Medical Grand Rounds
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Treating Hypertension: When, How, and How Far

In treating hypertension, rather striking differences exist between usual practices in the U.S. and the recommendations made by the British Hypertension Society working party (1989) (Table 1).

Table 1: Recommendations of the British Hypertension Society working party (Br Med J 1989;298:694-8)

- Treat patients under 80 with diastolic pressures over 100 mm Hg for three to four months
- Observe patients with pressures of 95-99 mm Hg every three to six months
- Use other agents if these are contraindicated, ineffective, or poorly tolerated
- Warn all patients against smoking and heavy alcohol intake
- Advise weight reduction in obese patients

Whereas the British may be too conservative, we are almost certainly too aggressive. From a third to a half of U.S. physicians begin drug therapy when diastolic blood pressure (DBP) is between 90 and 94 mm Hg (Cloher and Whelton, 1986) and 55% use drugs when systolic pressure is at 160 mm Hg or less for persons aged 60 to 69 (Breckenridge and Kostis, 1989).

I. When to Treat

A. The need to ensure presence of resistant hypertension

The first problem involves the tendency for most initial readings to be higher (Mancia et al, 1987) and for repeated readings to remain higher when they are taken by a physician (Pickering et al, 1988) (Table 2).

Table 2: 292 Patients with Clinic DBP 90-104
(Pickering et al: JAMA 1988;259:225-28)

How Common Is White Coat Hypertension?

Average awake ambulatory BP:	<134/90	>134/90
Number	60	249
Physician BP	146/96	154/98
Technician BP	128/89	145/98
Ambulatory awake BP	134/84	144/96

Among these patients who had been repeatedly found to be hypertensive when seen in physicians' offices over an average of 6 years, 60 of 292 (21%) were normotensive during the 16 awake hours of the day when ambulatory monitoring was performed as they went about their usual activities.

Ambulatory monitoring will be increasingly utilized, particularly as smaller and less expensive equipment becomes available. In the meantime, home monitoring is feasible for most with inexpensive (@ $50) and reliable semiautomatic devices, e.g. Radio Shack model number 63-661 (Evans et al, 1989).

An increasing body of data consistently document the better predictive value of out-of-the office readings than office readings for future cardiovascular complications (Perloff et al, 1983; Parati et al, 1987).

B. The level pressure wherein therapy is beneficial

The level of pressure considered in need of treatment has fallen progressively since the early 1960s when orally effective antihypertensive therapy became available. Even before there was evidence of benefit, most physicians began treating mild hypertension, defined as DBP = 90-104 mm Hg.

There have now been 9 controlled trials of the treatment of such patients, 7 comparing drug intervention against placebo, 2 comparing more versus less drug therapy. The results of these trials show that treatment provides protection against strokes but statistically insignificant protection against coronary disease (Figure 1).

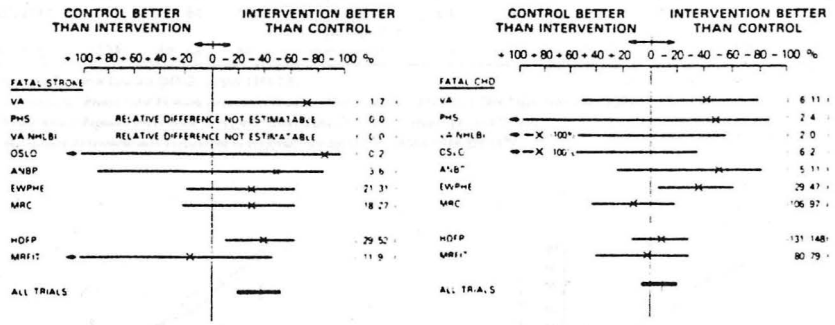


Figure 1: The results of nine clinical trials of the treatment of mild hypertension, portraying the effects of antihypertensive therapy (intervention) versus placebo (control) in the top seven trials and more therapy versus less therapy in the bottom two. The effects are shown for fatalities from strokes (left) and coronary heart disease (right). The X on each line represents the mean difference; the length of the line represents the 95 percent confidience interval. The actual number of events (intervention/control) is given on the right of each line. (MacMahon SW, Cutler JA, Furberg CD, et al: Prog Cardiovasc Dis 1986;29(3 Suppl 1):99-118)

These 9 trials (with the exception of half of the drug-treated patients in the MRC trial) all used a diuretic first, step-care approach and the metabolic derangements frequently accompanying the rather high doses of diuretics have been blamed for the failure to protect against CAD. The only one to show evidence of cardioprotection was the European Working Party on High Blood Pressure in the Elderly (EWPHE) trial, which carefully prevented diuretic-induced hypokalemia (and hypercholesterolemia) by using small doses of diuretic plus the K+-sparer triamterene (Amery et al, 1986).

In view of the problems noted with diuretics, high expectations were held for a better primary cardioprotective effect with beta-blockers since they have been found to provide secondary cardioprotection in post-MI patients.

Four trials (MRC, 1985; IPPPSH, 1985; HAPPHY, 1987; MAPHY, 1988) have been done comparing beta-blocker therapy to non-beta-blocker therapy, in 3 a beta-blocker versus a diuretic (Table 3). In 3 of the 4, no difference was found; in the fourth (MAPHY - which is clouded in controversy), the beta-blocker is claimed to have provided protection (Figures 2 and 3).

Table 3: Characteristics of the Trial Therapies for Hypertension, Including Mortality Rates for the Half of Subjects Receiving Beta-Blockers (BB) and the Half of Subjects Not Receiving Beta-Blockers (non-BB) (Kaplan NM: Am J Hypertens 1988;1:428-30)

					Cumulative mortality rates per 1000 patient years					
					Coronary		Stroke		Total	
Trial	N	Age range	Sex	β-blocker	BB	Non-BB	BB	Non-BB	BB	Non-BB
MRC*	8700	35–64	M, W	propranolol	2.3	2.7	0.7	0.5	5.5	6.0
IPPPSH†	6357	40–64	M, W	oxprenolol	3.2	3.2	0.4	0.6	8.3	8.8
HAPPHY‡	6569	40–64	M	atenolol or metoprolol	4.4	4.1	0.2	0.8	7.7	8.3
MAPHY§	3234	40–64	M	metoprolol	4.5	5.4	0.2	1.1	8.0	10.3

* *Medical Research Council (MRC). Lancet 1985;2:97*

† *International Prospective Primary Prevention Study in Hypertension (IPPPSH). J Clin Hypertens 1985;3:379*

‡ *Heart Attack Primary Prevention in Hypertensives (HAPPHY). J Hypertens 1987;5:561*

§ *Metoprolol Atherosclerosis Prevention in Hypertension (MAPHY). JAMA 1988;259:1976*

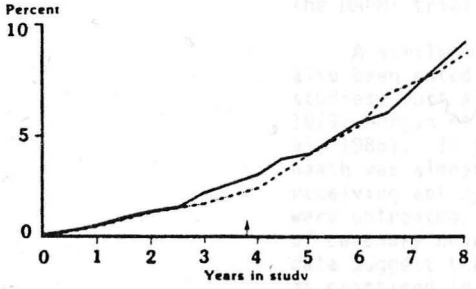


Figure 2: Cumulative total mortality in the HAPPHY trial; the solid line indicates diuretic-treated patients, the broken line indicates beta-blocker-treated patients. (Wilhelmsen et al. J Hypertens 1987;5:561-72)

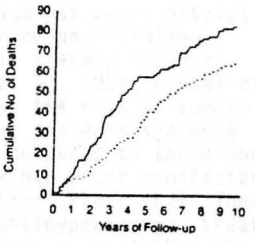


Figure 3: Cumulative total mortality in the MAPHY trial, the solid line indicates diuretic-treated patients, the broken line indicated metoprolol-treated patients. (Wikstrand et al. JAMA 1988;259:1976-82)

The major problems with the MAPHY trial are:

1) The use of 4.2 years, rather than the end of the trial, for calculation of differences
2) The design: the arbitrary separation of half of the patients included in the HAPPHY study
3) The beta-blocker treated half did not have a lower CAD death rate than seen in other trials; rather the diuretic treated half had a higher rate (Table 3)
4) The finding that smokers were better protected by beta-blockers unlike the MRC and IPPPSH trials which found that smokers were less well protected by beta-blockers

Nonetheless, if one uses a beta-blocker to treat hypertension, metoprolol is a perfectly acceptable choice and - if the MAPHY data are valid - it may be the preferable one.

Note that these 4 trials did not include a non-treated group so they do not provide evidence that beta-blocker therapy decreases overall or coronary mortality.

C. An overview of therapeutic trials

As I have written elsewhere (Kaplan, 1990):

"The overall results of these 11 large-scale controlled trials indicate that the treatment of mild to moderate hypertension with either diuretic or beta-blocker based therapy will clearly reduce morbidity and mortality from strokes but not heart attacks. Despite an overall lack of protection against heart attacks, a significant decrease in CHD mortality was observed in the EWPHE trial with diuretic-based therapy compared to a placebo and in the metoprolol treated (MAPHY) half of the HAPPHY trial compared against a diuretic. Since there were no untreated patients in the MAPHY trial, the apparent protection noted in the beta-blocker treated half could simply reflect a higher than expected mortality rate in the diuretic treated half. This possibility receives some support from the markedly higher mortality in diuretic-treated smokers in the MAPHY trial than in the other trials.

A similar lack of protection against heart attacks has also been noted in numerous smaller or uncontrolled studies, most also based on diuretic therapy (Stewart, 1979; Morgan et al, 1984; Calcott et al, 1984; Kannel et al, 1988). In the Framingham study, the risk of sudden death was almost doubled among those patients who were receiving antihypertensive therapy compared to those who were untreated, whether or not they had prior manifestations of coronary heart disease. The authors state that 'These data suggest that some feature of antihypertensive treatment as practiced in the general population my contribute to sudden death incidence' (Kannel et al, 1988)."

D. The unresolved risks of treated hypertension

"Beyond these formidable data documenting a failure to protect against coronary disease, an even more ominous fact emerges from studies involving relatively larger groups of patients who have been treated with antihypertensive medications for prolonged periods: the mortality rate of patients whose pressures have been 'successfully' treated remains higher than seen among untreated people with similar levels of blood pressure.

Perhaps the clearest demonstration of this failure of therapy to reduce risk to that seen in untreated people with similar levels of blood pressure is the experience of the Glasgow Blood Pressure Clinic were 3783 patients were treated between 1968 and 1983, for an average of 6.5 years. The mortality rates for those patients whose diastolic blood pressure was reduced to less than 90 mm Hg were compared to the rates for age and sex - matched populations in two nearby communities, Renfrew and Paisley (Isles et al, 1986) (Figure 4). It is obvious that mortality rates remained higher in the treated groups.

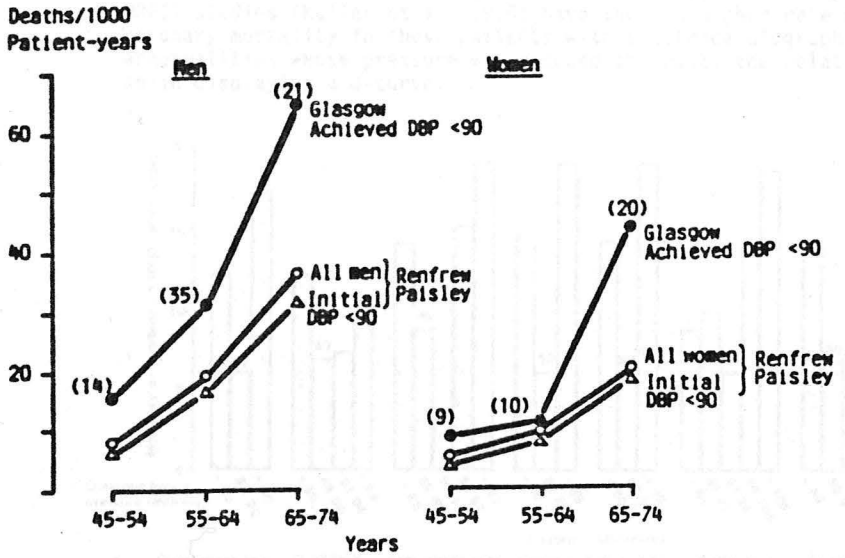


Figure 4: Age- and sex-specific mortality rates (deaths/1000 patient-years) in Glasgow Clinic patients whose diastolic blood pressure (DBPs) were reduced to less than 90 mm Hg by treatment at their last clinic visit, compared with subjects in the Renfrew/Paisley control population. Deaths in the Glasgow Clinic are given in parentheses. (Isles CG, Walker LM, Beevers GD, et al: J Hypertens 1986;4:141-56)

Why are the excess risks associated with elevated blood pressure not removed by prolonged reduction of the pressure to the levels seen in untreated people? A number of possibilities exist."

1) The multifactorial nature of CHD
2) The short duration of treatment
3) The lack of adequate control of the blood pressure
4) Hazards of the drugs used
5) The overtreatment of susceptible patients

This last possibility has recently received some major support. An association between reduction of blood pressure and ischemic injury was first suggested by Stewart (1979) who reported a 5-fold increase in myocardial infarction among patients whose diastolic blood pressure was reduced to below 90 mm Hg. Stewart's report was largely neglected but when Cruickshank et al (1987) reported the same phenomenon, interest immediately focused on the problem and has intensified progressively. As Cruickshank (1988) reported, 6 separate trials have demonstrated a "J-curve" relation between coronary morbidity or mortality and the extent of diastolic blood pressure reduction (Table 4 and Figure 5). In addition to these 6, data from both HDFP (Cooper et al, 1988) and the MRFIT studies (Kuller et al, 1986) have shown a higher rate of coronary mortality in those patients with electrocardiographic abnormalities whose pressure was reduced the most, the relation again displaying a J-curve.

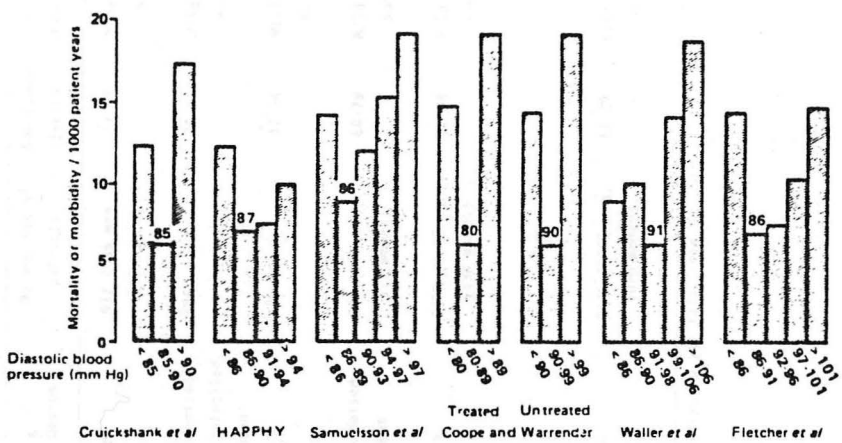


Figure 5: Relation of diastolic blood pressure (phase V) during treatment to mortality or morbidity from coronary heart disease. The six studies included 14 536 patients. Information on Heart Attack Primary Prevention in Hypertension (HAPPHY) is by personal communication (L Wilhelmsen). The numbers within histograms indicate diastolic blood pressure in mm Hg at which *J* point (lowest incidence of myocardial infarction) occurred. (Cruickshank JM: Br Med J 1988;297:1227-30)

Table 4: Details of studies of hypertension that showed a *J* curve relation between diastolic blood pressure and morbidity or mortality, or both, from myocardial infarction

	Design	No and sex of patients	Age range (years)	Degree of hypertension	Treatment	Length of follow up	
Cruickshank et al, 1987	Open	932 (585 men, 347 women)	17-77	Moderate to severe	Atenolol±diuretic± vasodilator±other	Up to 10-2 years (mean 6.1)	J curve only in patients with ischaemia (mortality)
Wilhelmsen et al, 1987	Randomised, controlled, open	6569 men	40-64	Mild to moderate	Atenolol, metoprolol, or diuretic	Mean 3.8 years	
Samuelsson et al, 1987	Open	686 men	47-54	Mild to moderate	β-Blocker± diuretic± vasodilator ±other	12 Years	
Coope and Warrender, 1987	Randomised, open	884 (273 men, 611 women)	60-79	Mild to moderate	Atenolol±diuretic or no treatment	Up to 10 years (mean 4.4)	J curve in both treated and untreated groups (mortality)
Waller et al 1988a	Open	3350 (1660 men, 1690 women)	25-84	Mild to severe	Not stated	Up to 15 years (mean 6.5)	J curve in both men and women with and without ischaemia; independent of treatment with specific drug (mortality)
Fletcher et al 1988	Open	2145 (1075 men, 1070 women)	13-89	Mild to severe	β-Blockers, diuretics, methyldopa, hydralazine, etc	Up to 10.5 years (mean 4.3)	J curve in both men and women (mortality)

(From Cruickshank JM: Br Med J 297:1227, 1988.)

Cruickshank (1988) postulates that the probable mechanism for the increase in coronary ischemia is an inability to maintain coronary blood flow as perfusion pressure falls due to impairment of autoregulation within atherosclerotic vessels, i.e. a fall in coronary flow reserve. As Strandgaard and Haunsø (1987) have demonstrated, the coronary circulation has poor autoregulatory reserve and, since oxygen extraction is nearly maximal at rest, lowering of perfusion pressure can lead to myocardial ischemia. The problem is obviously compounded in the presence of myocardial hypertrophy and high heart rates.

Nocturnal falls in blood pressure may be profound and further accentuated by inadvertent over-treatment. Floras (1988) has suggested that unrecognized nocturnal hypotension may contribute to the increase in coronary ischemia seen with more intensive therapy.

E. Other benefits of therapy

Beyond the effects on the two major end-points, coronary disease and stroke, there have been other benefits shown form effective antihypertensive therapy. These include:

1. Cardiac

   a. Decrease in overall coronary mortality. This has been attributed mainly to 2 changes in life style: dietary, with a resultant fall in population average cholesterol levels, and cessation of cigarette smoking (Goldman and Cook, 1984).

   b. Decrease in deaths from congestive heart failure among hypertensives but an increase in deaths from coronary artery disease. This increase has been attributed to the removal of other causes and the lengthened survival time which allows the development of more coronary disease, which is little affected by control of hypertension.

   c. Regression of left ventricular hypertrophy. In the Framingham population, reversal of LVH has been associated with a 25% reduction in cardiovascular events (Kannel et al, 1988). However, in the MRFIT study, regression of LVH was not accompanied by a decrease in cardiovascular mortality (MacMahon et al, 1989).

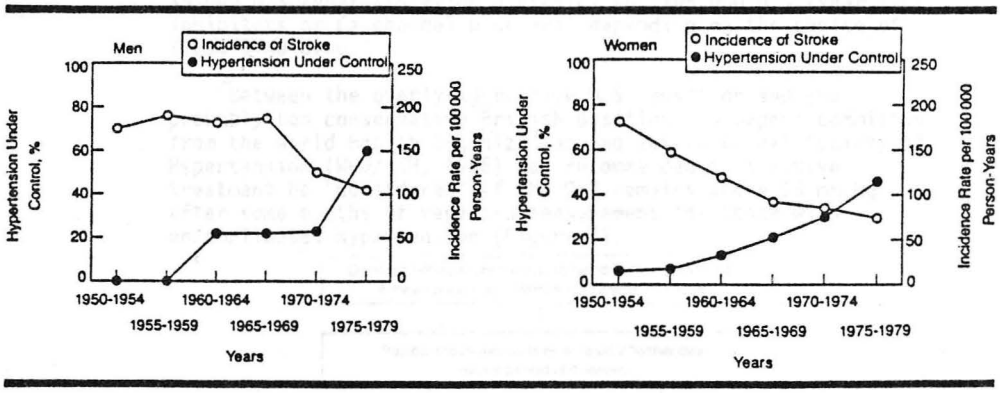
2. Cerebrovascular

   Despite the striking fall in stroke morbidity and mortality in the large clinical trials as shown in Figure 1, the treatment of hypertension has been estimated to be responsible for only about 25% of the reduction in overall stroke mortality seen in the U.S. over the past 20 years (Bonita and Beaglehole, 1989).

The acute treatment of stroke patients has not been favorably influenced by antihypertensive therapy but calcium entry blockers, e.g. nimodipine, may be helpful in overcoming cerebral vasospasm (Gelmers et al, 1988).

Stroke recurrences have not been reduced by expanded antihypertensive therapy in Rochester, Minnesota (Meissner et al, 1988) even though the overall incidence of strokes has fallen in close concert with increased control of hypertension (Garraway and Whisnant, 1989) (Figure 6).

Figure 6: Average annual incidence rates (adjusted for age to 1950 US white population) for stroke in Rochester, Minn, and percentage of persons with hypertension under control (diastolic blood pressure < 95 mm Hg) in various periods. Left, Men. Right, Women. (Garaway WM, Whisnant JP: JAMA 1987;258:214-17)



It has been estimated that about 850 patients with mild hypertension would need to be treated to prevent one stroke per year and it would cost between approximately $200,000 and $1,000,000 U.S. dollars (MRC, 1985) per year to prevent one stroke death (Malcolm et al, 1988).

3. Renal

It has been difficult to demonstrate renal protection except in small numbers of patients with diabetic nephropathy (Dworkin and Benstein, 1989).

4. Large arteries

Improved hemodynamics (Hartford et al, 1988) and partial regression of structural changes within human resistance vessels (Aalkjaer et al, 1989) have been seen after 1 year or more of therapy.

F. The dilemma and the proposed solution

All of the preceding points to a major dilemma as to knowing when to treat the largest part of the hypertensive population, those with fairly mild hypertension. The dilemma has been portrayed by Goran Bergland from Sweden thusly:

"According to the major trials, 300 patients with mild hypertension have to be treated one year to postpone one complication one year. Out of these 300 patients, 10 will develop severe side effects leading to withdrawal of the drug, around 50 will get subjective complaints decreasing their quality of life and 75 will get subjective complaints decreasing their quality of life and 75 will have worsened biochemical risk indicators like decreased serum potassium, increased blood sugar, LDL-cholesterol and uric acid. Thus, 135 out of 300 will have some form of negative effect from the given treatment. The cost of the drugs given to these 300 patients will vary from $5,000 U.S./year (thiazide diuretic) to $105,000 U.S./year (ACE inhibitors or Ca-channel blockers) depending on the choice of first line drug."

Between the overly aggressive U.S. position and the probably too conservative British position, an expert committee from the World Health Organization and International Society of Hypertension (WHO/ISH, 1986) has recommended that active treatment be "considered" if the DBP remains above 95 mm Hg after some months of repeated measurement for those with uncomplicated hypertension (Figure 7).

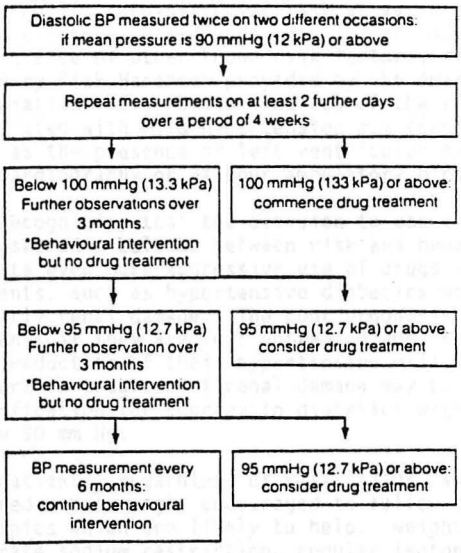


Figure 7: Recommendations for the definition and management of mild hypertension by participants at the Third Mild Hypertension Conference of the World Health Organization and the International Society of Hypertension. (World Health Organization/International Society of Hypertension. J Hypertens 1986;4:383-

Selectivity is advocated for the very sizeable number with DBP between 90 and 95 mm Hg, who make up 40% of the entire population with DBP above 90. Drugs should be provided more quickly to those at high risk, but only after a period of observation plus nondrug therapy for the majority. Hopefully, such selectivity in using drug therapy will protect those in immediate need while at the same time postponing or perhaps removing the need for such therapy in many more patients.

This approach is based upon these premises:

1. All patients should be kept under surveillance. In all the trials for mild hypertension, a certain percentage of patients, varying from 10 to 17%, have had a rapid progression of their blood pressure to levels where therapy is clearly indicated.

2. Those at relatively low risk will likely not suffer from deferral of active drug therapy. This was documented among the placebo-treated half of the patients in the Australian Trial: over 4 years, the average blood pressure fell below 95 mm Hg in 47.5% of those who started between 95 and 109 mm Hg, and excess mortality and morbidity were only increased significantly in those whose average DBP remained above 100 mm Hg.

3. Patients at relatively high risk can be identified. The Framingham data can be used to determine an individual's cardiovascular risk at various levels of blood pressure, based upon age, gender, and the coexistence of other known risk factors, utilizing the Coronary Risk Handbook provided by the American Heart Association. Even better indices of the risks associated with mild hypertension may soon be used, such as the presence of left ventricular hypertrophy by echocardiography or 24-hour ambulatory blood pressures.

4. The recognition that the decision to use drug therapy is based on a balance between risk and benefit may mandate even more aggressive use of drugs in some patients, such as hypertensive diabetics with evidence of early renal damage. The poor prognosis of such patients if they are left untreated and the evidence that reduction of their hypertension will slow the inexorable progress of renal damage may be used as justification for therapy in diabetics with DBP well below 90 mm Hg.

5. All patients, regardless of risk status, should be offered and strongly encouraged to follow those nondrug therapies which are likely to help: weight reduction, moderate sodium restriction, regular isotonic exercise, relief of stress and moderation of alcohol intake.

II. How to Treat

Once having decided to call a person "hypertensive," treatment must surely follow. Hopefully, one or more nondrug therapies will be effective for many with mild hypertension in reducing blood pressure to a level considered safe. If not, more careful use of antihypertensive drugs should lower blood pressure safely and with little or no interference with the quality of life.

A. Nondrug therapies

Overall, the evidence for the value of nondrug therapies continues to mount. Two studies have shown that a simple program of moderate sodium and caloric restriction, with either a bit of alcohol restriction or exercise will retard the reappearance of hypertension in patients who stopped antihypertensive drugs, compared to groups who simply stopped drugs (Langford et al, 1985; Stamler et al, 1988). A similar program worked better than a placebo or a beta-blocker (Kostis et al, 1989) (Table 5).

Table 5: Randomized Placebo Controlled Trial, 3 Months
(86 Men, with DBP = 95-105)
(Kostis et al: JACC 1989;13:104A)

	BP (mmHg)	Exercise tolerance (METS)	Body weight (lbs)	LDL-Chol-esterol	Tri-glyc-ides
Non-pharmacologic Rx	-13/-7	+1.2	-13	-11	-36
Propranolol, 80 bid	- 8/-7	+0	+ 1	+ 5	+11
Placebo	- 4/0	+0.3			

As of now, the following nondrug prescription seems practical for most hypertensives:

1. If body weight is excessive, weight reduction should be the primary goal. This is particular important for those with upper body obesity (Kaplan, 1989). Caution is needed not to use a high carbohydrate, low fat diet which may increase already high plasma insulin levels and thereby antagonize the effects of weight loss on blood pressure and lipids (Parillo et al, 1988).

   Supplemental fasting regimens, e.g. Optifast, using 400-500 calorie/day intake, are very popular, quite effective in getting the weight off, and probably as effective as gastric bypass and other more dangerous techniques in maintaining weight loss (Hovell et al, 1988).

2. Dietary sodium intake should be restricted to 2g/day (88 mmol/day), with caution not to reduce the intake of calcium-rich foods, i.e., lowfat milk and cheese products. The average fall in blood pressure achieved by a 100 mmol/day reduction of daily sodium intake in 11 controlled trials was 5.4/6.5 mm Hg (Staessen et al, 1989). This is comparable to that achieved by a 10 pound weight loss. Two more recent studies each involving over 100 patients have shown that moderate sodium restriction to @ 2g sodium (88 mmol/day) is practical and effective (Weinberger et al, 1988; Australian National Committee, 1989).

3. Dietary potassium intake need not be specifically increased because it will rise when sodium intake is reduced. Nonetheless, dietary potassium restriction will raise blood pressure (Krishna et al, 1989) and supplemental KCl will lower blood pressure in most hypertensives by about the same 5 mm Hg as reduced sodium or weight loss (Siani et al, 1987). We found that replenishing potassium lost through diuretics usually lowered blood pressure (Kaplan et al, 1985).

   A remarkably lower stroke mortality was noted in people who consumed more than 80 mmol/day (Khaw and Barrett-Connor, 1987).

4. Until their antihypertensive efficacy is established, supplemental calcium and magnesium should only be given to those who are deficient.

   a. McCarron and Morris (1985) showed that Ca++ supplements produced about a 5 mm Hg in systolic blood pressure. Subsequently, a number of studies have either confirmed or denied the effect (McCarron, 1989). In all studies, some patient's systolic (but usually not diastolic) blood pressure does fall. They tend to be the ones with lower ionized calcium and higher PTH levels (Lyle et al, 1988). My hypothesis is that these patients, likely because of high dietary sodium intake, have more hypercalcuria which leads to the other features. These, in turn, are ameliorated by additional dietary Ca++ but at a potential risk of kidney stones (Figure 8). For now, I do not believe calcium supplements should be given to lower blood pressure.

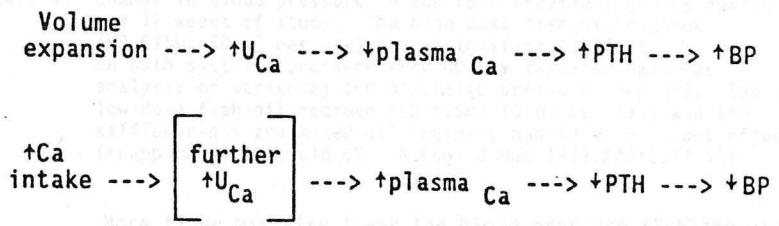


Figure 8: A potential explanation for a hypotensive action of increased dietary calcium intake. The postulated mechanism by which volume expansion leads to hypercalcuria, low plasma Ca++ and high PTH is shown to be ameilorated by increased Ca++ intake. (Kaplan NM: Sem Nephrol 1988;8:176-84)

b. Despite the recent marketing of an oral magnesium preparation (Slow-Mag), the overall impression is that magnesium supplements do not lower blood pressure in most patients, even those on long term diuretic therapy (Henderson et al, 1986). Some may respond and they may be those with high intracellular sodium concentration in whom the Mg++ may activate sodium pumps (Motoyama et al, 1989). The only certain value of Mg++ replacement is to enable concomitant K+ depletion to be replenished.

5. Macronutrients

Vegetarians tend to have lower blood pressure and a vegetarian diet may reduce an elevated blood pressure but what it is in the diet that is responsible is unknown (Sacks and Kass, 1988).

A reduction in total fat along with an increase in polyunsaturated fats may effect a fall in blood pressure (Nissinen et al, 1987). Even better may be a large intake of fish oil (Knapp and FitzGerald, 1989) (Figure 9).

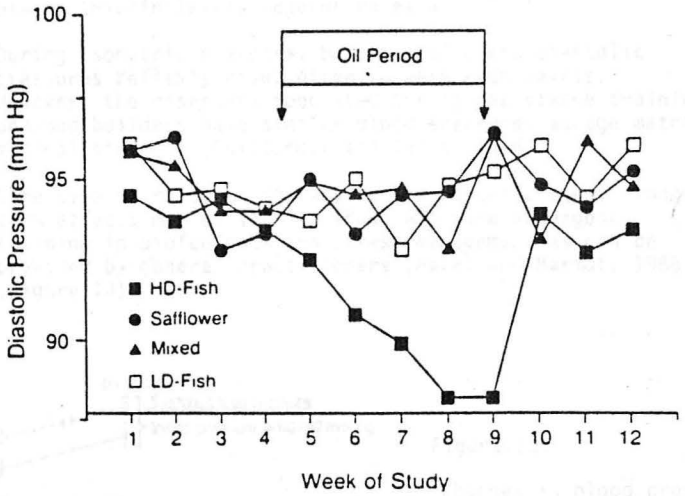


Figure 9: Change in blood pressure in the four treatment groups during the 12 weeks of study. The high-dose fish-oil regimen (HD-FISH; 50 ml per day) had a significant effect on both systolic pressure ($P<0.002$ by repeated-measures analysis of variance) and diastolic pressure ($P<0.02$). The low-dose fish-oil regimen (LD-FISH; 10 ml per day) and the safflower-oil and mixed-oil regimens had no significant effect. (Knapp HR, FitzGerald GA: N Engl J Med 1989;320:1037-43)

More fiber may also lower the blood pressure (Schlamowitz et al, 1987).

6. Caffeine- containing beverages need not be limited unless the patient is highly sensitive to their effects.

7. Smoking should obviously be discouraged, not to lower the blood pressure but to lower the overall risks for heart disease and stroke more than any other possible single action.

8. Alcohol should be limited to no more than 1 ounce (2 usual portions of beer, wine, whiskey) per day. More than that tends to raise the blood pressure (MacMahon, 1987) and reducing average daily intake from 60 to 15 ml will reduce the blood pressure (Usehima et al, 1987). There seems to be lower coronary morbidity and mortality in those who drink one or two portions on average each day. I agree with Dr. Burr (1988) that "A tot a day keeps disease away."

9. Regular isotonic exercise should be encouraged. The incidence of hypertension is lower in those who are physically fit (Blair et al, 1984), regular aerobic exercise will usually lower blood pressure (Duncan et al, 1985) and may favorably influence blood lipid levels, mainly raising HDL-cholesterol (Hespel et al, 1988). These benefits may occur via a reduction in plasma insulin levels (Bjorntorp et al, 1973).

   During isometric exercise, both systolic and diastolic pressures reflexly rise, often to very high levels. However, the rises are modulated during resistance training and bodybuilders have similar blood pressures as age-matched medical students (Colliander and Tesch, 1988).

10. Some type of relation therapy should be encouraged. Long term effects may be seen in those who have undergone training in biofeedback and stress management as can be provided by general practitioners (Patel and Marmot, 1988) (Figure 10).

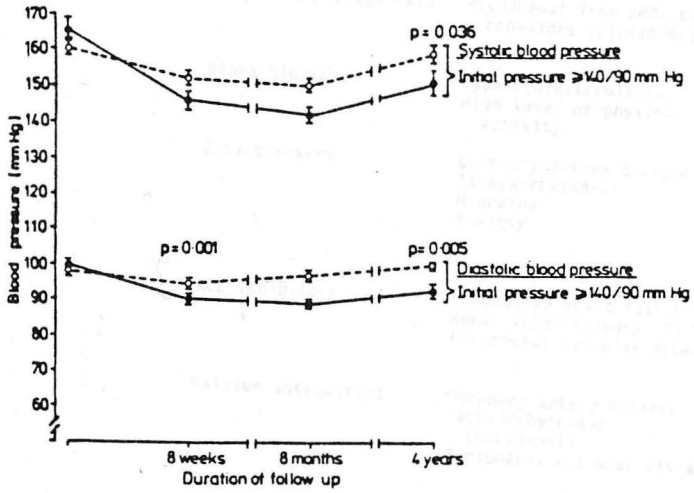


Figure 10:

Changes in blood pressure at each followup in subjects with high blood pressures initially. ●——● = Subjects taught relaxation. o---o = Controls. p values test differences between treatment and control groups in mean changes in blood pressure. (Patel C, Marmot MG, Terry DJ, et al: Br Med J 1985;290:1103-06)

Beyond their potential benefit for lowering the blood pressure of those with hypertension, these nondrug therapies also have an even greater (but unproved) potential for preventing the development of hypertension (Watt, 1989).

B. Drug Therapy

As the number of choices enlarges, the indications for their use also has expanded. There is less use of "diuretic first, step care" and more individualized therapy (Figure 11). The choice of initial drug should be based mostly upon the concomitant conditions that many hypertensive have (Table 6).

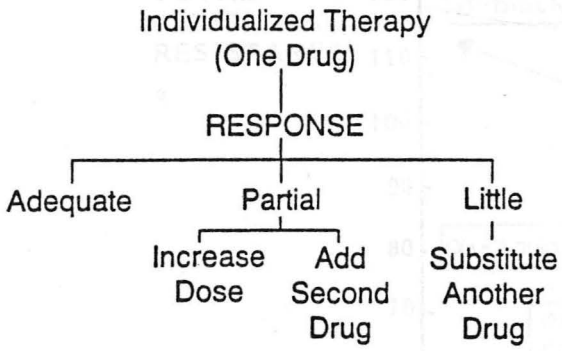


Figure 11: The individualized approach to the therapy of hypertension. The choice of initial therapy is based on multiple clinical features.

Table 6: Concomitant Diseases and the Choice of Antihypertensive Drug Therapy

	Indications	Contraindications
Diuretics	Congestive heart failure Volume retention	Diabetes Gout Hypercholesterolemia
Central alpha-agonists	Withdrawal from addictive behaviors (clonidine) (?)	Liver disease (methyldopa) Automimmune disease (methyldopa) Depression
Alpha-blockers	Hypercholesterolemia High level of physical activity	Postural hypotension
Beta-blockers	Coronary artery disease Tachyarrhythmias Migraine Anxiety	Asthma Diabetes requiring insulin Bradyarrhythmias Congestive heart failure Peripheral vascular disease Hypertriglyceridemia
ACE inhibitors	Congestive heart failure Renal insufficiency (?) Peripheral vascular disease	Renal failure Renovascular hypertension Volume depletion Pregnancy
Calcium antagonists	Coronary artery disease Tachyarrhythmias (verapamil) Peripheral vascular disease	Bradyarrhythmias (verapamil)

In addition, the use of drugs that act primarily as vasodilators seems inherently more attractive than those which act primarily to reduce cardiac output (Figure 12).

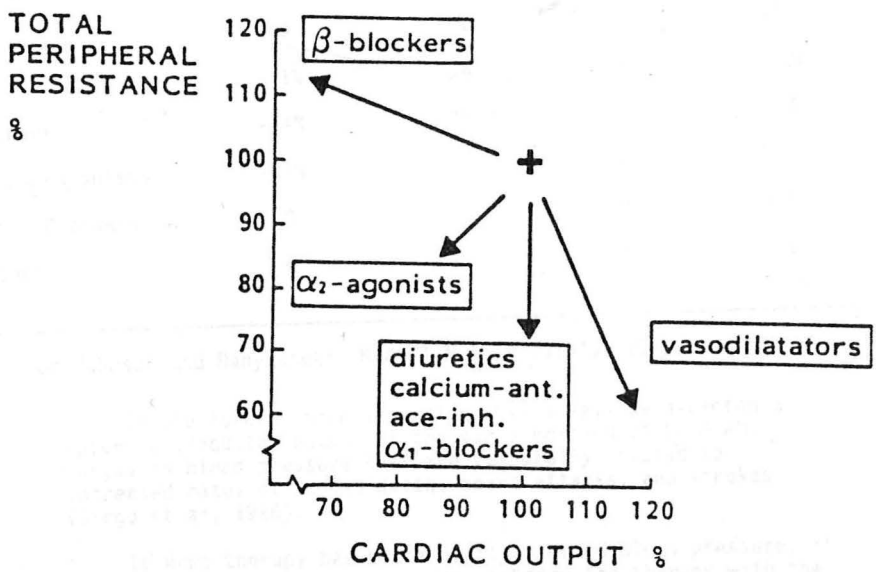


Figure 12: The major action of the 7 classes of antihypertensive agents on peripheral resistance and cardiac output. (Man in't Veld AJ, Van den Meiracker AH, Schalekamp MA: Am J Hypertens 1988;1:91-6)

If diuretics are used, they should be given in even lower doses than most have prescribed. The equivalent of 8 mg of hydrochlorothiazide provided all of the antihypertensive effect of a dose 4 times larger with less hypokalemia, no hyperuricemia and surprisingly, no rise in plasma renin activity (McVeigh et al, 1988).

Care should be taken to monitor blood lipids and anticipate the potential adverse effects of diuretics and non-ISA beta-blockers (Table 7).

Table 7: Calculated Approximations of the Extent of Drug Effect on Plasma Lipids

	Total Cholesterol	LDL Cholesterol	HDL Cholesterol	Triglycerides
Thiazides	+ 7%	+10%	+ 2%	+14%
Beta-blockers				
Propranolol	0	- 3%	-11%	+16%
Atenolol	0	- 2%	- 7%	+15%
Pindolol	- 1%	- 3%	- 2%	+ 7%
$Alpha_1$-Blockers	- 4%	-13%	+ 5%	- 8%
Central $Alpha_2$-agonists	- 7%	-	-	-
Calcium Entry Blockers	0	0	0	0
ACE Inhibitors	0	0	0	0

Modified from Johnson and Danylchuk: Med Cl N Amer 73:449, 1989.

In the future, more attention will likely be directed at ensuring adequate control of the early morning (4 to 8 AM) surges in blood pressure that are temporally related to increased rates of sudden death, heart attacks, and strokes (Sirgo et al, 1988).

If drug therapy has successfully reduced blood pressure, it may be possible to reduce or even withdraw the therapy with the expectation that as many as 30% will remain normotensive for at least one year after withdrawal (Fletcher et al, 1988).

More and more attention is being directed to ensuring that drugs do not cause bothersome side effects or interfere with the quality of life. Sexual dysfunction can be seen with every drug, probably more of a consequence of reduction of blood flow through genital vessels already sclerotic from the ravages of smoking, hypercholesterolemia and diabetes (Bonsal, 1988). This is another reason to go slow so as to allow tissue perfusion to be well maintained.

III. How Far to Lower the Blood Pressure

The exacerbation of sexual dysfunction and the even more serious one of coronary ischemia (Figure 5) by inadvertent reduction of blood pressure below the ability to maintain adequate tissue perfusion has caused a major reconsideration of the goal of therapy.

The issue is portrayed by the 3 models representing the possible relationships between varying levels of blood pressure and the risks of cardiovascular disease (Figure 13).

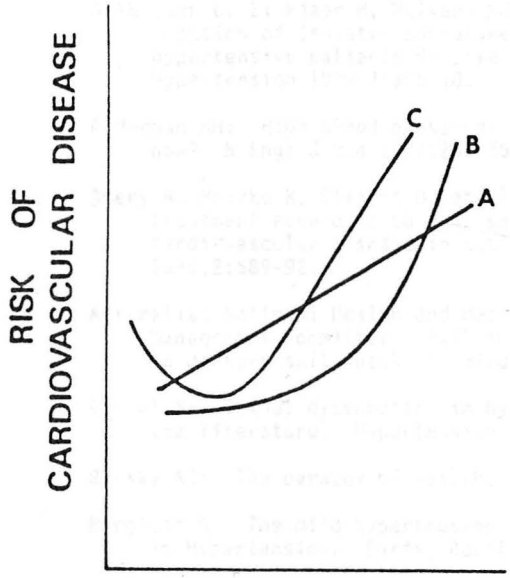


Figure 13: Three models representing hypothetical relationships between levels of blood pressure and risk of cardiovascular disease. (Safar M: Am Heart J 1988;115:702-10)

In the untreated state, "A" probably holds true, although this was seen only for systolic and not diastolic pressure in the Framingham population. With therapy, "B" clearly exists, with little if any additional protection against coronary disease seen in most trials when DBP is reduced below 90 and likely 95 mm Hg. For protection against stroke and perhaps CHF and renal damage, reductions below 90 may prove to be beneficial.

However, as noted earlier, curve "C" has now been noted in multiple trials. The break in the J curve appears to be between 85 and 90 mm Hg, at least among middle-aged and older men who have preexisting coronary disease. So, the bottom line regarding the J-curve is the need for greater caution in lowering the blood pressure of patients with preexisting CHD, with the goal of therapy being a slowly reached diastolic level of 90 and, if no harm has been noted at that level, perhaps down toward but seldom below 85. Such caution is probably advisable for all middle-aged and older hypertensives, considering the virtual ubiquity of coronary atherosclerosis. There is a need to be particularly cautious in treating the elderly with predominant systolic hypertension where the systolic pressure should be lowered probably no more than to 150-160 mm Hg.

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