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Current hypertension management: separating fact from fiction

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■ In medicine, as in other fields, myths or speculations may be repeated so often and so widely that they are perceived as fact. To some extent, this may have occurred with regard to the treatment of hypertension, especially concerning the use of diuretics and beta blockers and the significance of their metabolic effects. An analysis of the available data indicates that the use of diuretics and, to some extent, beta-adrenergic inhibitors will effectively lower blood pressure and reduce morbidity and mortality. Similar analyses strongly suggest that the metabolic changes induced by these agents may not be of major clinical importance. The widespread dissemination of theories and speculations designed to convince physicians to avoid their use may have been overdone. Scientific facts, not extrapolations of data, should be used to make treatment decisions.

□ INDEX TERMS: HYPERTENSION; DIURETICS; ADRENERGIC BETA RECEPTOR BLOCKADERS □ CLEVE CLIN J MED 1993; 60:27–37

EFFORTS TO IMPROVE control of hypertension and reduce morbidity and mortality require continuous review of available scientific data. Only in this way can we separate fact from speculation and theory.[1]

Clinical trials that evaluate long-term results of therapy on specific endpoints—ie, stroke, coronary artery disease, congestive heart failure, and overall mortality in treated vs control or placebo subjects—must be evaluated carefully for guidance in managing hypertension. Less clearly defined endpoints such as adverse effects of therapy must also be considered.

Unfortunately, in recent years physicians have often been sidetracked from this pursuit by repetitive publications and statements based on either small studies or inappropriate extrapolation of data.[2] This has led to shifts in their approach to treatment that may not have been justified by the available data. Many of these speculations center around diuretics and, to a lesser extent, the beta blockers. It is argued that the metabolic changes that result from the use of these medications may negate their beneficial effects on blood pressure or indeed, in some instances, actually increase the risk of coronary heart disease (CHD).[3] It is important to examine some of these observations and put them in perspective so that the clinician can make decisions based on fact regarding specific treatments.

Most of the available data on the long-term treatment of hypertension have been derived from studies of patients who received diuretics as initial monotherapy: ie, the clinical trials have been diuretic-based.[4–9] These studies have clearly demonstrated that the lowering of blood pressure over time prevents the progression of mild hypertension to more severe hypertension; induces regression of left ventricular hyper-

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trophy (LVH) in a high percentage of patients; decreases the incidence of stroke and stroke deaths; and prevents the development of congestive heart failure.[10] Many of the studies, especially the more recent ones, have also reported a reduction in CHD-related deaths in treated patients vs placebo patients.[4,7,8]

In spite of these results, some investigators argue that benefit might have been greater if agents that produce fewer metabolic effects had been used. Assumptions have been repeated widely and have gained a measure of acceptance in the medical community, the chief assumption being that the clinical trials failed to demonstrate a decrease in CHD-related mortality because of adverse effects of antihypertensive drugs (specifically diuretics and, to some extent, beta blockers). But such speculations ignore available clinical data. A detailed review is in order to determine the validity of these speculations. Many of the conclusions arrived at to support these hypotheses have resulted from the extrapolation of data or post hoc subgroup analyses and a failure to recognize that many of the individual long-term clinical trials were not designed to answer some of the questions in dispute.[11]

This discussion will attempt to shed light on the debate by reviewing the current treatment of hypertension. Hopefully, this will put to rest some of the theories that have emerged.

RATIONALE FOR STEPPED-CARE OR INDIVIDUALIZED CARE

Before discussing the controversies, a brief review of the rationale behind stepped-care is in order.

The stepped-care treatment of hypertension was initiated to provide guidelines for a systematic approach to therapy.[12] The fundamental concept of stepped-care treatment is that, if initial lifestyle changes or a single drug in fairly low doses proves ineffective, a second drug should be added. If blood pressure is reduced to normotensive levels, the initial therapy might be withdrawn at a later date to judge whether or not the second drug alone is effective.[13,14] By using low doses of different classes of antihypertensive drugs, adverse effects of each drug will be minimized.

In 1977, the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC)[12] recommended that diuretics be used as initial monotherapy. This recommendation, based on comparative data, cited the effectiveness of diuretics, their ease of titration, high patient tolerability, relatively low cost, and low incidence of significant subjective side effects. In 1984, JNC III modified the stepped-care approach and included beta-adrenergic blockers as alternative first-step therapy.[15] These agents were suggested as particularly appropriate in patients with angina, rapid heart rates, or wide variations in pulse pressure. In 1988, JNC IV added angiotensin-converting enzyme (ACE) inhibitors and calcium-channel blockers to the list of drugs recommended for possible initial therapy.[16] The 1992 JNC report suggested other agents—ie, alpha-beta- and alpha-1-adrenergic inhibitors—as acceptable alternative initial therapy.

As the availability of alternative therapies increased, the literature began to emphasize the need for so-called "individualized" care, based on a patient's particular needs or conditions, and on the different pharmacologic actions of available agents (in fact, physicians had been individualizing antihypertensive therapy for years).[17] Centrally acting drugs have not been recommended as initial monotherapy because they have not proved as effective as other agents, primarily because of the frequency of side effects.[14] In general, we would agree with these ongoing recommendations.

As new classes of antihypertensive drugs have been introduced, it has become common practice (particularly among authors who espouse these drugs) to attempt to present previous treatment results in an unfavorable light. It should be remembered, however, that the 1977,[12] 1980,[18] and 1984[15] JNC reports advanced a number of reasons for using diuretics as initial monotherapy; and even though several acceptable alternative therapies exist today, the originally cited advantages are still valid.[19] In fact, additional data validate the continued use of these agents as initial therapy in a majority of patients, and the 1992 JNC report suggested the use of diuretics (or beta blockers) as preferred first-step therapy.[20]

STEP 0: LIFESTYLE CHANGES

Unless a patient's blood pressure is very high (170-180/105-110 mm Hg), nonpharmacologic management should be tried before drug therapy.[16] Weight loss, if appropriate, is particularly important. A low-sodium diet, a modified exercise program, moderation of alcohol intake (one to two drinks of whiskey or the equivalent in wine or beer), and the avoidance of tobacco are also indicated. About 20% to 25% of patients with less severe hypertension can be controlled without drug therapy.[13] If lifestyle changes fail to maintain blood pressure at levels below 140/90 mm Hg, antihypertensive drugs should be started.[16,21]

STEP 1: KEY QUESTIONS IN SELECTING INITIAL THERAPY

In recent years, doubts have arisen about the appropriateness of diuretics as first-step therapy in the treatment of hypertension, based on speculations ranging from "Diuretics have done nothing to reduce coronary heart disease mortality" to specific arguments that diuretics induce hypokalemia, which can lead to ventricular arrhythmias and, possibly, sudden death.[22]

The use of thiazide diuretics results in certain metabolic changes: an increase in serum uric acid levels, a decrease in serum potassium, a short-term increase in cholesterol and low-density lipoprotein cholesterol (LDL) levels, and probably a long-term increase in serum triglyceride levels.[23] In addition, thiazide diuretics tend to increase insulin resistance in patients with hypertension who may have pre-existing abnormalities in glucose tolerance and insulin utilization.[24,25] But are these effects of clinical importance? Do they increase cardiovascular risk or minimize or negate the benefits of lowering blood pressure?

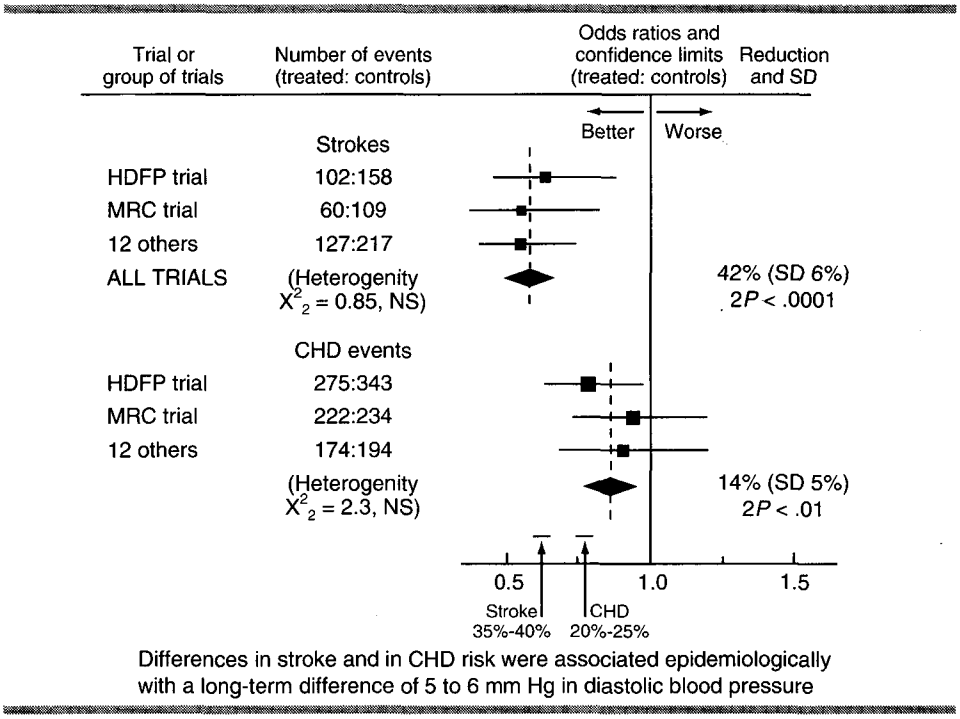

FIGURE 1. Reduction in the odds of stroke and of coronary heart disease (CHD) in the HDFP and MRC trials, and in all 12 other smaller unconfounded randomized trials of antihypertensive therapy (mean diastolic blood pressure difference was 5 to 6 mm Hg for 5 years). SD, standard deviation; NS, not significant. Adapted from reference 25.

A recent meta-analysis[26] and several recently reported studies in the elderly[7,8,27] cast doubt on the contention that initial therapy with diuretics does not reduce the incidence of CHD events in hypertensive individuals. Recent trials present strong evidence of benefit when these medications are used.[28]

Has the use of diuretics decreased CHD events?

Approximately 75,000 patients have been studied in various clinical trials, all of which have used diuretics as initial therapy. Some were placebo-controlled,[5–7] while others compared a rigorously treated group with a less rigorously treated group[4] or with a control group.[29] Several compared a diuretic with a beta blocker as initial therapy.[6,27,30] Beta blockers, alpha-methyldopa, reserpine, and hydralazine were among the agents used as second- or third-step therapy in the diuretic-based trials. Most of these studies were not specifically designed to address the question of whether or not CHD-related mortality was reduced with antihypertensive therapy. Several trials—eg, the Australian[6] and the Medical Research Council[5] (MRC)—included only patients without evidence of target organ involvement or other complications of vascular disease. It could have been predicted that the number of cardiovascular events would be small and that the benefits of treatment would be difficult to prove given the short duration of the studies (3 to 5 years) and the numbers of patients evaluated. For example, in the Australian study, the *placebo* group of patients experienced approximately one third the number of deaths compared with an age- and sex-matched group of the Australian population, making it difficult to demonstrate an even lower mortality in treated subjects. Thus, it is not surprising that many of the *individual* hypertension treatment trials failed to show a statistically significant decrease in CHD events in treated groups compared with control groups.

Speculations were advanced suggesting that it was

TABLE 1
MORTALITY RATE AND DIURETIC DOSE* IN MRFIT†

Diuretic dose	Special-intervention group death rate (Per 1,000 patient-years) Abnormal electrocardiogram
Chlorthalidone	3.31
<50	4.84
>50	1.84
Hydrochlorothiazide	7.61
<50	7.20
>50	8.01

*Lowest mortality with highest dosage of chlorthalidone (with the greatest degree of hypokalemia)
†MRFIT, Multiple Risk Factor Intervention Trial

the medication used rather than the trial design that resulted in these findings; yet a decrease in CHD events was noted in treated groups in trials that included elderly subjects[7–9,31] or subjects with evidence of pretreatment target-organ involvement[4] where the numbers of complications were sufficient to demonstrate differences in outcome.

Observational estimates that a decrease of 5 to 6 mm Hg in diastolic blood pressure over a long period of time would decrease stroke deaths by approximately 35% to 40% were realized in the clinical trials; a 42% decrease was noted in the 3- to 5-year trials, with a decrease in diastolic pressure of this magnitude[26,28,32] (*Figure 1*). On the other hand, epidemiologic or observational data had suggested that a decrease in diastolic pressure of 5 to 6 mm Hg should decrease CHD events by approximately 20% to 25%. The 14 randomized clinical trials analyzed by Peto and Collins[26] prior to the Systolic Hypertension in the Elderly Program (SHEP) trial,[7] the recent MRC trial,[8] and the Swedish Trial in Older Patients with Hypertension (STOP-Hypertension)[27] showed a statistically significant decrease of 14% in CHD events (*Figure 1*). In the latest MRC trial in the elderly,[8] CHD events were reduced by 44%, strokes by 31%, and overall cardiovascular deaths by 29% with low-dose diuretic therapy as compared with placebo. It should be noted that if the SHEP study had been included in the recent meta-analysis, the resultant decrease in CHD events would have been approximately 16%; and if data from the most recent MRC[8] and STOP[27] studies had been included, this percentage would probably be about 17% and closer to epidemiologic estimates.

But to many observers, even these latest data continue to suggest a shortfall in benefit. Logic suggests that the so-called shortfall (if present at all) was probably related to the short duration of the individual trials rather than to any specific adverse effects of medication. Epidemiologic data had assumed a *long-term* (perhaps over decades) decrease of 5 to 6 mm Hg in diastolic blood pressure to achieve a decrease of 20% to 25% in CHD—not a decrease in diastolic pressure for only 3 to 5 years. If it is the short duration of the trials that accounted for the less-than-expected benefits for CHD, one might question why stroke deaths decreased to the predicted level over the 3- to 5-year period of the clinical trials. The slope of increase in stroke events with increases in blood pressures is a steep one (*Figure 2*). A minimal decrease in diastolic pressure will have a major effect on stroke. The slope is less dramatic with CHD events; it may take a longer period of time to decrease CHD deaths with the same reduction in blood pressure. Some credence is given to this assumption by the 8- and 10-year data from the Hypertension Detection and Follow-up Program Cooperative Group (HDFP)[31] and Multiple Risk Factor Intervention Trial Research Group (MRFIT)[33] studies, respectively: CHD events were reduced further in the longer-term follow-up. These new data, however, are not based on careful observations.

Of course, it is also possible that lowering blood pressure will not have a sufficient impact on CHD; other risk factors may have to be addressed. But at present, there are few data to substantiate a negative impact of diuretic therapy on cardiovascular risk. However, several of the diuretic-induced metabolic changes should be specifically addressed.

Hypokalemia: a risk factor for sudden death?

Hypokalemia (serum potassium <3.5 mEq/L) is not uncommon when diuretics are given in high doses (equivalent of 50 to 100 mg of hydrochlorothiazide); itis less common with lower doses of 25 mg/day.[34] The use of a thiazide diuretic along with amiloride, triamterene, or spironolactone will minimize this effect. Importantly, total body potassium is not reduced to a significant extent with thiazide diuretics.

But does hypokalemia increase cardiovascular risk? The answer is probably "No, except in unusual situations." Major impetus for the theory of hypokalemia and increased CHD mortality arose from the MRFIT[35] study in the United States. The controversy centered around a subgroup of patients in a special-intervention group with abnormal resting electrocardiograms (ECGs) who were treated with relatively high doses of diuretics. They experienced a higher mortality rate (mostly sudden death) when compared with a group of usual-care patients *who were also treated with diuretics*,

though presumably with lower doses. It has been suggested that thiazide-induced hypokalemia may have accounted for the poor outcome. However, it is important to realize that this type of subgroup analysis lacks statistical power. We have reviewed the many problems with these data[36] and offer the following four observations:

1) No correlation was found between mortality and the dosages of the diuretics used or the last potassium level obtained prior to death.

2) The *lower* mortality with chlorthalidone compared with hydrochlorothiazide in the special-intervention group with abnormal ECGs is difficult to explain if hypokalemia was a factor (*Table 1*), since chlorthalidone produced a greater degree of hypokalemia than hydrochlorothiazide. The *lowest* mortality was actually noted with *higher* doses (100 mg/day) of chlorthalidone. Interestingly, overall mortality continued to be lower in the chlorthalidone group at the 10.5-year follow-up.

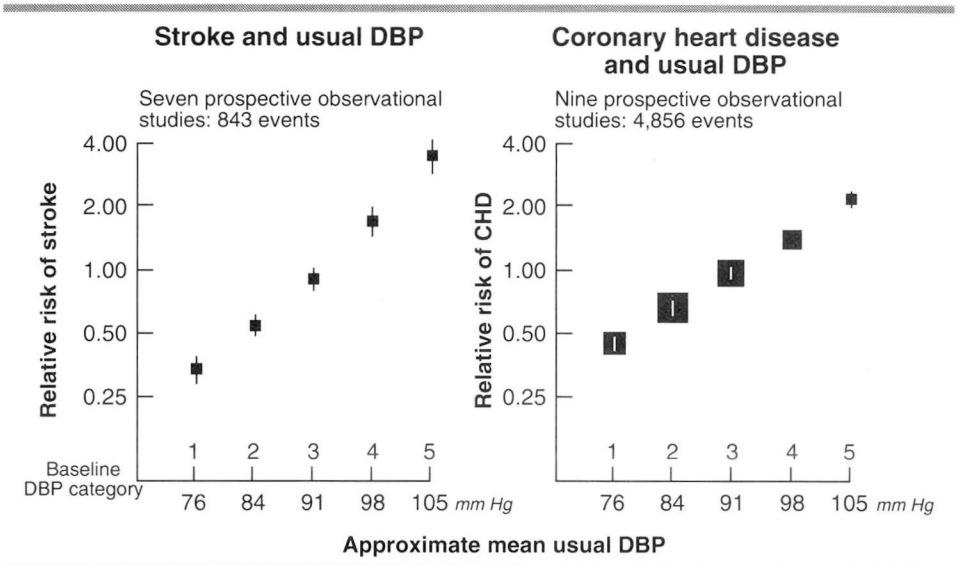

FIGURE 2. Risk of stroke and coronary heart disease (CHD), estimated from combined studies. DBP, diastolic blood pressure. Adapted from reference 31.

TABLE 2
FIVE-YEAR MORTALITY RATES FOR CORONARY HEART DISEASE*

Subgroup	MRFIT deaths Number SI	Number UC	Rate† SI	Rate† UC	HDFP mortality rate per 1,000 SC	RC
Hypertensive patients with normal ECGs	2785	2808	15.8	20.7	33.7	47.3
Hypertensive patients with abnormal ECGs	1233	1185	29.2	17.7	57.9	75.7

*Abbreviations are as follows: MRFIT, Multiple Risk Factor Intervention Trial; HDFP, Hypertension Detection and Follow-up Program; SI, special intervention group; UC, usual care; SC, stepped care; RC, routine care; ECG, electrocardiogram

†Note the unusual findings in the UC MRFIT group where subjects with abnormal ECGs had a better prognosis than subjects with normal ECGs at baseline.

3) Patients in the special-intervention group with *abnormal pretreatment exercise stress tests* (those with probable ischemic heart disease?) *had a lower mortality rate* than those in a similar usual-care subset. This should have been the group with an increased mortality rate if the theory of "an adverse effect from treatment" were valid.

4) Importantly, the hypertensive patients with *abnormal* pretreatment ECGs in the "low-dose" diuretic *(usual-care)* group had a *lower* mortality rate than patients in the same group with normal ECGs (*Table 2*) (17.7 per 1,000, compared with 20.7 per 1,000). This finding is at variance with *all* other studies of hypertensive subjects; a higher mortality rate is universally noted with abnormal ECGs regardless of treatment or lack of it. There has been no explanation for this finding in this subset of patients. HDFP data did not confirm the MRFIT findings (nor did the recent SHEP study).

Although several small studies have suggested a relationship between thiazide-induced hypokalemia and increased ventricular ectopy and possible sudden death, only selected subjects were included in these investigations.[37,38] Several other more carefully performed studies in nonselected patients using 24- and 48-hour Holter monitoring have not confirmed these observations. Quite the contrary[39,40]: No increase in ectopy has been noted in subjects with or without

TABLE 3
EFFECT OF DIURETIC-BASED THERAPY ON SERUM CHOLESTEROL IN LONG-TERM CLINICAL TRIALS*†

Trial‡	Duration (years)	Total cholesterol level (mg/dL)		
		Baseline	Treated	Difference
Berglund & Anderson	6	267	255	−12
MRC trial	3+			
Men				
Active treatment		245	245	0
Placebo		244	239	−5
Women				
Active treatment		261	260	−1
Placebo		260	256	−4
MAPHY study	6	244	243	−1
HDFP	5			
SC group		232	223	−9
Oslo	4			
Active treatment		272	273	+1
Control		278	280	+2
MRFIT	6			
SI group		254	236	−18
UC group		254	240	−14
HAPPHY trial	4	242	242	0
EWPHE study	3			
Active treatment		256	238	−18
Placebo		259	239	−20
MRC in Elderly*	5			
Active treatment		228	232	+4
Placebo		228	232	+4

*Estimated from available data
†All trials used diuretics in doses equivalent to 50 mg or more per day of hydrochlorothiazide
‡Abbreviations for trials are as follows: MRC, Medical Research Council; MAPHY, Metoprolol Atherosclerosis Prevention in Hypertensives; HDFP, Hypertension Detection and Follow-up Program; MRFIT, Multiple Risk Factor Intervention Trial; HAPPHY, Heart Attack Primary Prevention in Hypertensives; EWPHE, European Working Party on High Blood Pressure in the Elderly

LVH, before and after exercise, on high-dose diuretics (100 mg/day of hydrochlorothiazide) and definite hypokalemia.

Recent reviews by Freis,[41] Siegel et al,[40] and McInnes et al[42] conclude that cardiovascular risk is not increased by thiazide-induced hypokalemia. An apparent increase in ectopy in a cohort of subjects treated with high-dose diuretics in the MRC study was not confirmed when pretreatment and posttreatment monitoring was carried out.[5] The hypothesis that diuretic-induced hypokalemia leads to arrhythmias and an increase in sudden death has not been substantiated. If there is a concern about hypokalemia, especially in elderly patients (particularly diabetic patients or those on a low-potassium diet), patients with ischemic heart disease, or patients with congestive heart failure who are receiving digitalis, then a potassium-sparing diuretic can be used with a thiazide diuretic. Potassium-sparing agents should be used with caution in diabetic patients who may be at risk of hyperkalemia because of hyporeninemic hypoaldosteronism. This is a more effective and less costly approach than using a potassium supplement. Hypokalemia is less problematic if smaller doses of a diuretic (equivalent to 25 mg of hydrochlorothiazide) are used.

Diuretics: What are the effects on lipids?

The use of thiazide diuretics over a period of less than 1 year will result in a 5% to 7% increase in serum cholesterol levels, with no significant change in high-density lipoprotein cholesterol (HDL) levels, but with an increase in LDL and triglyceride levels.[43] Many of the studies reported either included only small numbers of subjects or lacked a control group. When looking at cholesterol changes in long-term clinical trials, different findings emerge.[23] Although none of the trials in the 1970s and 1980s was designed specifically to study lipids and lipid fractions, data were collected in large numbers of subjects over a 2- to 5-year period. *Table 3* summarizes the data on cholesterol changes in diuretic-based trials lasting longer than 1 year. None showed a definite increase in cholesterol levels when thiazide diuretics were used. Since beta blockers were used concomitantly in several of the trials, it might have been expected that adverse effects would have been exaggerated rather than minimized. In one 58-week trial,[44] total cholesterol levels increased 5% (LDL levels increased 10%). However, as the author of this trial states, the increase occurred in subjects with initially low levels; in those with baseline cholesterol levels of 240 to 250 mg/dL, no change was noted. This suggests regression to the mean, as noted by other investigators,[45,46]

rather than a specific medication effect.

The HDFP data are of interest. In this study baseline elevated cholesterol levels decreased on thiazide diuretic therapy, while a slight increase in serum cholesterol levels was noted in subjects with low baseline levels[46] (*Figure 3*). This study suggests that thiazide therapy need not be avoided in patients with hyperlipidemia, as suggested by some.[22] In two studies,[5,35] cholesterol levels remained the same or decreased on thiazide therapy, but not to the extent that they had in placebo-treated patients or those treated less vigorously. It was suggested that the degree of lipid lowering (which is noted frequently in any clinical trial) may have been blunted by thiazide therapy. This may have been true in the MRC study where, for example, a difference of 3 mg/dL between placebo and diuretic therapy in women and 5 mg/dL in men was noted. A decrease in serum cholesterol levels following withdrawal of thiazide diuretics has also been reported; the weight gain that accompanies the withdrawal of thiazide therapy suggests that hemodilution may at least partly explain the chemical changes. Extracellular fluid volume remains contracted to a slight degree during long-term diuretic therapy.

In a study reported in 1979,[47] we noted that, while mean serum cholesterol levels did not change significantly in diuretic-treated subjects, in some patients the levels decreased or increased by as much as 20 to 40 mg/dL. Serum lipid levels should be reviewed within 3 to 6 months after thiazide therapy is started to detect (in the few patients who might experience it) an increase of more than 5% to 10% in cholesterol or LDL levels. This should not add to cost of care, since serum levels need only be obtained one to two times a year during therapy.

It is questionable that the minimal long-term effects of thiazide diuretics on serum lipids could explain the alleged shortfall in CHD events in the clinical trials, or that these have a definite adverse effect on outcome in treated patients. The authors of a recent meta-analysis[26] state that their review suggests a 1% increase in cholesterol levels in diuretic-treated subjects. Even if we accept the Lipid Research Council analysis that a 1% increase in cholesterol levels increases CHD-related mortality by 2%,[48] it would not explain an alleged shortfall of 6% to 8%. As noted, the shortfall (which may not even exist if the new studies are included in the analysis) is more easily explained by the short duration of the clinical trials and the type of subjects used therein.

Beta blockers have been found to increase triglyceride levels, and those without intrinsic sympathomimetic activity may also decrease HDL levels. These appear to be long-term effects, although their clinical significance has yet to be determined. Beta blockers may have a distinct advantage over other antihypertensive agents as initial monotherapy in certain patients. They are highly effective in treating angina, and they are the only antihypertensive agents that have consistently been shown to decrease the incidence of recurrent myocardial infarction in patients with ischemic heart disease.[49]

ACE inhibitors and calcium-channel blockers do not adversely effect serum lipid levels.

Other metabolic effects of diuretics that are possibly related to an increase in cardiovascular risk include an elevation of serum uric acid levels. But no solid evidence has been forthcoming that this metabolic change will increase cardiovascular risk or negate the beneficial effects of blood pressure lowering.

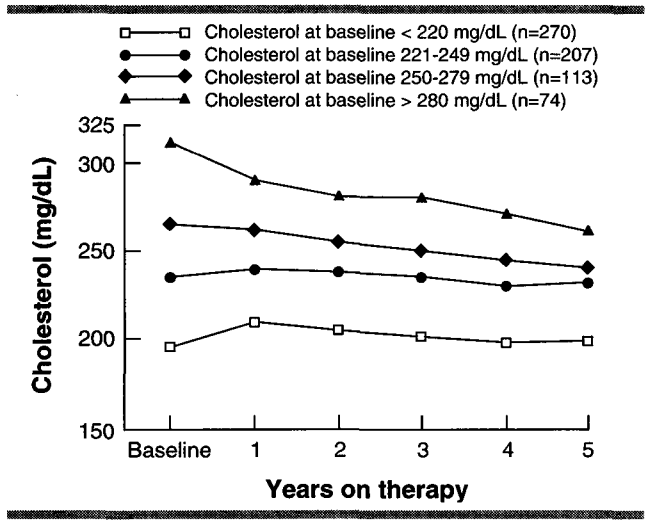

FIGURE 3. Effect of diuretic-based therapy on cholesterol levels in the Hypertension Detection and Follow-up Program study. Adapted from reference 45.

How do diuretics affect insulin resistance and glucose metabolism?

Increased insulin resistance has been identified as an independent risk factor for cardiovascular disease.[50] Thiazide diuretics may have an adverse effect on insulin resistance and may decrease glucose utilization.[24,25] Since many individuals with hypertension demonstrate an increased insulin resistance and abnormal glucose tolerance before any treatment, it has been suggested that the possible effects of diuretics on

TABLE 4
EFFECTS OF HIGH-DOSE DIURETIC THERAPY ON GLUCOSE METABOLISM

Study*	Duration in years	Serum glucose	Hyperglycemia or diabetes
Oslo	5	No difference (diuretics vs placebo)	
EWPHE	3	Increase of 6.6 mg/dL (diuretics vs placebo)	Excess of 6 new cases per 1000 patient years* } diuretics compared with placebo
MRC	3		Excess of 6 new cases per 1000 patient years* } diuretics compared with placebo
HAPPY	4		Excess of 6 new cases per 1000 patient years* } diuretics compared with placebo
HDFP	5		1.6% (57/3,563)
SHEP	1	Difference of 5 mg/dL (diuretics vs placebo)	1 of 483†
MRFIT	6		Excess of 7%‡—Special intervention group (diuretics) vs Excess of 2%‡—Usual care group (no diuretics)

*Abbreviations for trials are as follows: EWPHE, European Working Party on High Blood Pressure in the Elderly; MRC, Medical Research Council; HAPPHY, Heart Attach Primary Prevention in Hypertensives; HDFP, Hypertension Detection and Follow-up Program; SHEP, Systolic Hypertension in the Elderly Program; MRFIT, Multiple Risk Factor Intervention Trial

†Patients were diabetic; diuretics compared with placebo

‡Fasting glucose > 110 mg/dL

glucose metabolism may aggravate these changes and increase cardiovascular risk.

However, clinical trials do not appear to validate this theory (*Table 4*). Changes in preprandial and postprandial serum glucose levels are minimal, and the incidence of hyperglycemia or diabetes is only increased in most of the clinical trials by approximately 0.6%.[51] Since the effect of increased insulin resistance may not manifest itself as clinically detectable diabetes for many years, the clinical trial results may not answer the question about the dangers of thiazides with regard to this specific cardiovascular risk. But most subjects in these trials were age 40 and older and were not newly discovered hypertensive patients; increased insulin resistance was probably present in many of them for at least several years before the trial began. If therapy were to produce an adverse effect over an additional 5 years, more patients should have developed diabetes or significant hyperglycemia. This did not occur, even in studies of elderly subjects (eg, European Working Party on High Blood Pressure in the Elderly,[9] SHEP,[7] STOP,[27] and MRC[8]). In our experience, only a few patients become diabetic or note exacerbation of pre-existing diabetes following diuretic therapy. As in the case of lipids, serum glucose levels should be checked within 3 to 6 months after thiazide therapy is started to detect those few individuals who may experience a change in glucose metabolism. Additional studies are obviously needed to clarify this issue. But at present, there is little solid evidence to justify withholding diuretic therapy in diabetic patients.

How do diuretics affect LVH?

The presence of LVH increases the risk for cardiovascular complications and serious ectopy; this is well established. Some investigators have reported that the use of diuretics does not result in a reduction of left ventricular mass, despite the lowering of blood pressure.[52,53] These findings have been widely quoted. However, other investigators have demonstrated reductions in both left ventricular mass and wall thickness when blood pressure is lowered using sodium restriction, diuretics alone, or diuretics in combination with other drugs.[54,55] A recent 2-year study which compared six different classes of drugs noted that significant regression of LVH had occurred with a diuretic. Beta blockers, calcium-channel blockers, and ACE inhibitors have also been shown to induce regression of LVH. Overall, the ACE inhibitors are probably the most effective. However, any of these agents can be used as initial monotherapy in hypertensive patients with LVH.[56] LVH will probably regress in many patients if blood pressure is lowered to normotensive levels.

STEP II: WHEN MONOTHERAPY IS INEFFECTIVE

If initial monotherapy with any of the recommended step I agents proves ineffective, the dosage of the initial drug can be increased, a different drug can be substituted for the initial drug, or a second drug can be added to the first. While additional blood pressure lowering may be achieved by increasing the dose of one drug, the potential benefits may be outweighed by the

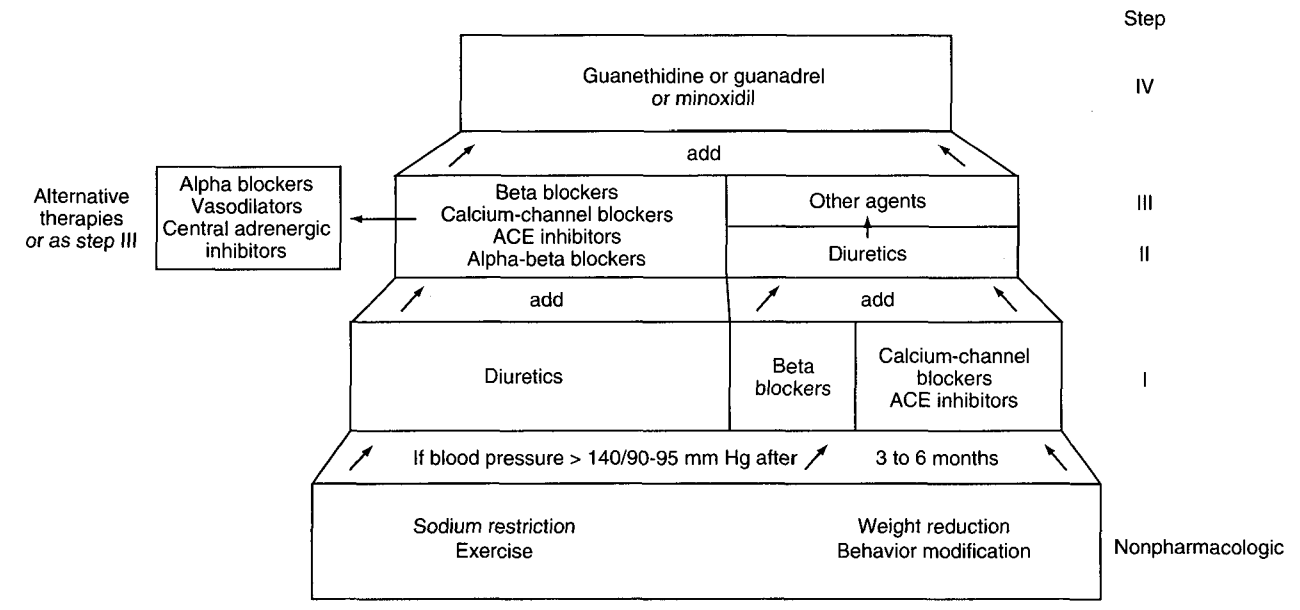

FIGURE 4. Suggested stepped-care approach to the management of hypertension. Step I is to start with a minimum dosage of one of the suggested agents. In step II, a small dose of another agent is added, rather than increasing the initial agent to maximum dose. It should be noted that diuretics are the preferred initial therapy in a majority of patients.[50] The 1992 JNC guidelines suggest the use of diuretics or beta blockers as preferred initial therapy. Alternative initial therapy includes ACE inhibitors, calcium antagonists, alpha-1 blockers, and alpha-beta blockers.

possible increase in side effects or metabolic changes.

Substituting one drug for another until an effective agent is found ("sequential monotherapy") can be a protracted and expensive process. The most reasonable course is to use small doses of two different classes of drugs instead of changing drugs or increasing the first medication to a maximum dosage. This will reduce the blood pressure by different physiologic mechanisms. For example, long-term diuretic use increases the activity of the renin-angiotensin system. If a diuretic proves ineffective, the addition of an ACE inhibitor or beta-adrenergic inhibitor will negate this effect: The combination is often highly effective with few adverse reactions.[57] As noted, if small doses of two drugs produce normotensive blood pressure levels, the first drug can be withdrawn after about 6 to 9 months to determine whether the second drug alone will be effective.[13] About 40% to 50% of patients will respond to step I monotherapy; about 80% to 85% will respond to combination therapy.

If one of the alternative step I drugs (ie, a calcium-channel blocker or an ACE inhibitor) has been used as initial therapy, a diuretic should most probably be added as step II therapy. This is also true if one of the preferred step I drugs is used (ie, a beta blocker). If a diuretic has been the initial therapy, as one group has consistently recommended over the years, a medication from one of the other classes of drugs can be given as step II therapy (*Figure 4*). ACE inhibitors might be chosen preferentially in diabetic patients and especially in subjects with diabetic nephropathy. Although the use of any medication that reduces blood pressure may decrease proteinuria and slow progression of renal disease, the ACE inhibitors may have a specific effect on mesangial changes, in addition to reducing intraglomerular pressure. Calcium blockers and beta blockers or alpha-beta blockers might be selected preferentially in patients with angina, and an alpha blocker might be selected in patients with prostatic hypertrophy.

STEP III: RESISTANT CASES

If combination therapy with two drugs fails to normalize blood pressure, other antihypertensive agents may be considered. An alpha blocker or ACE inhibitor might be added to a diuretic-beta blocker combination, or a calcium antagonist might be added to a diuretic-ACE inhibitor combination. Alpha blockers have been shown to improve serum lipid levels and are

effective when used with diuretics or beta blockers. Centrally acting drugs may also be considered for step III therapy.

SUMMARY AND CONCLUSIONS

As the number of available antihypertensive agents has grown, the options for treatment have increased exponentially; a drug may be used alone or in combination with one or more other drugs. The concept of stepped-care offers a methodical approach to treatment. Within these guidelines, drugs should be chosen on the basis of efficacy, proof of long-term benefit, incidence of adverse effects, and (by no means an unimportant consideration) cost.

Diuretics have been used successfully for many years in the treatment of hypertension, and their usefulness has not diminished as other drugs have become available. Diuretics, and to some extent beta blockers, are the only classes of drugs for which long-term studies have demonstrated a reduction in morbidity and mortality. This has proven true in both young and elderly patients. While it is probable that long-term ACE inhibitor or calcium blocker therapy might yield the same results, there is no proof of this.

The 1992 JNC report noted that six different classes of medications can be used as initial monotherapy: diuretics, beta blockers, calcium-channel blockers, ACE inhibitors, alpha blockers, and alpha-beta blockers. We continue to believe that diuretics should be chosen as initial therapy in the majority of patients, and the 1992 JNC report has recommended them as preferred initial treatment (along with beta blockers). Diuretics should probably be avoided in patients with a history of gout, although in some instances, if it is necessary to use them to normalize blood pressure levels, they can be given with a medication like allopurinol. Beta blockers should be avoided in patients with a history of asthma, chronic obstructive pulmonary disease, peripheral arterial disease, or marked bradycardia. ACE inhibitors are particularly useful in patients with congestive heart failure but should be avoided in pregnant women or in patients with bilateral renal artery disease.

As newer agents become available, they should be evaluated carefully and compared against presently available therapy. Scientific facts should be used in justifying their use in treatment. Exaggerated claims should be carefully critiqued lest we let them influence treatment decisions. The concerns about possible adverse effects of diuretics and beta blockers on cardiovascular risk have been overstated; speculations that have led many physicians to abandon the use of diuretics have not proven to be of clinical relevance in most instances.

There is evidence that the use of thiazide diuretics produces changes in serum lipids, glucose, and potassium, but few data indicate that these are of clinical significance or that they adversely affect cardiovascular risk. The effects on uric acid and potassium appear to be dose-related, but the effects on lipids may not be dose-related.

On the other hand, there is increasing evidence that the use of thiazide diuretics, either as monotherapy or in combination with small doses of other medications, will not only prevent progression of mild hypertension, reduce LVH and the incidence of congestive heart failure, strokes, and stroke-related deaths, but also reduce CHD events. Smaller doses may be less effective in some individuals, but in general they will lower blood pressure without some of the metabolic effects of higher doses.

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