Newer Approaches to the Therapy of Hypertension

Medicine Grand Rounds

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I. The Current Status of Hypertension Therapy

The treatment of hypertension is being pursued more actively than ever before, more so in the U.S. than in the rest of the world. Hypertension is now the most common medical cause for office visits to physicians in the U.S., the number of visits for hypertension having increased from 19.6 million in 1960 to 55.4 million in 1983 and projected to increase to 111.9 million visits by 1995 (1). When Americans are seen for hypertension, they almost always are given one or more prescriptions for antihypertensive drugs, at a rate significantly higher than for other medical diagnoses (2). Physicians in the U.S. tend to treat patients with lesser degrees of hypertension, often all of those with diastolic blood pressure (DBP) readings above 90 mm Hg (3), compared to the usual practice in England (4) and Canada (5) of withholding drug therapy until the DBP is above 100 mm Hg.

Not only do U.S. physicians treat more patients with more medications than do physicians elsewhere, but their approach seems more stereotyped into the diuretic-first, stepped care regimen as advocated by the 1977 and 1980 Joint National Committee reports (6). Hydrochlorothiazide is the most frequently dispensed drug and the combination of hydrochlorothiazide with triamterene, Dyazide, is the most frequently dispensed brand-name item (7). Elsewhere, other drugs, particularly adrenergic inhibitors, are more frequntly chosen as initial therapy (8).

A. Future Projections

Further growth in the number of patients being treated and sales of drugs is certain:

- the number of hypertensive in the U.S. has been estimated to be as high as 57.7 million, only one-third of whom are being treated (9). (This estimate is likely exaggerated by 15 to 20 million people since it is based on one set of readings.)
- with increased screening of asymptomatic people, more and more people will be identified as hypertensive and put on therapy. (Many will be falsely labelled. Since their subsequent pressures will be in the normal range, the percentage of "controlled" hypertensives will increase disproportionately (10)).
- the risks of even minimally elevated blood pressure continue to be emphasized, with people having DBP between 80 and 89 mm Hg categorized as being at "intermediate risk" (11).
- the "pressure to treat" will be accented by the availability of more and more antihypertensive drugs that are easier to take and more widely advertized. Sales of antihypertensive drugs have grown from $125 million in 1960 (in constant 1983 dollars) to $634 million in 1983 (1).

Is this more aggressive approach and the widespread use of a diuretic-first, stepped care regimen justified? Many think so, particularly because mortality rates from heart disease and strokes have fallen dramatically in the last 15 years (12). Along with overall reductions in plasma cholesterol and the frequency of cigarette smoking, the improved control of more hypertensives has been given credit for these significant falls in mortality.

These dramatic falls should not, however, be automatically assumed to justify "early and aggressive" treatment of all patients with mild hypertension. The risks of hypertension are not equal for all patients and the benefits of reduction of hypertension are not equally shared. In particular, therapy with the diuretic-first stepped care approach may provide less protection from coronary disease than is expected from the reduction in blood pressure that it induces.

I will examine the recently published evidence from therapeutic trials to see if it justifies the current practice of many U.S. physicians in treating most patients with mild hypertension with a diuretic-first, stepped care regimen.

B. Recent Evidence Concerning the Value of Drug Therapy

Trials were begun in the early 1970s to document the benefit of drug therapy for mild hypertension (Table 1). Results of two were published recently (13,14). As shown in Table 1, the trials have uniformly shown protection from stroke by reduction of the blood pressure but protection from heart attacks has not been clearly demonstrated. Numerous reasons may be responsible for this disparity. Stroke may be more directly related to the presence of high blood pressure, whereas coronary disease is caused by multiple factors; it may, therefore, take longer than 5 years and the correction of more than just hypertension to show protection from coronary disease. On the other hand, the therapy used in these trials - a diuretic-first, stepped care regimen - may have produced risks for coronary disease while reducing the risks for stroke and other cardiovascular complications which are more directly related to the high blood pressure. This possibility will be addressed later.

Table 1: MORTALITY RATES PER 1000 PERSON-YEARS

TRIALS	Cerebrovascular Disease			Coronary Heart Disease		
Drugs vs Placebo	No Rx	Rx	Difference	No Rx	Rx	Difference
Australian, 1980	0.9	0.4	-56%	1.6	0.7	-56%
Oslo, 1980	1.0	0	-100%	1.0	2.7	+170%
Elderly, 1985	16.	11.	-32%	24.	15.	-38%
MRC, 1985	0.6	0.4	-33%	2.3	2.5	+9%
More vs Less Drugs	Less	More		Less	More	
HDPF, 1979	1.6	0.9	-41%	5.6	4.5	-20%
MRFIT, 1982						
Normal ECG		not reported		3.4	2.6	-24%
Abnormal ECG		not reported		2.9	4.9	+70%

1. The Medical Research Council Trial (13)

The results of this, the largest of the trials, were summarized thusly (13):

"The main aim of the trial was to determine whether drug treatment of mild hypertension (phase V diastolic pressure 90-109 mm Hg) reduced the rates of stroke, of death due to hypertension, and of coronary events in men and women aged 35-64 years. Subsidiary aims were: to compare the course of blood pressure in two groups, one taking bendrofluazide and one taking propranolol, and to compare the incidence of suspected adverse reactions to these two drugs. The study was single blind and based almost entirely in general practices; 17,354 patients were recruited, and 85,572 patient years of observation have accrued. Patients were randomly allocated at entry to take bendrofluzaide or propranolol or placebo tablets.

"The primary results were as follows. The stroke rate was reduced on active treatment: 60 strokes occurred in the treated group and 109 in the placebo group, giving rates of 1.4 and 2.6 per 1000 patient years of observation respectively ($p<0.01$ on sequential analysis). Treatment made no difference, however, to the overall rates of coronary events: 222 events occurred on active treatment and 234 in the placebo group (5.2 and 5.5 per 1000 patient years respectively). The incidence of all cardiovascular events was reduced on active treatment: 286 events occurred in the treated group and 352 in the placebo group, giving rates of 6.7 and 8.2 per 1000 patient years respectively ($p<0.05$ on sequential analysis). For mortality from all causes treatment made no difference to the rates. There were 248 deaths in the treated group and 253 in the placebo group (rates 5.8 and 5.9 per 1000 patient years respectively).

"Several post hoc analyses of subgroup results were also performed but they require very cautious interpretation. The all cause mortality was reduced in men on active treatment (157 deaths versus 181 in the placebo group; 7.1 and 8.2 per 1000 patient years respectively) but increased in women on active treatment (91 deaths versus 72; 4.4 and 3.5 per 1000 patient years respectively). The difference between the sexes in their response to treatment was significant ($p=0.05$). Comparison of the two active drugs showed that the reduction in stroke rate on bendrofluazide was greater than that on propranolol ($p=0.002$). The stroke rate was reduced in both smokers and non-smokers taking bendrofluazide but only in non-smokers taking propranolol (Figure 1). This difference between the responses to the two drugs was significant ($p=0.03$). The coronary event rate was not reduced by bendrofluazide, whatever the smoking habit, nor was it reduced in smokers taking propranolol, but it was reduced in non-smokers taking propranolol (Figure 2). The rate of all cardiovascular events was not reduced by bendrofluazide, whatever the smoking habit, or in smokers taking propranolol but was reduced in non-smokers taking propranolol. The difference between the two drugs in this respect was significant ($p=0.01$)."

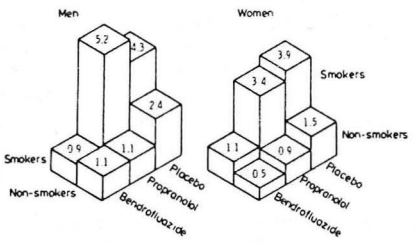

Fig 1: Incidence of stroke per 1000 person years of observation according to randomised treatment regimen and cigarette smoking status at entry to trial. (From Medical Research Council Working Party. MRC trial of treatment of mild hypertension: principi- results. Br Med J 1985;291:97-104.)

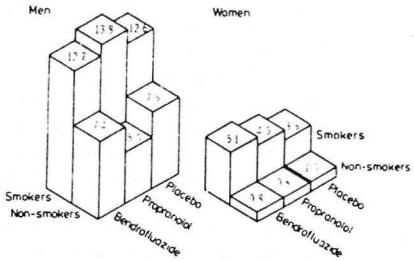

Fig 2: Incidence of coronary events per 1000 person years of observation according to randomised treatment regimen and cigarette smoking status at entry to trial. (From Medical Research Council Working Party. MRC trial of treatment of mild hypertension: principal results. Br Med J 1985;291:97-104.)

In conclusion, the report stated:

"The trial has shown that if 850 mildly hypertensive patients are given active antihypertensive drugs for one year about one stroke will be prevented. This is an important but an infrequent benefit. Its achievement subjected a substantial percentage of the patients to chronic side effects, mostly but not all minor. Treatment did not appear to save lives or substantially alter the overall risk of coronary heart disease. More than 95% of the control patients remained free of any cardiovascular event during the trial.

"Neither of the two drug regimens had any clear overall advantage over the other. The diuretic was perhaps better than the beta-blocker in preventing stroke, but the beta-blocker may have prevented coronary events in non-smokers.

"For all categories of events, and in both treated and placebo groups, rates were lower in non-smokers than in smokers, adding to previous evidence that starting smoking considerably increases the risk of cardiovascular disease. For stroke and also for all cardiovascuar events the difference between rates in smokers and non-smokers was greater than the effect of drug treatment."

2. International Prospective Primary Prevention Study in Hypertension (IPPPSH) (15)

This trial was designed not to compare the effects of therapy against no therapy but rather to compare the specific ability of beta-blocker therapy to control hypertension and reduce coronary and cerebrovascular

events against therapy not including a beta-blocker. 6357 men and women aged 40-64 years were randomly assigned to either a beta-blocker (oxprenolol) or a placebo and followed for 3 to 5 years in a double-blind manner. Supplementary drugs, exluding beta-blockers, were used as necessary in both groups, with the aim of reducing DBP to 95 mm Hg or less. Hypokalemia was carefully avoided by use of potassium sparers and supplements; the initial serum K+ averaged 4.2; the last serum K+ was 4.17 among those on oxprenolol and 4.07 among those not on beta-blocker.

Although beta-blocker therapy was associated with lower blood pressure, earlier ECG normalization, less hypokalemia and fewer withdrawals for uncontrolled hypertension, there were no significant differences in outcome between the two groups. Relative risks were:

- Myocardial infarction = 0.83 (confidence interval 0.59 - 1.16)
- Sudden death = 1.08 (CI 0.68 - 1.72)
- Cerebrovascular accident = 0.97 (CI 0.64 - 1.47)

Lower blood pressures during the trial were associated with substantially lower rates for both cardiac and cerebrovascular events. As in the MRC trial, smoking had a profound influence: smokers had a doubled cardiac event rate; only non-smoking men had a benefit from beta-blocker therapy.

Table 2: Smoking status at entry and critical cardiac events as rates/1000 patient years during double-blind treatment

	Number of critical cardiac events			
	Men		Women	
	BB	Non-BB	BB	Non-BB
Non or ex-smokers	5.4	11.6	4.1	2.1
Smokers	18.1	14.5	6.6	8.0

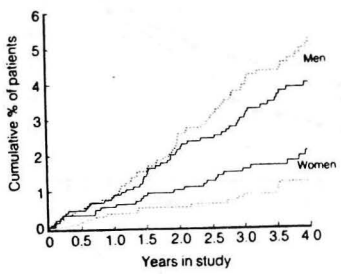

Fig 3: Cumulative percentage of patients with critical cardiac events; ——— = beta-blocker based treatment; ----- = non-beta-blocker based treatment. (From The IPPPSH Collaborative Group. Cardiovascular risk and risk factors in a randomized trial of treatment based on the beta-blocker oxprenolol: the international prospective primary prevention study in hypertension (IPPPSH). J Hypertension 1985;3:379-92.)

3. European High Blood Pressure in the Elderly Trial (14)

This was a double-blind randomized placebo-controlled trial of antihypertensive treatment in patients over the age of 60. Of 840 patients who started, 70% were women, the average age was 72, average blood pressure 183/101. Therapy was either placebo or hydrochlorothiazide + triamterene and, in the 35% whose blood pressure remained high, methyldopa. At year 3, the average blood pressure had fallen 10/7 on placebo, 23/9 on active drugs.

Unfortunately only 35% of the participants remained in the trial. With intention-to-treat analysis, total mortality was insignificantly reduced by -9%, but cardiovascular mortality was significantly reduced by -27%, due to a decrease in both cardiac (-38%) and cerebrovascular (-32%) mortality (Table 3). Deaths from non-cardiovascular causes were more common among the treated half. Despite the decrease in the cardiac mortality rate (including sudden death) (Figure 4), non-fatal myocardial infarction was more frequent in the treated group.

Table 3: Deaths in the Intention-to-Treat Analysis

Causes of death	Placebo group n = 424		Active group n = 416		Percentage change† for active treatment		
	No of patients	Rate*	No of patients	Rate*	Mean	95% confidence limits	p‡
All causes	149	76	135	69	−9	−28 to +15	0·41
Non-cardiovascular non-renal	54	28	61	31	+14	−21 to +64	0·48
All cardiovascular	93	47	67	34	−27	−46 to −1	0·037
Cerebrovascular	31	16	21	11	−32	−61 to +19	0·16
Cardiac	47	24	29	15	−38	−61 to −1	0·036
Other cardiovascular	15	8	17	9	NC	NC	NC
Renal	1	NC	4	2	NC	NC	NC
Unknown	1	NC	3	2	NC	NC	NC

*Rates are the number of patients having an event per 1000 patient years of observation and include all deaths up to July 1, 1984, whether or not the patients were still in the double-blind part of the trial. In 24 patients the life/death status was not known on July 1, 1984, but survival was known to an earlier date. 12 of these persons were in the actively treated group and 12 in the placebo group.

†This mean and the 95% confidence limits were calculated for the actively treated group, placebo rate = 100%.

‡Comparison of both treatment groups with Mantel-Cox statistics from life-table analysis.

NC = not calculated, since the rate in the placebo group was less than 10 per 1000 patient years.

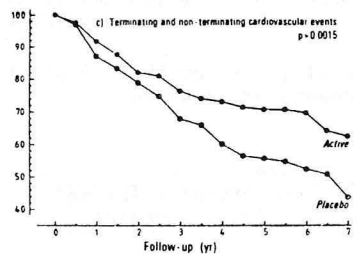

Fig 4: Cumulative percentage of survivors without events calculated for the patients randomised treatment by life-table method. (From Amery A, Brixko P, Clement D, et al. Mortality and morbidity results from the European working party on high blood pressure in the elderly trial. Lancet 1985;1:1349-54.

4. MRFIT-HDFP

Additional analyses have been published of these two massive trials done in the U.S. (16-18). These analyses confirm but still do not explain a major point of controversy: more therapy (and lower blood pressure) was associated with a higher death rate from coronary disease (mainly sudden death) among hypertensive patients who entered the trial with certain abnormalities in the resting ECG.

The most common ECG abnormalities were high R waves and ST-T changes but a higher CAD mortality was seen in those with other abnormalities as well (16). The CAD mortality rate was independent of the baseline level of blood pressure or of the findings on the exercise ECG. Within-group analysis showed an interaction between ECG abnormalities at rest and diuretic treatment, with risk of CAD death for men prescribed diuretics relative to men not prescribed diuretics = 3.34 among those with baseline ECG abnormalities versus 0.95 among men without such abnormalities (16).

The possibility that diuretic-induced hypokalemia could have been responsible looked likely since the average serum potassium fell from 4.36 at baseline to 3.98 at 72 months among those in the SI group, but only from 4.38 to 4.22 among those in the UC group (17). This difference likely reflects the use of lower doses of diuretic in the UC group than in the SI group. However, analyses did not uncover an effect of either diuretic dose or the most recent serum potassium level on CAD mortality in the SI patients (16). Unexpectedly, the use of hydrochlorothiazide was associated with more CAD mortality than the use of chlorthalidone (16).

Unfavorable trends of the same magnitude were found after analyses of the data on patients in the Hypertension Detection and Follow-up Program (HDFP) who were similar to those in the MRFIT trial, i.e. white men not on antihypertensive medication and free of end organ damage at entry (18) (Table 4). Since men with left ventricular hypertrophy have been found to have more ventricular ectopic activity, even in the absence of diuretic therapy, and since hypokalemia is accentuated in the presence of epinephrine, therby lowering the threshold for ventricular fibrillation, Kuller et al conclude: "It is possible that excess CHD mortality among MRFIT special intervention men with ECG abnormalities may have been caused by a combination of increased left ventricular mass in the presence of coronary atherosclerosis, and hypokalemia caused by good compliance with diuretic therapy and accentuated by stress-induced increases in circulating catecholamines."

Table 4: CHD mortality in hypertensive HDFP (white men) and MRFIT patients by presence of ECG abnormalities/1000

	ECG abnormalities			
	Present		Absent	
	Special Intervention (Stepped Care)	Usual Care (Referred Care)	Special Intervention (Stepped Care)	Usual Care (Referred Care)
MRFIT	29.2	17.7	15.8	20.7
(HDFP)	35.1	22.0	10.3	14.8

It appears then that the evidence from the controlled trials that have been completed (and that are likely the last ones ever to be performed) leaves considerable uncertainty about the value of antihypertensive therapy in reducing the risks of premature coronary disease, although the risks of stroke seem clearly to be reduced. As we have written (19):

"We simply cannot be sure that the therapy of mild hypertension, as it has been provided, has not induced a certain level of harm at the same time that it has reduced the risks of an elevated blood pressure. In an analysis of data from England, Bulpitt (20) concluded that treated hypertensive subjects under the age of 50 years still had a fourfold increase in mortality compared with the general population. Similarly, the incidence of coronary heart disease remained higher than that predicted by posttreatment blood pressure levels among a small group of patients treated for 6 years (21). Moreover, among 7610 Japanese men in Hawaii, those who initially received antihypertensive therapy had a higher subsequent 10-year mortality from cardiovascular diseases, including heart attacks and strokes, as compared with untreated men at every level of blood pressure (22). Although the authors of this study assume that this 'apparently paradoxical finding probably reflects more advanced status of hypertension existing before treatment rather than adverse effects of drugs per se,' they add that 'this latter possibility cannot be dismissed.'"

Although some would argue that, regardless of the data from these therapeutic trials, the steady fall in mortality rates from cardiovascular diseases including CAD since 1968 must reflect, at least in part, the benefits of antihypertensive therapy. An analysis of available data suggests that the major reasons for the fall in coronary mortality are the cessation of smoking and the fall in serum cholesterol from dietary changes (23).

We should not overlook the possibility that the improvement in overall and cardiovascular mortality since 1968 could also reflect the greater access to health care provided to the indigent and elderly by Medicare and Medicaid, which were introduced in 1965 (24). Recent cutbacks in such programs have been shown to adversely affect health, specifically the level of blood pressure control (25). Whatever else we do, we should not lose sight of the higher prevalence and severity of hypertension among the indigent and the elderly and of the need to ensure that their access to health care is not curtailed further.

C. Quality of Life

Most patients with mild hypertension are asymptomatic and most, if left untreated, would not suffer an obvious cardiovascular complication or a shortening of life. Therefore increasing attention is being directed to the effects of therapy upon the quality of life. As noted by Brett (26):

"When proposing drug therapy, the physician cannot make an asymptomatic person feel any better, but might make him feel worse, since most drugs have some incidence of adverse effects. But how should side effects be quantitated on a balance sheet of net drug benefit? If a successful antihypertensive drug causes impotence in a patient, how many months or years of potentially increased survival make that side effect acceptable?

There is obviously no dogmatic answer; accordingly, global statements such as 'all patients with asymptomatic mild hypertension should be treated' are inappropriate, even if treatment were clearly shown to lower morbidity or mortality rates."

In none of the trials shown in Table 1 were attempts made to measure the effects of therapy on the quality of life or on functional capacity. But side effects did occur. In the HDFP trial, for example, more than a third of the patients in the Stepped Care group experienced an adverse reaction. In the Medical Research Council of England trial, almost 20% of patients taking either a diuretic or a beta-blocker withdrew from therapy because of side effects. The prevalence of impotence increased from 10% among those receiving a placebo to 13% among those receiving a beta-blocker and to 22% among those receiving a diuretic.

Obviously we need better indices of risk to sharpen our ability to select those patients in need of therapy. Better indices likely are available, including echocardiographic evidence of left ventricular hypertrophy (though it may be too sensitive) and 24 hour ambulatory blood pressure recordings (29).

In summary, the concept that therapy must viewed as a balance between risk and benefit should result in a more cautious, conservative use of drug therapy. However, the same approach may mandate even more aggressive use of drugs in some patients, such as hypertensive diabetics with any evidence of renal damage. The poor prognosis of such patients if left untreated and the evidence that reduction of their hypertension will slow the inexorable progress of renal damage (3) can be taken as justification for therapy in those with diastolic levels well below 90 mm Hg.

II. Update on Non-drug Therapies

Regardless of the decision as to the use of drugs, various non-drug therapies have a place in the management of hypertension (31). A brief update of the evidence for their use follows.

A. Weight Reduction

The evidence for a causal role of obesity in raising the blood pressure and for a beneficial role of weight loss in reducing the blood pressure continues to grow. However, the relationship between obesity and hypertension may not be simple.

1. Association of hypertension with obesity

The association between weight and blood pressure appears to be mainly seen in people with centrally deposited body fat (32). Among a group of 399 obese subjects, those with a greater upper body fat pattern (arms compared to thighs) had higher blood pressures (33). Those with central obesity (apples) also have more diabetes, gout, and atherosclerosis than do those with peripheral obesity (pears), which appears to be related to the higher proportion of intra-abdominal fat in those with central obesity (34).

Another link between obesity and hypertension may be insulin resistance. In a large population in Israel, 83% of hypertensives were either glucose intolerant or obese and, independent of both glucose intolerance and obesity, had significantly higher fasting and post-glucose load insulin levels (35). The authors found higher intracellular sodium concentrations in a small subsample who had abnormal glucose tolerance, obesity, and hypertension. They conclude that insulin resistance is present in most hypertensives and may be "a common pathophysiologic feature of obesity, glucose intolerance, and hypertension." A similar association has been reported among 33 very obese women from Detroit (36).

2. Severity of hypertension in obese people

In three large populations, the severity of the blood pressure and the risks for cardiovascular disease have been found to be less among obese hypertensives than among those with normal weight (37-39) (Figure 5). Thus obese hypertensives may be considered, as a group, less in need of antihypertensive therapy.

However, a more tightly controlled study of over 7500 Japanese-American men aged 45-65 followed for 12 years found no difference in the higher risk for coronary heart disease among hypertensives with various degrees of obesity (39a).

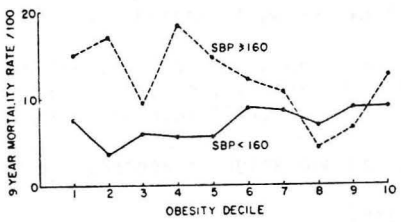

Fig 5: Nine year age-adjusted ischemic heart disease mortality rate by obesity decile and systolic blood pressure (SBP) category. (From Barrett-Connor E, Khaw K-T. Is hypertension more benign when associated with obesity? Circulation 1985;72:53-60.)

3. Effect of weight loss on blood pressure

Nonetheless, weight loss will usually lower the blood pressure and, thereby, minimize further the need for drug therapy. Although, in a randomized trial of weight reduction versus no treatment, an average of 4.1 kg weight loss did not result in a fall in blood pressure, the subjects had only borderline hypertension (135/90) on entry (40). As with all modalities, the degree of blood pressure fall is directly related to the level of pretreatment blood pressure and most studies continue to report a significant fall in blood pressure with weight loss (41,42). The data of MacMahon et al are particularly instructive since they showed that weight reduction not only lowered blood pressure better than did metoprolol but that it favorably altered blood lipids, whereas the beta-blocker worsened them (Figure 6).

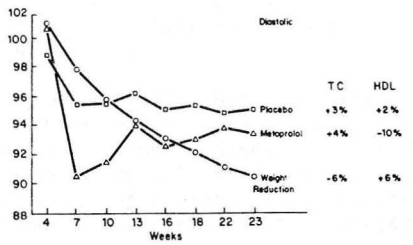

Fig 6: Diastolic blood pressure, total cholesterol, and HDL-cholesterol from weeks 4 to 25 in the three study groups. (From MacMahon SW, MacDonald GJ, Bernstein L, Andrews G, Blacket RB. Comparison of weight reduction with metoprolol in treatment of hypertension in young overweight patients. Lancet 1985;1:1233-6.)

The fall in blood pressure with weight loss may be enhanced (or dependent upon) a decrease in sodium intake. In a study of 18 moderately obese men, the 10 who kept sodium intake unchanged did not have a fall in blood pressure despite a 9.1 kg decrease in weight whereas the 8 who reduced sodium intake by 95 mmol/day had a 4 to 19 mm Hg fall in blood pressure with a similar 9.3 kg weight loss (43). The investigators found a fall in plasma norepinephrine with weight loss and sodium restriction whereas those who kept sodium intake unchanged had no fall in plasma norepinephrine and a heightened pressor response to norepinephrine infusion.

4. Effect of weight loss on cardiac hypertrophy

In the study by MacMahon et al, echocardiography revealed a significant decrease in left ventricular mass in those who lost weight but not in those who took metoprolol (44).

Table 5: Changes in Three Groups After 21 Weeks of Therapy

	Weight Reduction	Metoprolol	Placebo
Weight (kg)	-8.3	+2.5	+0.5
Systolic blood pressure	-14.2	-12.4	-8.9
Diastolic blood pressure	-12.7	-7.5	-4.4
LVMI (g/m^2)	-14.8	-1.3	-1.5

data from: MacMahon SW, Wilcken DEL, Macdonald GJ. The effect of weight reduction on left ventricular mass. N Engl J Med 1986;314:334-9.

Even more impressive reductions in LVH and improvements in left ventricular function were reported in a group of morbidly obese patients after gastric resection resulted in a 56 kg (73%) reduction in body weight (45).

As pointed out by Messerli (46), obesity not only increases preload by expanding intravascular volume but, by inducing hypertension, also increases afterload. This "double burden places a heavy toll on the heart, and patients with obesity and hypertension often have early left ventricular dysfunction, which may herald premature congestive heart failure" (46).

In view of all these benefits, obese hypertensives should obviously be encouraged to lose weight, even if their hypertension is less serious in regards to coronary disease. Better results than previously noted are being reported with more strenuous weight reducing programs such as very low, 330 calorie diets (47), protein-sparing modified fasts (48) and combined behavorial modification (49).

B. Potassium Supplementation

Correction of diuretic-induced hypokalemia may be accompanied by a fall in blood pressure (50). However, in normokalemic hypertensives, additional potassium does not do much to the blood pressure. The addition of 64 mmol of KCl per day for 4 weeks did not lower the blood pressure of a group of hypertensives who were already following a moderately restricted (70 mmol/day) sodium intake (51).

Nonetheless, evidence continues to mount that hypertensives in the population tend to ingest less potassium along with more sodium (52,53). Furthermore, studies in both rats (54) and people, normotensive (55) and hypertensive (56), support a protective role for potassium against various deleterious effects of high sodium intake.

The situation seems clear enough: diuretic-induced hypokalemia should be avoided and corrected for various reasons; normokalemic people, regardless of their blood pressure, should be advised to increase potassium intake, not by potassium supplements but naturally through the diet: replacing processed foods with fresh foods will, with almost no exceptions, increase potassium and reduce sodium intake.

If potassium supplements are needed, particularly in people who have had kidney stones, K citrate may be preferable to KCl (57).

C. Magnesium

A double blind randomized crossover study, the first to be reported, failed to show any effect on the blood pressure of one month's treatment with 15 mmol of magnesium per day (58).

Nonetheless, the infusion of magnesium sulfate in pregnant animals reduced the pressor response to both angiotensin and norepinephrine (59). The widespread use of $MgSO_4$ to prevent convulsions in pregnancy induced hypertension, long advocated by Dr. Pritchard, may then serve as more than just an anticonvulsant. Moreover, 50 mmol of I.V. magnesium given on the day of admission to half of 130 patients with an acute myocardial infarction was associated with a decrease in 4 week mortality from 19% (placebo) to 7% (magnesium), related to a reduction of serious arrhythmias from 47% to 21% (59a).

D. Calcium

Based mainly on the work of Dr. David McCarron (60), the hypothesis that hypertension is associated with dietary calcium deficiency and that calcium supplements can reduce blood pressure is gaining increasing acceptance. The hypothesis lacks a theoretical basis but there are both animal and human data in its support. The data, however, are by no means unequivocal, there are other data which counter the hypothesis (61) and a great deal of more work needs to be done.

In brief, the evidence includes these findings in hypertensive people:

1. Calcium intake, assessed by inexact dietary recalls, appears to be lower than in normotensives (60)

2. Serum total calcium is slightly increased (62) but serum ionized calcium is slightly decreased (63)

3. Serum parathyroid hormone levels are slightly elevated (64)

4. Calcium excretion is increased (65)

5. Calcium supplements (800 to 1000 mg/day) will lower the blood pressure in some hypertensives (66,67)

On the surface, these data lend support to McCarron's hypothesis: lower calcium intake reduces serum ionized calcium, raising serum PTH (which may be serving as a compensatory hypotensive hormone) and increasing urine calcium excretion. However there is no rational reason why a lower calcium intake and ionized calcium level should raise the blood pressure. Increased intracellular calcium is likely involved in the increased vascular tone and reactivity that raise peripheral resistance, the hemodynamic hallmark of primary hypertension. Calcium entry blockers lower blood pressure, calcium infusions raise blood pressure.

A logical explanation for some of these findings is the effect of increased dietary sodium intake and excretion which are known to increase urinary calcium excretion (68). If this is the primary event, a fall in ionized calcium concentration could then lead to elevation of serum PTH.

The data on calcium supplements remains preliminary and inconsistent (Table 6). We and McCarron find that some hypertensives have a pronounced fall in blood pressure when given calcium carbonate or citrate but others have just as pronounced a rise in blood pressure and there is nothing now known that can separate those who respond favorably from those who respond adversely.

Table 6: The Effects of Calcium Supplements on Blood Pressure

Reference	N	Study Design	Calcium Supplement Dose	Calcium Supplement Duration	Blood Pressure Response
Normotensives					
Belizan 1983	30	Parallel with placebo (27)	1g	22 wks	↓ DBP 6-9 %
McCarron 1985	32	Crossover with placebo	1g	8 wks	No change
Sunderrajan 1984 (abst)	7	Crossover with placebo	1g	6 wks	↑ 5/2 mm Hg
Hypertensives					
McCarron 1985	48	Crossover with placebo	1g	8 wks	↓ 4/2 mm Hg (supine)
Resnick 1984 (abst)	15	Open, no placebo	2g	5 mos	↓ DBP 4 mm Hg
Strazzullo 1985 (abst)	15	Crossover with placebo	1g	15 wks	↓ 0.6 Mean BP mm Hg
Singer 1985 (abst)	18	Crossover with placebo	1.6g	4 wks	↓ 4/1 (supine) compared to placebo
Meese 1985 (abst)	26	Crossover with placebo in 2/3	0.8g	8 wks	↓ 2 mm Hg Mean supine BP

For now, I suggest that calcium supplements not be given to treat hypertension and, if calcium is used for osteoporosis, the blood pressure checked to ensure that it does not rise. On the other hand, there seems good reason to encourage higher dietary calcium intake, particularly among thin white women, and there is no need to reduce calcium intake while reducing sodium intake.

E. Alcohol

The bad news is that more than 2 ounces of ethanol per day will raise the blood pressure. The good news is that less than 2 ounces of ethanol per day may lower the blood pressure and will likely protect against coronary disease. (One beer, one 4 ounce glass of wine or one shot of whiskey = one-half ounce of ethanol.)

The evidence for a direct pressor effect of ethanol continues to grow. When given acutely to normal people, alcohol increases systolic blood pressure and heart rate, associated with a rise in plasma catechols and cortisol (69) and renin-angiotensin levels (70). At the same time, it depresses myocardial contractility (71).

When ingested chronically, moderate amounts of ethanol (45 to 70 g/day) will raise the blood pressure in normotensive (72) and hypertensive (73) people. This more persistent pressor action may be related to a reduced vascular reactivity to catechols (74).

When heavy alcohol abusers are detoxified, the high prevalence of hypertension usually falls. This occurs despite a reduction in urinary sodium and water excretion (75).

The larger body of data support a pressor effect of chronic alcohol intake above 2 ounces per day. Less than that either does not raise the blood pressure or may actually lower it (76) (Figure 7).

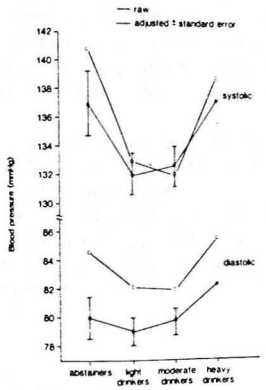

Fig. 7: Mean systolic and diastolic blood pressure (raw and adjusted for potential confounders) by alcohol consumption in men aged 35-64 years in Auckland, New Zealand, 1982. Light drinkers = 1-9 g/day; moderate = 10-34 g/day; heavy = > 34g/day. (From Jackson R, Stewart A, Beaglehole R, Scragg R. Alcohol consumption and blood pressure. Am J Epidemiol 1985;122:1037-44.)

As to the protection against coronary disease, two more sets of data among 1271 older people (77) and 1910 men aged 38 to 55 (78) show lower rates of coronary mortality among those who usually consume some ethanol each day. The mechanism likely involves HDL-cholesterol. Both the levels of HDL-cholesterol fractions 2 and 3 and the levels of the apolipoproteins A-I and A-II which make up most of its protein content have been shown to be increased by moderate (15 to 40 ml) alcohol intake in controlled studies (79-81). Moreover, in baboons chronically given rather large amounts of ethanol, large increases in plasma HDL-cholesterol and in the hepatic removal and excretion of cholesterol were noted, suggesting that alcohol favors mobilization of tissue free cholesterol for excretion (82).

F. Exercise

More solid evidence has been presented for a reduction in blood pressure by regular isotonic exercise. Robert Cade and co-workers showed a fall in mean blood pressure from 117 mm Hg to 97 mm Hg among 105 hypertensives after 3 months of daily walking or running for 2 miles (83). The falls in blood pressure were not correlated with changes in body weight. Further, when 15 of these patients became sedentary for 3 months, the blood pressure rose in 10.

At least 3 more tightly controlled studies have also shown a reduction of blood pressure in the range of 10 mm Hg after regular isotonic exercise for 1 to 3 months (84-86). These falls in blood pressure are accompanied by and probably related to falls in plasma catechols (84), with a reduction in both peripheral resistance and heart rate (86).

Not only does blood pressure tend to fall but total and LDL-cholesterol also tend to fall after regular exercise, even more so if body weight falls (87).

In summary, more evidence has been provided to document the efficacy of various non-drug therapies but the value of some remains in question. Although many are effective over the short time-span of most controlled studies, the issue remains - will they work over the long term in ordinary clinical practice. Little such data are available but long-term trials are in process and preliminary evidence suggests that non-drug therapy may keep the blood pressure down in many patients. The evidence includes:

- 31 patients were recruited from a general medical clinic in Birmingham, England with hypertension that was poorly controlled on drug therapy (88). They were put on a high fiber, low-fat, low-sodium diet and followed for 4 years by their general practitioners. Of the 31, 3 died, 3 moved and 7 were lost to follow-up. The 19 who remained on the dietary regimen had these effects:

	Initial	After 4 years
Blood pressure	161/101	148/87
Weight (Kg)	77	73
Anti-HT Rx (No. tablets)	123	63
Serum cholesterol (mmol/L)	5.74	5.79
HDL-cholesterol (mmol/L)	0.95	1.19

- 189 patients who completed 5 years of successful drug therapy in the Hypertension Detection and Followup Program were randomly assigned to one of 3 regimens - 1) no drug; lower calorie, lower sodium diet plus lower alcohol intake; 2) no drug; no diet; 3) continued drug. The number of patients whose DBP rose to 90 mm Hg or higher over the subsequent 3 years was 53% of group 1 who used non-drug therapy but 84% of group 2 who did not (89)

- 496 of the same type of former HDFP participants were randomly assigned into a control group which continued drug therapy and intervention groups who discontinued drugs and used either sodium restriction or weight reduction. After 56 weeks, the numbers whose DBP remained below 95 mm Hg (and who therefore were not restarted on drugs) was greater in the intervention groups than in the control group (90).

- 103 patients with isolated systolic hypertension (SBP > 160, DBP < 90) were given either diuretics or a low-sodium diet (91). The average SBP fell from 178 to 152 on diuretics and from 174 to 156 on the diet

III. The Choices for Initial Drug Therapy

After even successful use of non-drug therapies, many - probably most - patients with systolic levels above 160 and diastolic levels above 95 should receive antihypertensive drug therapy. The clinician then must face another major decision: which drug to use. The decision is important for two interrelated reasons: first, if that initial drug is successful, as it likely will be, it may be taken for the rest of the patient's life, for as long as 40 years or more; second, the long-term side effects of antihypertensive drugs may not be easily recognized, either because we are not aware of them or because our patients do not call them to our attention. Remember that the cholesterol-raising effect of diuretics was not identified until these drugs were widely used for almost 20 years and the problem would likely not have been identified if hypercholesterolemia was not being independently looked for.

Table 7: Prescriptions for Antihypertensive Drugs, U.S., 1984 and 1985

	1984 (1000s)	1985	% Change	Market Share
Diuretics				
Thiazide	29,226	24,895	-14.8	15.9
K-Sparers	28,522	32,629	+14.4	20.9
Dyazide	21,996	21,803	-0.9	13.9
Total	65,613	64,882	-1.1	41.5
Rauwolfias	1,415	1,256	-11.2	0.8
Central Agonists				
Aldomet	12,460	11,516	-7.5	7.4
Catapres	5,085	5,797	+14.0	3.7
Wytensin	1,076	1,139	+5.9	0.7
Alpha Blocker (Minipress)	6,722	7,156	+6.5	4.6
Beta Blockers				
Inderal	11,329	10,801	-4.6	6.9
Tenormin	7,496	8,511	+13.5	5.4
Lopressor	7,756	7,657	-1.3	4.9
Others	4,947	5,057	+2.7	0.8
Combined α and β-blockers (Labetalol)				
Normodyne and Trandate		1,402		0.5
Vasodilators				
Apresoline	2,394	1,892	-21.0	1.2
Capoten	1,885	3,159	+67.6	2.0

A. Diuretic As First Choice

As noted, diuretics are now chosen by most practitioners as the first drug. The practice rose empirically: diuretics were among the earliest orally-effective drugs made available, they were effective, relatively well-accepted by patients, and capable of sustaining their antihypertensive action indefinitely. Other types of drugs were tried as initial agents but a tendency for fluid retention to blunt their effectiveness was often noted. The increase in plasma volume reflects a tendency by the kidneys of hypertensive patients to retain sodium and water whenever the blood pressure is lowered by non-diuretic agents. Such reactive fluid retention is a natural reaction to the lowering of the blood pressure by the kidneys of hypertensive patients which have their pressure-sodium excretion relationship reset at a higher level. With direct vasodilators, an additional mechanism is involved, the activation of the renin-angiotensin system with secondary increases in aldosterone.

The use of a diuretic as initial therapy therefore seemed logical: up to half of patients could be controlled on it alone and, if another drug were needed, the diuretic was usually required to obtain maximal effectiveness. However, concerns about the routine use of diuretics as the initial choice of therapy have been raised in the past few years.

1. Side Effects of Diuretics

MECHANISMS BY WHICH CHRONIC DIURETIC THERAPY MAY LEAD TO VARIOUS COMPLICATIONS

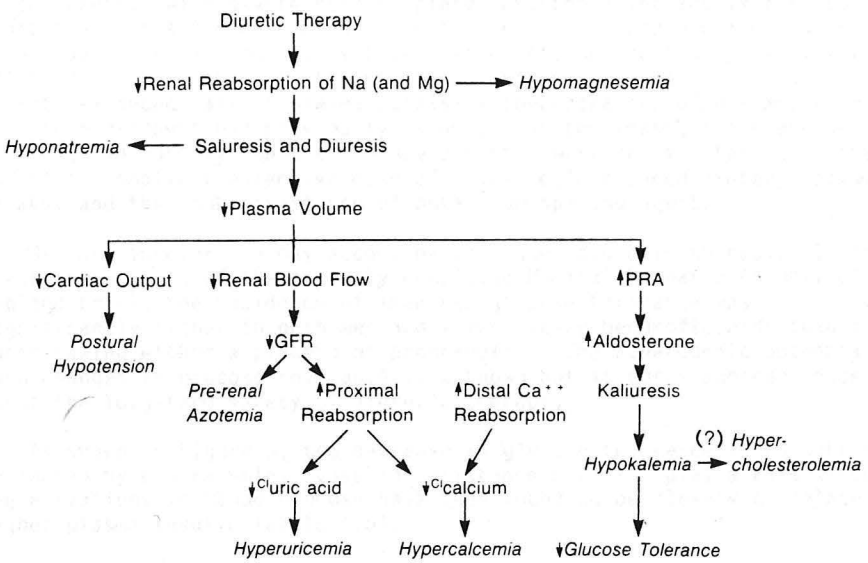

Figure 8: Diuretic Side Effects

Numerous side effects have been known to follow the continuous use of diuretics in the therapy of hypertension (Figure 8). Some, such as postural hypotension, hyponatremia, and pre-renal azotemia, are unusual or of little apparent consequence. Others such as hyperuricemia and hypercalcemia are common but seldom harmful. But others may be a cause of increased risk for cardiovascular complications, reducing or blunting the protection provided by the lowering of the blood pressure. These include hypokalemia, worsening of glucose tolerance, and rises in plasma cholesterol, a complication which is shown in Figure 8 with a question mark as to its mechanism, since its relationship to hypokalemia has not been proved.

Hypokalemia appears in about 30 percent of patients given long-term diuretic therapy (92). The average fall in plasma potassium with sustained use of diuretics is about 0.7 mmol/l. The primary hazard of diuretic-induced hypokalemia is its tendency to increase myocardial irritability, inciting ventricular ectopic activity. This may become clinically apparent only when the myocardium suffers acute ischemia as after an acute myocardial infarction. The higher frequency of ventricular fibrillation after an infarction in those who have diuretic-induced hypokalemia is of concern because coronary artery disease is far and away the most common cause of death among hypertensives. The danger is known to be greater in those who are taking digitalis and in those with left ventricular hypertrophy, a significant portion of hypertensive patients (93).

The hazards of diuretic-induced hypokalemia may only be exposed after acute stress. With severe stress, plasma catecholamine levels rise to concentrations which have been shown themselves to reduce plasma potassium levels by 0.5 to 1.0 mmol/l by accelerating the movement of potassium into cells (94). When added to the effects of stress, the usual diuretic-induced fall in plasma potassium concentration of 0.7 mmol/l may be more hazardous than previously assumed. At the least, these potential risks should justify steps to reduce diuretic wastage of potassium: the use of the smallest effective dose of diuretic, a reduced dietary sodium intake, and the concomitant use of potassium-sparing agents.

Glucose intolerance may accompany prolonged diuretic therapy. In the first three years of the recently completed Medical Research Council of England trial, the incidence of impaired glucose tolerance was significantly higher in both men and women taking bendrofluzaide than in those taking either a placebo or propranolol. The atherogenic potential of such changes in glucose tolerance is unknown but it poses another concern about the long-term safety of diuretic therapy.

As shown in Figure 8, the decrease in glucose tolerance is thought to be caused by hypokalemia. Insulin resistance may also play a role since the elevations in blood glucose have been found to be closely correlated to higher plasma insulin levels (95).

Elevations of plasma cholesterol of 10 to 20 mg/dl usually occur with diuretic therapy and are also correlated to higher plasma-insulin levels (96). The atherogenic potential of a 20 mg/dl rise in plasma cholesterol can be shown by use of the Framingham data of the risks for coronary heart

disease to completely reverse the reduction in risk provided by the 10 to 15 mm Hg fall in systolic blood pressure that might be expected with chronic diuretic therapy.

2. Protection Against Coronary Disease

These three biochemical aberrations may be responsible for a worsening of cardiovascular risk. Separately or collectively they may be involved in the failure to find protection from coronary artery disease in three of the six trials of therapy of hypertension which have been completed, all of which used a diuretic as the first step in treatment (Table 1). Note that in the European Trial in the Elderly wherein hypokalemia was effectively prevented by concomitant use of a potassium sparing agent, protection against coronary disease was equal to that against stroke (14). These data, overall, suggest that diuretics provide less protection from the progression of coronary artery disease than their antihypertensive potency should offer. Since antihypertensive potency of usual doses of a diuretic is comparable to that of moderate doses of a beta-blocker or other adrenergic inhibitors, the biochemical aberrations which accompany the diuretic may reduce or ablate the protection they provide by their reduction in blood pressure.

These concerns about the side effects and potential dangers from diuretics should not detract from their proven antihypertensive potency and the overall protection from cardiovascular diseases they have been shown to provide along with other antihypertensive drugs in patients with DBP above 100 mm Hg. But recall that we are treating more and more patients with less elevated pressures, including a larger portion of those with a diastolic blood pressure in the 90 to 100 range who make up more than half of all hypertensive patients. Such patients are at less risk from their hypertension; therefore they can be provided less protection from a reduction of their blood pressure than patients with higher pressures. Therefore, any additional risk, be it ever so small, from the therapy used to lower their blood pressure must be weighed on a balance with correspondingly less counter-weight. For example, among those with a level of blood pressure high enough to impose a 50 percent excess risk of premature cardiovascular disease, the use of a therapy that removes that excess risk while in itself adding a 10 percent risk can easily be defended as beneficial. But for those with a lower level of blood pressure which in itself increases risk by only 10 percent, the use of such a therapy cannot be defended.

In view of the problems attendant to diuretic use, the use of other drugs which are available and which pose fewer potential risks need to be considered as alternative choices for the initial therapy of hypertension. One point should be re-iterated: there is little to choose between the various available anti-hypertensive drugs as to their efficacy in lowering the blood pressure in the majority of hypertensives. Therefore, the choice of inital drug should be based mainly upon safety and side effects (Table 8). Unfortunately, there is only one controlled study, the MRC trial, which compared two choices, a diuretic and a beta-blocker. Among the patients in the MRC trial, overall mortality was similar with the two drugs, with only non-smoking men showing a lower rate of coronary mortality if they were given a beta-blocker than if they were given a diuretic (13).

Table 8: Characteristics of Non-Diuretic Antihypertensive Drugs for Initial Therapy

	Advantages	Disadvantages
Central Agonists	Little decrease in cardiac output Reduce lipids (guanabenz)	Sedation Dry mouth "Auto-Immune" reactions (Aldomet)
Alpha Blockers	Vasodilate Reduce lipids	Hypotension
Beta Blockers		
Non-ISA	Relieve concomitant problems (angina, migrane, etc.)	Beta$_2$ blockade (bronchospasm, etc.) Vasoconstrict (cold extremities) Reduce cardiac output (fatigue, loss of exercise ability) Raise triglycerides, lower HDL-cholesterol CNS effects: depression, sleep disturbances
ISA	No decrease in cardiac output No alteration of lipids	
Converting Enzyme Inhibitors	Vasodilate No cns effects No decrease in cardiac output	Rare but serious toxicity (renal, neutropenia) Rash Loss of taste
Calcium Antagonists	Vasodilate No cns effects Relieve angina	Variable bothersome but rarely serious side effects

B. Use of Beta-Blockers

If a diuretic is not chosen, the alternative approach recommended by the Third Joint National Committee (97) is to start therapy with a beta-blocker. There are now 7 available in the United States and likely more on the way. These drugs, as a class, offer numerous advantages.

On the other hand, beta-blockers also pose numerous disadvantages. Some, such as bronchospasm, are immediate and obvious and therefore not much of a long-term problem. But, similar to the biochemical changes seen with diuretics, beta-blockers may adversely affect blood lipids (96) and, to a lesser extent, carbohydrate metabolism (98). In multiple studies, rises in triglycerides and falls in cardioprotective HDL-cholesterol levels have been observed. Though this is less of a problem with those beta-blockers having high intrinsic sympathomimetic activity (ISA) (99), lipid levels should be monitored in all patients given any beta-blocker. For various reasons, those with ISA (pindolol and acebutolol) seem to be more attractive than those without.

C. Alpha-Blockers

Unlike the adverse effects on lipids seen with beta-blockers, alpha-blockers appear to be either neutral or beneficial. Though the manner by which they may improve lipid levels - or the manner by which beta-blockers may worsen them - remains unknown, numerous studies with prazosin and preliminary data with other alpha-blockers have shown beneficial effects (100).

Beyond the beneficial effects upon lipids, alpha-blockers lower the blood pressure in a hemodynamically more favorable manner. Whereas much of the antihypertensive effect of beta-blockers resides in their reduction of cardiac output, alpha-blockers primarily reduce peripheral resistance and tend to have little effect on cardiac output (101). This may translate clinically into little beyond a lesser frequency of fatigue and cold extremities but, since the hemodynamic abnormality of established hypertension is an increased peripheral resistance, drugs that lower resistance should provide even more "physiologic" reduction in the blood pressure.

D. Converting Enzyme Inhibitors (CEI)

The first of these, captopril, has recently been approved for use in the treatment of patients with mild hypertension and the second, enalapril, has recently been approved as once a day therapy. With captopril, smaller doses of the drug than used to treat more severe hypertension appear to cause relatively few side effects and less of the more common problems that interfere with the quality of life such as sedation, fatigue and, perhaps, impotence (102). The second of these to be approved, enalapril, may provide all of the advantages with somewhat fewer side effects (103).

Clinical research conducted over the past 15 years by Drs. Norman Hollenberg, Gordon Williams and their colleagues suggests that as many as 40% of all hypertensive patients will be particularly responsive to CEI therapy (104). These patients appear unable to modulate their adrenal or vascular responses to variations in sodium intake, apparently because of high, fixed levels of angiotensin II within the target tissues. These "non-modulators," therefore, are unable to increase aldosterone secretion normally in response to sodium restriction, which, in turn, decreases the degree of sodium retention and fails to dampen the further release of renin. Thereby, more angiotensin II is generated when sodium intake is low, leading to more vasoconstriction and hypertension.

On the other hand, under the more usual circumstance of high sodium intake, these "non-modulators" fail to increase renal blood flow and therefore do not excrete the sodium load as well. Body fluid volume expands and the blood pressure rises.

Beyond the demonstration that half of hypertensive patients with normal to high plasma renin levels are "non-modulators," these investigators have shown that even short-term therapy with CEI corrects the problems within both the adrenals and the renal vasculature. As a result, the majority of such patients have a significant fall in blood pressure with CEI monotherapy.

The results of this research need to be confirmed and extended to a larger population. If it holds up, the data strongly support the use of a CEI to correct an underlying defect that is responsible for hypertension in a considerable portion of the population. The prospect of using such specific therapy, rather than the empirical approaches that lower blood pressure because they happen to alter one or another mechanisms that sustain the blood pressure, is an exciting one. Even if the relationship turns out to be less common or if it is impractical to identify the individual patients who have it, a CEI will likely be increasingly used as initial therapy. When one is used in unselected populations, about half of patients have a significant fall in blood pressure and side effects noted frequently with other antihypertensives are uncommon. Moreover, CEIs may offer a particular advantage in reducing renal vascular resistance by vasodilating the renal circulation, thereby protecting the kidneys more than other vasodilators (105).

E. Calcium Antagonists

This class of drugs lowers the level of free calcium within vascular smooth muscle cells, mainly by blocking its entry from the extracellular fluid. With lower levels of free calcium, vessels relax, lowering tone and vascular resistance, thereby reducing blood pressure.

These drugs may also be acting to correct a fundamental mechanism responsible for hypertension (106). Increased concentrations of free intracellular calcium have been measured within tissues of hypertensive animals and people, perhaps as a consequence of defects in cell membrane transport mechanisms. The use of calcium antagonists may, then, correct the cause for increased vascular tone and resistance.

Whether or not they, too, are specific "corrective" therapies, calcium antagonists are potent antihypertensive agents (106). All three currently available in the United States, diltiazem, nifedipine and verapamil, have been shown to lower blood pressure comparably to other antihypertensive drugs with relatively few side effects. When they are approved for use in hypertension and when longer-lasting formulations become available so that they may be used on a once or twice-a-day basis, they will likely be widely used early in the course of therapy.

F. Central Alpha Agonists and Others

Although alpha-blockers, CEIs and calcium antagonists seem to be likely replacements for the current widespread use of diuretics and beta-blockers, some of the old stand-bys still have a valid place among the available choices.

Reserpine is still an appropriate choice - inexpensive, once-a-day, relatively free of side effects if used in the small doses, 0.05 to 0.25 mg per day, shown to be as effective as larger doses (107). However, it has a bad reputation for causing severe depression and cancer, neither likely true but hard to dispel.

Methyldopa, clonidine and guanabenz share many features as centrally acting alpha-agonists. Clonidine may cause more sedation and dry mouth but neither it nor guanabenz are associated with the multiple "auto-immune" reactions reported with methyldopa (108). Both of these latter drugs may not cause as much fluid retention as other non-diuretic antihypertensive agents. Guanabenz has been found to lower total serum cholesterol levels (109). Clonidine may be used in a transdermal patch with the hope of a smoother antihypertensive effect and lesser side effects (110).

IV. Substitution Versus Stepped Care

The preceding sections described a number of choices which can be made as initial (and often only) therapy for patients with mild hypertension. In addition to using one of them rather than a diuretic, another change in the present common practice of stepped care is likely in the offing - rather than adding a second drug if the first is not enough, stop the first and substitute another as sole therapy.

The approach using substitution rather than addition is based on the premise that some patients respond better to one class of drugs than to another. Despite the generalization made earlier that all of the drugs have comparable anti-hypertensive potency, there are some patients who respond better to one or another. Elderly and blacks seem to respond less well to beta-blockers (111) and, perhaps, CEIs (112) and better to diuretics (113) and calcium antagonists (114). Elderly hypertensives may have an unusual but perhaps more common than previously recognized syndrome of severe concentric cardiac hypertrophy, often presenting with dyspnea suggesting heart failure or chest pain (115). Their excessive left ventricular emptying and reduced diastolic filling are aggravated by vasodilator therapy but improved by beta-blockers or calcium antagonists.

Differences in response may be caused by differences in adherence to therapy with different drugs. If a patient develops such intolerable side effects as to stop therapy, the problem is usually obvious and a second agent would routinely be substituted. However, patients may not volunteer or admit problems with their drugs, rather just not take them. For whatever reason, if a patient does not have the desired effect from the initial drug, a logical next step might be to stop it and try a drug from another category. Thereby, the patient may be more successfully treated with fewer medications.

This approach differs in specifics but not in principle from that advocated for many years by Dr. John Laragh (116). His approach is based upon a renin profile, with a beta-blocker or CEI to be given to those with high or normal renins and a diuretic or calcium antagonist to those with low renin. The problems of renin profiling seem to be so great as to preclude its routine use. Moreover the responses to either a diuretic or a beta-blocker have not been uniformly found to be predicted by the pre-existing plasma renin level (117). The decision as to which drug to choose can be made on the basis of the age and race of the patient.

In the future, the choice may be made on the basis of the potential for reversal of cardiac and arterial smooth muscle hypertrophy. Most, if not all, of the adrenergic inhibitors and both CEIs and calcium antagonists

have been shown experimentally to reverse left ventricular hypertrophy (118). Whether that will be included in the decision to treat and the choice of therapy remains to be seen.

Another issue that likely influences the choice of drug, but which should not be a factor, is cost. Most brand-name tablets cost the patient 30 to 50 cents each. Generic brands are cheaper and likely as effective. Obviously, the use of once-a-day formulations will reduce the cost.

A. Beyond the First Drug

If one drug is well tolerated but is only partially effective, the addition of a second of another class, in keeping with the stepped-care approach, is rational. Half or more of the patients in various trials require a second drug and about 10% require three.

There is little comparative evidence upon which to decide which drugs should be chosen as second or third. The tradition has been to include a diuretic if there are two and to include a direct vasodilator if there are three. Other combinations may work as well. The best study was done on 240 patients whose DBP remained above 95 on a full dose of a diuretic and a beta-blocker (119). Prazosin and hydralazine were best tolerated, whereas minoxidil was most effective. Neither CEI's nor calcium antagonists were included in that study. CEIs or calcium antagonists may increasingly be chosen as the vasodilator rather than the "direct" acting hydralazine or minoxidil (120). Since they do not induce as much reflex sympathetic activity as the direct vasodilators, CEIs or calcium antagonists can likely be used as first, second or third choices, as can the various adrenergic inhibitors.

CONCLUSION

Despite the widespread current use of the diuretic first, stepped-care approach, the extensive broadening of antihypertensive therapy to many millions more who are at relatively low overall risk from mild hypertension should bring about a reassessment of current practice. The use of other alternatives to a diuretic as initial therapy and the substitution of another single agent rather than the sequential addition of drugs should be given careful consideration in order to provide the most benefit at the least risk.

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