices in New York state, 92% reported that anti-hypertensive medications were prescribed for adults with DBP between 90 and 104 mm Hg (Thomson, 1981).

The British are more conservative. In response to the question, "At what level of diastolic blood pressure would you begin to treat an asymptomatic man for hypertension?", 37 hospital staff physicians in Birmingham, England, gave these replies: 46% in the range of 90 to 104 mm Hg, 24% at 105 to 109, and 30% only if the level were 110 or higher (Taylor, 1979).

B. The Choice of the First Drug

Once having decided to treat and not having achieved the desired reduction by non-drug therapies, three issues should be addressed:

1. Which type of drug should be used first? The choice most widely advised and followed is a diuretic, but some argue for a beta-blocker.
2. If a diuretic is the first drug, what should be the second, as will be needed for at least half of all patients. Increasingly, this is a beta-blocker.
3. If a beta-blocker is the second (or the first) drug used, which should be chosen from the three available as of mid-April, 1981, or the three others that will likely soon be available in the U.S. (personal communication from Dr. Robert Temple, Director, Division of Cardio-Renal Drug Products, Bureau of Drugs, Food and Drug Administration, December 30, 1980).

About one half of patients deemed in need of antihypertensive drug therapy will need only one drug to lower their DBP to below the goal of 90 mm Hg (HDFP, 1979; Management Committee, 1980). In the U.S. today, a diuretic is chosen by the majority of practitioners as this first drug (Pettine, 1979). The reasons are good patient acceptance, proved effectiveness, and minimal side effects (Table 10). However, beta-blockers have been advocated and used increasingly in Europe (Buhler, 1976). They provide equal efficacy, but less patient acceptance and more frequent--and more bothersome--side effects. Among previously untreated patients given various antihypertensive drugs, 6% of those given diuretics stopped taking them, whereas 23% of those given beta-blockers stopped (Beilin, 1980). However, they offer certain advantages in those with certain concurrent diseases and a potential for protection from coronary heart disease.

The case for and against diuretics: For: All of the 5 trials previously covered used diuretics first, proving their efficacy and overall safety. A single tablet daily of a moderately long-acting diuretic such as hydrochlorothiazide will lower the blood pressure about 10 mm Hg, as much as can be accomplished with many more tablets of other drugs, saving the patient trouble and expense.

The dose-response curve is flat, so that if a daily dose equivalent to 50 mg of hycrochlorothiazide does not lower the blood pressure enough, it is unlikely that more diuretic will be much more effective in those without renal insufficiency. With chlorthalidone, 25 mg a day may provide as much antihypertensive effect and less hypokalemia than larger doses (Tweeddale, 1977) (Figure 20).

Diuretics lower the blood pressure by overcoming the hemodynamic defect--an elevated peripheral resistance--that is responsible for primary (essential) hypertension. Though their antihypertensive action requires an initial natriuresis, the persistent effect of diuretics is mediated through a decrease in peripheral resistance (Shah, 1978).

TABLE 10

A comparison between diuretic and beta-blocker therapy of hypertension

	DIURETICS	BETA-BLOCKER
Efficacy (DBP 90)	@50%	@50%
Side effects:		
Minor	15%	20%
Major	1%	2%
Number of daily doses	One	One or two
Cost per day ($)	.05-.20	.25-2.00
Special indications	Age over 50 Blacks CHF	Young, "hyperkinetic" Concomitant disease: CAD, arrhythmias, migraine, anxiety ? Protection from CAD
Contraindications		Asthma A-V conduction defects Peripheral vascular disease (CHF) (Heavy exercise)
Additional considerations:		
Hemodynamic effects		
Peripheral resistance	Decrease	Increase
Cardiac output	Slight decrease	Decrease
Effect on plasma renin	Increase	Reduce
Effect on plasma catecholamines	Slight increase	Increase
Effect on body potassium	Decrease	No change or increase
Potential for paradoxical rise in BP if used alone	In the 10% with high renin	In the 30% with low renin

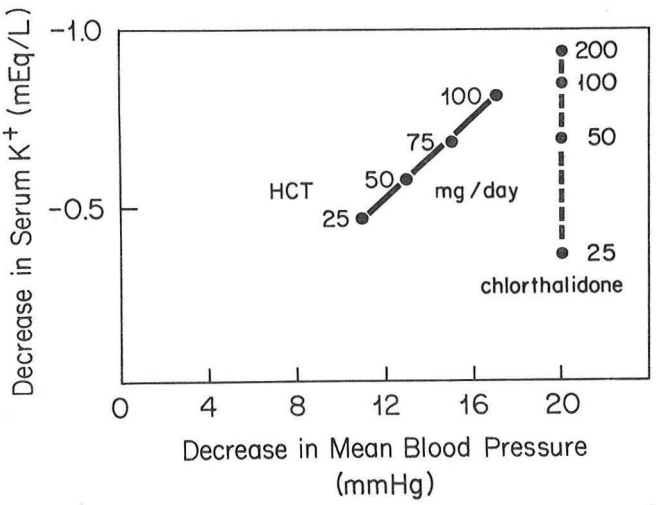


Figure 20. The effects of varying doses of hydrochlorothiazide (HCT) and chlorthalidone on the blood pressure and serum potassium in two groups of hypertensives. The different doses of chlorthalidone and HCT were given for 6 to 8 week periods in random order. Data on HCT from Degnbol *et al: Acta Med Scand* 193:407, 1973; data on chlorthalidone from Tweeddale *et al: Clin Pharmacol Therap* 22:519, 1977.

Patients who start with a low renin--particularly the elderly and blacks--may respond particularly well to a diuretic (Vaughan, 1973), but some effect is almost always seen, regardless of the pre-existing renin level.

If additional drugs are indicated, a diuretic is usually needed to prevent the reactive fluid retention that often accompanies successful reduction of the blood pressure by any and all non-diuretic agents.

Against: Diuretics have a rather limited antihypertensive action, and their effect may be overwhelmed by the large amounts of sodium that many people ingest. With renal insufficiency, larger amounts of more potent diuretics are needed.

Their side effects may be more serious than they appear. Diuretic-induced hypokalemia may induce serious arrhythmias (Holland, 1981). A rise in serum cholesterol and triglycerides frequently accompanies diuretic use, thereby counteracting the improvement in cardiovascular risk provided by the lowered blood pressure (Grimm, 1981).

The usual 2 to 3 mg/dl rise in serum uric acid, the average 0.7 mEq/L fall in serum potassium, and the slight rise in serum glucose levels may pose more serious long-term hazards to cardiovascular health than now appreciated.

The case for and against beta-blockers: For: Of all the adrenergic inhibiting agents, beta-blockers seem most acceptable to most patients. When compared to methyldopa, the antihypertensive efficacy is equal but the side effects fewer with beta-blockers (Lorimer, 1980).

With beta-blockers, the blood pressure is reduced gradually and smoothly with little alteration by changes in posture or activity. Along with the fall in blood pressure, nervous patients experience fewer of the somatic manifestations of tension and anxiety (Taggart, 1973). If they have concomitant angina, arrhythmias, migrane, or glaucoma, these problems may also be helped by the beta-blocker.

When hypertensive patients exercise or undergo mental stress, the systolic blood pressure usually rises. This rise is blunted to a greater degree by beta-blockers than by either diuretics (Franz, 1980) or methyldopa (Lorimer, 1980).

Once a day dosage will likely provide 24-hour control of the blood pressure, probably with all beta-blockers (Watson, 1979) and most certainly with the water soluble, long-acting ones such as nadolol and atenolol.

Beta-blockers have been found to reduce recurrences of myocardial infarction when given to patients after their initial MI (Norwegian Study, 1981). Whether they provide protection from initial occurrences of coronary disease is unknown. Trials of primary prevention are underway.

Beta-blockers are well tolerated by most patients if those with preexisting allergies, peripheral vascular disease, or cardiac conduction defects are excluded from therapy. In common with diuretics, few experience sedation, impotence, or fatigue. Beta-blockers do not induce potassium wastage or hypokalemia, the most bothersome side effect of diuretics. In fact, beta-blockers impair the extra-renal disposition of potassium and tend to raise the serum potassium (Rosa, 1980).

Against: These drugs have multiple and profound effects, and beta-blockade may expose the patient to multiple risks. Beyond the well recognized exascerbation of bronchospasm, bradyarrhythmias, peripheral vascular disease, and congestive failure, the blockade of beta-receptors may worsen glucose tolerance and interfere with normal lipid metabolism with resultant rises in triglycerides and falls in HDL-cholesterol (Leren, 1980).

The exact mechanisms by which beta-blockers work to lower the blood pressure remain unknown but, however that is accomplished, peripheral resistance--already high--tends to go higher from unopposed alpha-mediated vasoconstriction (Lund-Johansen, 1978). Not only does this limit the antihypertensive potential of the drug, but it also is responsible for the cold extremities, decreased exercise tolerance, and easy fatigability experienced by some (Anderson, 1979).

Both the elderly and the black hypertensive may respond poorly, if at all, to monotherapy with beta-blockers. In the large experience by Buhler and co-workers (1976), only about a third of those above age 50 had a fall of their diastolic blood pressure to less than 95 mm Hg on beta-blockers alone. The finding by Humphreys and Delvin (1968) that propranolol, up to 360 mg a day, was ineffectual in native Jamaicans has been duplicated in other black populations (Salako, 1979). A possible reason for this lesser response is the lower renin levels among both the elderly and the black.

Though once a day therapy may work for many, most physicians still prescribe multiple doses with as many as 8 tablets a day, making it both an expense and a bother for patients to remain on therapy.

If beta-blockers are abruptly stopped, a withdrawal syndrome of tachycardia, angina, myocardial infarction, or death may occur (Miller, 1975). Though usually noted in patients receiving propranolol for angina, it should be anticipated in those with hypertension among whom coronary artery disease is frequent.

On the basis of these considerations, I agree with the Joint National Committee (1980) that a diuretic is the appropriate first choice if drugs are needed to treat hypertension. If beta-blockers are proved to provide primary protection from myocardial infarction and sudden death, the balance could tip toward their use as initial therapy.

Direct evidence in favor of this position comes from a randomized trial in which 106 patients were treated with either a diuretic or a beta-blocker for 6 years. The end results were almost identical, with a slight preference for the diuretic (Berglund G, Andersson O: *Lancet* 1981; 1:744-747).

The choice of the second drug: The Joint National Committee (1980) simply listed the various adrenergic inhibiting agents now available in alphabetical order with the disclaimer that, "This does not indicate preferential order of usage." However, on the basis of fewer side effects (Lorimer, 1980) and better patient acceptance (Beilin, 1980) with equal efficacy, beta-blockers are quickly becoming the most popular of these, taking over the top position so long held by methyldopa.

When used as the second drug, beta-blockers diminish the degree of diuretic-induced renal potassium loss and hypokalemia (Neuvonen, 1978) (Table 11). This may reflect a dampening of the activation of the renin-aldosterone system but direct blockade of adrenergic effects on extra-renal handling of potassium is also involved (Rosa, 1980).

TABLE 11

The effect of beta-blocker on diuretic-induced hypokalemia*

	Placebo	Chlorthal-idone	Beta-Blocker	Chlorthalidone + Beta-blocker
Supine Blood Pressure	158/106	143/96	142/95	136/91
Serum Potassium	4.04	3.55	4.07	3.88

[Data from: Neuvonen *et al: Br J Clin Pharmacol* 6:363, 1978)

*All drugs were given to 18 patients, in random order, for 6-week periods.

Patients who have contraindications to the use of beta-blockers or who develop bothersome side effects from them can be given any of the other second-step agents. Moreover, the other adrenergic inhibitors may have other advantages. Beta-blockers raise both peripheral resistance (Lund-Johansen, 1978) and plasma catecholamine levels (Irving, 1974), whereas they are lowered by methyldopa and clonidine (Lund-Johansen, 1978; Polak, 1978). The post-synaptic alpha-blocker prazosin lowers peripheral resistance even more and maintains a favorable hemodynamic profile during progressive exercise (Lund-Johansen, 1980). In a randomized crossover trial, the unfavorable changes in blood lipids seen with propranolol were not seen with prazosin (Leren, 1980). Since it seldom causes sedation or dryness, as occurs frequently with methyl-dopa or clonidine, prazosin is a particularly attractive alternative to the beta-blockers as the second drug to treat hypertension.

In the elderly, clonidine may be particularly useful since beta-blockers work less well and prazosin may cause bothersome postural hypotension. Methyl-dopa is widely used among the elderly, but clonidine will work as well with less hepatic, hematologic, and other "autoimmune" side effects.

The choice of beta-blockers: If a beta-blocker is chosen as the first or, more likely, the second drug, which beta-blocker is best? Since only 6 of the large number currently under study will likely be available in the U.S. in the near future, we will focus on them (Table 12).

TABLE 12

Properties of beta-adrenergic blocking agents

GENERIC NAME	TRADE NAME®	CARDIO-SELECTIVITY	INTRINSIC SYMPATHOMIMETIC ACTIVITY	LIPID SOLUBILITY	PHARMACOLOGIC HALF-LIFE (in hours)
Those now or (presumably) soon to be available:					
Atenolol	Tenormin	+	0	-	21
Metoprolol	Lopressor*	+	+	+	24
Nadolol	Corgard*	0	0	-	39
Pindolol	Visken	0	+++	+	8
Propranolol	Inderal*	0	0	+++	10
Timolol	Blocadren	0	0	+	15
Others under active investigation:					
Acebutolol	Sectral	+	+	+	24
Alprenolol	Aptine	0	++	++	24
Oxprenolol	Trasicor	0	++	+	13
Sotalol	Sotacor	0	0	-	12

*Available in the United States as of April, 1981.

Though they have not all been tested against one another, they appear to have fairly equal antihypertensive efficacy (Davidson, 1976; Wilcox, 1978). In the randomized crossover study by Wilcox (Figure 21), atenolol seemed to be more effective, but its dose may have been higher relative to that of the other beta-blockers. In similar crossover studies, atenolol was found to be more effective than propranolol (Van Rooijen, 1979) or than either propranolol, oxprenolol, or pindolol (Waal-Manning, 1979). Though atenolol is also said to have a fairly flat dose-response curve, allowing for quick titration to maximal antihypertensive effectiveness, other beta-blockers are probably similar: in a double-blind crossover study, the hypotensive response to 40 mg of propranolol twice daily was equal to that found with doses of 80, 160, or 240 mg twice daily (Serlin, 1980).

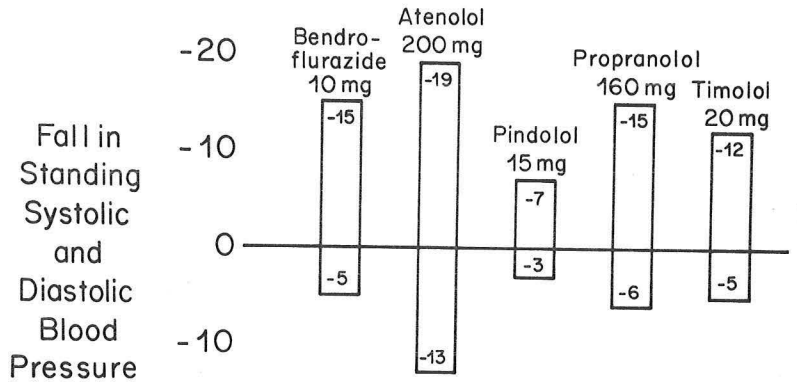


Figure 21. The effect of 5 different drugs on the standing blood pressure of 15 hypertensives with an initial blood pressure of 169/113. Each drug was given for 4 weeks, once daily, in random order without a washout interval between them. Data from Wilcox: *Br Med J* 2:383, 1978.

Other differences between beta-blockers exist that may influence the choice. These include cardioselectivity, intrinsic sympathomimetic activity, and lipid solubility, which in turn influences duration of action (Table 12).

Cardioselectivity: Atenolol and metoprolol are among those beta-blockers that have a relatively greater blocking effect on the $beta_1$ receptors in the heart than on the $beta_2$ receptors in the bronchi, peripheral blood vessels, and pancreas. In small doses this cardioselectivity can easily be demonstrated; but, in the often rather high doses used to treat hypertension, it may be lost.

Nonetheless, comparative studies have shown less of the bothersome $beta_2$ blocking effects with atenolol and metoprolol than with the nonselective agents, particularly propranolol. In the peripheral vasculature, single doses of 100 mg of metoprolol did not reduce skin or resting muscle blood flow, but 80 mg of propranolol caused them to fall (McSorley, 1978). With the loss of vasodilation that accompanies the blockade of peripheral beta-receptors, alpha-mediated vasoconstriction is left unopposed. During times of stress wherein circulating catecholamines increase, such as during exercise or following hypoglycemia, this unopposed vasoconstriction may cause the blood pressure to go even higher with non-cardioselective agents, but to a lesser degree with selective ones (Lager, 1979).

As for the bronchi, single doses of atenolol (but not metoprolol) failed to reduce the one-second forced expiratory volume in 10 asthmatic patients, whereas pindolol, propranolol, and timolol significantly reduced the FEV_1 (Decalmer, 1978). Considering the pancreas and other tissues involved in intermediary metabolism, metoprolol may cause less of a rise in blood sugar concentration than does propranolol when given to mild diabetics (Wright, 1979). The metabolic responses to hypoglycemia may be blunted with all beta-blockers, but again less so with the cardioselective ones (Lager, 1979). Though the cardioselective agents may also impair exercise tolerance less, some reduction in maximal performance is probable with all beta-blockers (Anderson, 1979).

In the presence of certain concomitant diseases, a non-selective $beta_2$ antagonist effect may be desired. Examples include migrane, high intra-ocular pressure, and tremor--all of which seem to be helped because of blockade of $beta_2$ receptors.

Intrinsic sympathomimetic activity: Pindolol alone of these six beta-blockers has significant intrinsic sympathomimetic activity. In the absence of primary agonists such as epinephrine, pindolol will interact with beta-receptors to cause a measurable agonist response, but the maximal response is considerably less than that seen with epinephrine. In the presence of primary agonists, the beta-blocking effect of pindolol is much stronger than its intrinsic sympathomimetic activity.

Pindolol's intrinsic sympathomimetic activity may be clinically reflected in one beneficial and one bothersome feature: less bradycardia but, with higher doses, a paradoxical rise in blood pressure (Waal-Manning, 1976). In addition, the agonist activity may prevent the fall in renin levels that usually accompanies beta-blockade, but this effect, as with other beta-blockers, seems to relate little to the antihypertensive effect of the drug (Gavras, 1979).

Lipid solubility: Atenolol and nadolol are less fat soluble and more water soluble than the other four agents. Lipid solubility increases the drug's uptake in the "first pass" through the liver where considerable metabolic changes may occur. This translates into a number of possibly important differences in their clinical use.

Duration of action: Those which are lipid soluble tend to be metabolized and inactivated rather quickly in the liver; those which are more water soluble tend to remain unchanged in the body fluids and more slowly excreted by the kidneys. Thus, atenolol and nadolol have relatively longer serum half-lives.

Logically, those which remain longer in the circulation in an unchanged form would have a longer pharmacological half-life as well. However, other features--degree of absorption, protein-binding, and activity of metabolites--also are involved so that the duration of action may not relate directly to serum half-life.

In fact, all beta-blockers act longer than the pharmacokinetic data would imply. What is obviously important is the time of effective beta-receptor blockade, as reflected in the duration of the inhibition of the action of infused agonists or, clinically more relevant, the length of time the blood pressure remains lower. In moderate doses, all of these six beta-blockers will keep the blood pressure down when given once daily (Watson, 1979; Johansson, 1980) (Figure 22). Though an occasional patient may need two doses a day of propranolol or metoprolol, they will usually maintain good control when given once daily. To ensure adequate control, early morning blood pressures should be measured before the daily dose is taken.

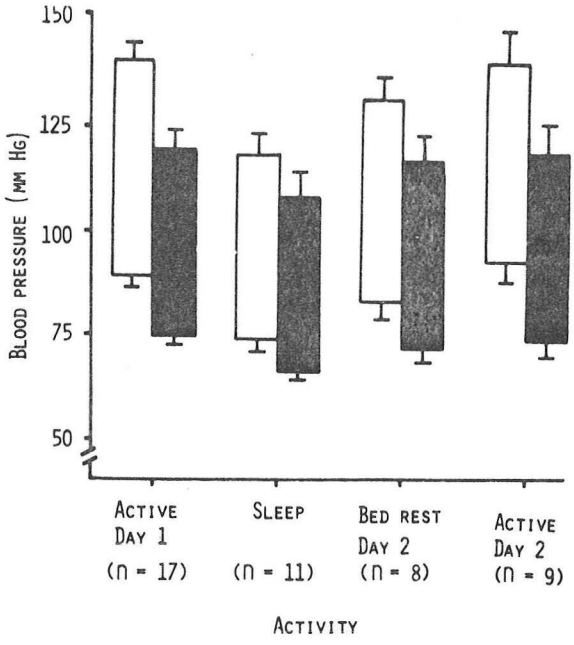


Figure 22. The average intra-arterial blood pressures (± S.E.M.) recorded at varying times before and during long-term (mean 11 weeks) therapy with propranolol (240 mg), metoprolol (200 mg), or acebutolol (400 mg) given once daily between 7 and 8 AM. The number of patients in whom measurements were made during each activity are shown at the bottom. On day 2, no drug was given and the bed rest was from 6 to 8:30 AM, the active, ambulatory period from 8:30 to 10:00 AM. Data from Watson *et al: Lancet* 2:865, 1979.

Stability of blood concentrations: Those which escape hepatic uptake will maintain more stable plasma concentrations which will be reached more quickly. It is unlikely that this makes much difference with the relatively large doses used to treat hypertension, though it might with smaller doses as used to treat coronary disease or arrhythmias.

Central nervous system effects: Those which are less lipid soluble enter the brain tissue less well (Van Zwiefen, 1979). Atenolol, found in very low concentration in the brain, has been found to relieve the CNS side effects (depression, insomnia, nightmares, hallucinations) in 24 of 33 patients who developed them while on propranolol (Henningsen, 1979). However, some CNS side effects have been seen with atenolol as well (Zacharias, 1977).

Effects in patients with renal insufficiency: Those which are more water soluble such as atenolol and nadolol are dependent mainly on renal excretion. In patients with renal insufficiency, higher blood levels are seen with usual doses (McAnish, 1980). Though there is little evidence of greater effects--either good or bad--from these higher blood levels, the doses should be progressively reduced in those with renal insufficiency.

A 20% fall in glomerular filtration rate and renal blood flow has been observed in normotensive and hypertensive patients with normal kidney function given propranolol (Bauer, 1979; Wilkinson, 1980), although clinically manifest renal impairment is very unusual. Other beta-blockers, either cardioselective (atenolol) or non-cardioselective (nadolol), have not been found to reduce renal function (Wilkinson, 1980; Waal-Manning, 1980).

Considering all of these pharmacologic and clinical features, there seems to be some advantage in choosing a relatively cardioselective, lipid-insoluble agent such as atenolol to provide the certainty of prolonged action and the likelihood of fewer side effects. When atenolol was compared to propranolol in a large series of patients, about one-third fewer side effects were noted among those on atenolol and only about one-fifth as many patients had to stop beta-blocker therapy (Zacharias, 1977). Nonetheless, the usefulness of the less cardioselective and lipid-soluble agents should not be forgotten: propranolol has been both effective and safe for millions of patients--in some for as long as 15 years.

As with other types of drugs, different people may respond differently to similar agents, and it is good to have a number of beta-blockers from which to choose. However, six are likely enough to provide all of the advantages and to minimize the disadvantages of the beta-blocker family.

Two drugs as initial therapy: Since about half of patients will end up on two drugs, some prefer to start with the combination of a diuretic and an adrenergic inhibitor. That practice is, in general, unwise for these reasons: (1) even with fairly high blood pressure, many will respond adequately to one drug, and there is no certain way to know who will need more than one; (2) if side effects appear, it is preferable to know which drug is responsible; (3) the dose response curves differ with various drugs, so fixed-dose combinations may be inappropriate; and (4) except in those with dangerously high levels of blood pressure, a gradual, gentle reduction in pressure with one drug at a time is easier to tolerate than is a sudden, drastic fall from two or more drugs.

Conclusion: A single morning dose of an intermediately long-acting thiazide diuretic, such as 25 or 50 mg of hydrochlorothiazide, seems to be the best choice for the first drug to treat most patients with primary (essential) hypertension. If that is not enough, a single morning dose of a long-acting, relatively cardioselective beta-blocker such as atenolol should be added. Thereby, over 80% of all hypertensives will have their blood pressure brought to safer levels without bothersome side effects, improving the likelihood of patient adherence to long-term therapy.

Other second-step drugs, particularly prazosin, may be as or more acceptable than a beta-blocker, but the use of a diuretic and a beta-blocker will likely continue to be the most popular combination therapy for hypertension for some time.

V. The Goal of Therapy

Regardless of the drug chosen, the physician should have a clearly defined goal of therapy. In the past, a diastolic blood pressure of 90 was generally accepted. Despite an occasional voice of dissent for a higher pressure as the goal, the increasing awareness of the data from the HDFP and the Australian Trial will likely lead to a lowering of the goal to below 90.

The goal in both of these trials for those with mild hypertension was to bring the diastolic pressure to 90 mm Hg or lower. After 2 years, the goal was lowered to 80 mm Hg in the Australian Trial. In the HDFP, those on stepped-care whose mean diastolic level was reduced to 83.4 had 20% less mortality than those receiving referred care whose mean DBP was 87.8 (Table 5). It, therefore, seems logical that, in order to achieve the maximal benefits from therapy, the goal should be less than 90--probably 85 or even lower.

Whether the experts and the medical community will accept these lower levels as the appropriate goal remains to be seen. Epidemiological data can be found both to confirm and to deny the wisdom of a goal lower than 90. Support comes from the Life Insurance actuarial data (Figure 23). The least excess mortality among 20,000 hypertensive men receiving antihypertensive therapy at the time of their insurance exam was seen in those with the lowest pressures, less than 127 systolic and less than 83 diastolic.

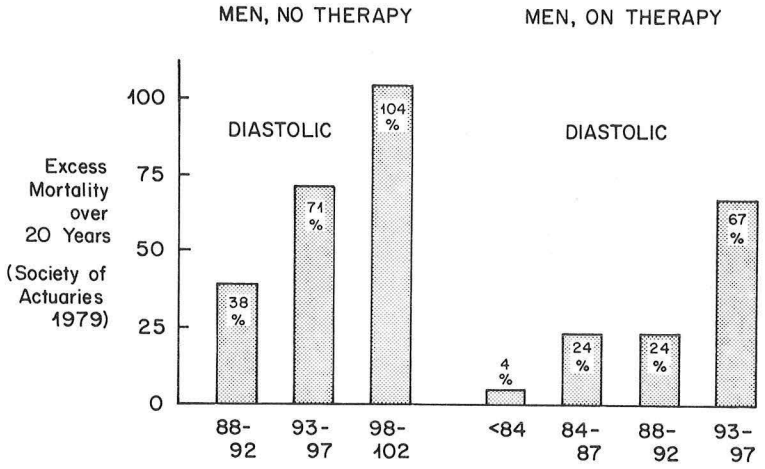


Figure 23. The excess mortality over 20 years observed among men who were initially not on antihypertensive drug therapy (left) versus that observed among a much smaller group of 20,000 men who were on therapy (right) at the time of taking out insurance (composed from: Lew, 1978).

On the other hand, a careful look at the Framingham data reveals that there was no decrease in cardiovascular morbidity (events) over 18 years of follow-up among those with diastolics below 90 (Anderson, 1978). In fact, there is a hint of increased morbidity as the diastolics diminish from 90 down to 70. These low pressures are not the result of antihypertensive therapy, so it may be inappropriate to use them as evidence for possible harm when they are achieved in the treatment of hypertension. Nonetheless, the relationship between diastolic pressure and cardiovascular morbidity may be complicated and there may be a threshold for the greatest benefit to be achieved.

At this time I would predict that a goal of 85 mm Hg for the diastolic pressure will be increasingly accepted and recommended. This recommendation seems antithetical to the prior argument against immediate, active therapy for most patients otherwise not at risk who have a DBP below 100. Perhaps the difference between, on the one hand, the need to only treat the low-risk patients with DBP above 100 and, on the other hand, the extra protection obtained by bringing the DBP to below 85 once therapy is used represents the inherent "toxicity" of currently used antihypertensive drugs. This is a highly hypothetical argument that really cannot be defended, but I leave it with you as a *mea culpa* in the confession of a former therapeutic enthusiast.

It is worth remembering that the Framingham data show lower cardiovascular risk with progressively lower systolic pressures, even below 120 mm Hg. It may be necessary to include the systolic level as part of the goal of therapy, though most trials have disregarded it. The benefit of therapy for those with predominantly or purely systolic hypertension has not yet been proved; but, based on the clear evidence of increased risk when it is left high and the epidemiological data showing lesser risk with lower systolic pressures, the prudent course for now would be to lower the systolic to below 160 and, if possible without bothersome side effects or large amounts of medications, to below 140. Hopefully, data about the benefits of treating systolic hypertension will soon be available. In the meantime, a gentle, gradual approach to lowering high systolic pressures should be taken.

In final summary, the decision to start drug therapy for most patients with mild hypertension should not be made lightly. Once started, therapy will likely be needed for the rest of the patient's life and will likely cause some side effects, hopefully transient. Problems with drugs are not unexpected: it is difficult to make an asymptomatic person feel better. However, with proper use of currently available drugs, along with the enthusiastic use of appropriate non-drug therapies, virtually all hypertensives can be offered protection from premature cardiovascular disease. Hopefully, as we apply the principles of selection based upon overall risk profiling, we can sharpen our therapeutic aim, actively treating those at significant risk and carefully monitoring the remainder.

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