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In Defense of Traditional Antihypertensive Therapy

MARVIN MOSER

IN an editorial in the October 1986 issue of *Hypertension*,¹ Dr. Randall Zusman suggests a new approach to the therapy of patients with mild hypertension that, I believe, ignores many of the aspects of treatment that have proved to be important over the past 15 to 20 years. He speculates that presently accepted initial therapy (i.e., diuretics or β -blockers) may in fact increase cardiovascular risk in patients whose blood pressures have fallen. If, for example, diuretics are used, the increase in uric acid or plasma cholesterol levels, as well as a decrease in serum potassium, may contribute to an increase in the incidence of coronary artery disease, angina pectoris, myocardial infarction, and congestive heart failure. He speculates still further that the use of β -adrenergic blocking agents may increase cardiovascular mortality because of their effects on cholesterol and triglycerides. If one were to accept these speculations, it would be easy to conclude, as suggested, that α -adrenergic receptor blockers, angiotensin converting enzyme inhibitors, or calcium channel blockers should be used as initial or first-step therapy in most patients with hypertension. However, there are few facts to validate these speculations.

First, data from the long-term clinical trials strongly indicate that a clinically significant increase in cholesterol levels in diuretic-based treatment programs does *not* occur in most of the trials (Table 1).²⁻¹⁰ In the Multiple Risk Factor Intervention Trial,⁹ however, where cholesterol levels were actually lower after 3 years of treatment compared with baseline levels in diuretic-treated patients, there was a greater decrease in patients who did not receive diuretics. The design of this study was such that those who did not receive diuretics were probably not hypertensive and, as noted, entered the study with higher cholesterol levels. The effects of a low fat diet in these patients would be expected to be greater than in subjects with lower pretreatment cholesterol levels. It is possible, of course, that diuretics did blunt some of the effects of a low fat diet in this trial. In a recent analysis of all the subjects in the Medical Research

Council trial,¹¹ cholesterol levels rose from 240.9 to 241.3 mg/dl in men in the placebo group at 3 years and from 241.6 to 245.4 mg/dl in men treated with high dose diuretics (equivalent to 100 mg/day of chlorthalidone or hydrochlorothiazide). The difference between groups was 3.4 mg/dl, or about 1.5%; it is difficult to assign clinical relevance to this change. Changes in women were from 257.1 to 259 mg/dl during placebo treatment and from 257.5 to 262.9 mg/dl during diuretics treatment, a difference between treated groups of 3.5 mg/dl. (Table 1 shows reported results in 5473 subjects at 3 years; conclusions are similar.)

Second, there are no data to suggest that adverse effects of diuretics on uric acid metabolism increase cardiovascular risk.

Third, while some studies have suggested that the hypokalemia induced by diuretic use may produce potentially dangerous arrhythmias,¹²⁻¹⁴ numerous other carefully controlled investigations have failed to demonstrate this relationship even in patients with left ventricular hypertrophy.¹⁵⁻¹⁷ It is speculative at best to claim that the use of these agents increases the frequency of sudden death, except perhaps in selected subsets of patients (e.g., patients receiving digitalis).

Fourth, as to whether the use of diuretics may contribute to an increase in myocardial infarctions or congestive heart failure, there are no data on which to base this conclusion. On the contrary, in at least one major trial, a diuretic-based treatment program resulted in a reduction in the incidence of and deaths caused by myocardial infarctions,¹⁸ and in another, a significant decrease in deaths from coronary heart disease was noted in diuretic-treated patients.¹⁹ In most every trial, the incidence of congestive heart failure has been reduced, not increased, in treated patients as compared with placebo or control groups.

There is also little or no evidence that β -adrenergic agents used as initial monotherapy produce a negative effect on coronary disease mortality because of their effect on lipids. There is little question that triglyceride levels are increased and high density lipoprotein levels may be decreased in some patients on long-term β -blocker therapy; yet the benefits of these agents (i.e., lowering of blood

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TABLE 1. *Effect of Diuretic-Based Therapy on Serum Cholesterol*

Reference	Length of trial	No. of subjects	Cholesterol (mg/dl)		
			Control	Treated	Difference
VA Cooperative Study ²	58 wk	167	226	223	-3
Berglund and Andersson ³	6 yr	49	267	255	-12
MRC Trial ^{4*}	3 yr				
Treated					
Men		913	245	245	0
Women		940	261	260	-1
Placebo					
Men		1831	244	239	-5
Women		1789	260	256	-4
VA-NHLBI Cooperative Study ⁵	1 yr				
Treated		302	203	213	+10
Placebo		308	197	197	0
SHEP ⁶	1 yr				
Treated		443	238	238	0
Placebo		408	242	243	+1
Williams et al. ⁷	5 yr				
SC group		716	232	223	-9
Oslo Study ⁸	4 yr				
Treated		26	272	273	+1
Control		33	278	280	+2
MRFIT ⁹	6 yr				
SI group					
Treated nonsmokers		818	246	244	-2
Untreated nonsmokers		293	254	231	-23
SI group					
Treated smokers		549	225	216	-9
Untreated smokers		266	234	219	-15
Wilhelmsen et al. ¹⁰	4 yr	3272	242	242	0

VA = Veterans Administration; MRC = Medical Research Council; NHLBI = National Heart, Lung, and Blood Institute; SHEP = Systolic Hypertension in the Elderly Program; SC = stepped care; MRFIT = Multiple Risk Factor Intervention Trial; SI = special intervention.

*Initial report: 5473 subjects.

pressure, reduction of cardiac work or arrhythmias) appear to outweigh the risks.²⁰ Secondary prevention of myocardial infarction has been demonstrated repeatedly,²¹ and benefits in the management of angina are well documented. Several studies have failed to demonstrate an advantage of β -blockers over diuretics in the management of hypertension vis-à-vis reduction of deaths caused by coronary heart disease,^{4, 10, 22} but a recent study (MAPHY)²³ suggests that this may be true.

Dr. Zusman suggests that drugs (i.e., diuretics and β -blockers) recommended for initial treatment carry with them "... unacceptable adverse metabolic and physiologic side effects . . ." and that these variables may have canceled out the benefits being derived from reductions in blood pressure. Yet all of the major clinical studies that were based on diuretic or β -blocker therapy, including the Medical Research Council⁴ and the Australian studies,²⁴ demonstrated that stroke deaths and overall cardiovascular events were reduced by therapy. As noted, two other trials, the Hypertension Detection and Follow-up Program¹⁸ and the European Working Party Study,¹⁹ also demonstrated a significant decrease in deaths caused by coronary heart disease. It is quite possible that the

failure of the Australian and Medical Research Council trials to demonstrate a statistically significant decrease in coronary deaths in treated subjects is related to the type of study population, the duration of the studies, and the statistical problems relating to subset analyses, rather than to adverse effects of the drugs. For example, in the Australian Study the placebo group experienced one third of the expected mortality of an age and sex-matched group of Australians.²⁴ It would have been difficult to demonstrate a statistically significant decrease in coronary mortality in the treated patients when the placebo group had such a low mortality. (The actual decrease in ischemic heart disease events was -6 and -11%, respectively, in the Medical Research Council and Australian studies,^{11, 24} but results failed to achieve significance.) It is a giant leap forward to conclude that adverse effects of β -blockers or diuretics produce an increase in deaths caused by coronary heart disease. The leap is not justified by the facts.

The suggestion to initiate therapy with an α -adrenergic receptor blocker, an angiotensin converting inhibitor, or a calcium channel blocker ignores the fact that there are no long-term data (3-5 years) on adherence rates, efficacy, or outcome with these

agents. The cost factor is completely ignored. It is possible to treat a patient with a β -adrenergic inhibitor, a diuretic, or a combination of these medications as first-step therapy for as little as \$5 to \$15/month; the use of any of the agents suggested, especially a calcium entry blocker or a converting enzyme inhibitor, might cost the patient \$40 to \$60/month. Recent data have demonstrated that, for the first time, cost has become a major factor in determining long-term adherence to therapy.²⁵ Long-term benefits of hypertension treatment will only be achieved if patients remain in treatment and continue to follow a prescribed regimen. I believe that if Dr. Zusman's recommendations are followed, adherence and, perhaps, long-term outcome may actually decrease. This assumption, of course, remains to be demonstrated.

None of the α -blockers, calcium entry blockers, or converting enzyme inhibitors have been shown to be more efficacious than diuretics or β -blockers; titration to an effective dosage is often more difficult, and subjective side effects, especially with an α -blocking agent or some of the calcium blockers, may be more troublesome than those experienced with a diuretic or a β -blocker.

We should continue to make treatment decisions based on long-term experience and not on speculations or theories. Dr. Zusman is correct in questioning whether or not a change to this new approach to treatment would be associated with a greater reduction in cardiovascular mortality than has been observed with traditional methods of therapy. The question remains unanswered, however, and until we have better data (studies are underway to obtain these), we should not discard a system of treatment that has proved to be relatively simple, relatively inexpensive, and effective, with a good adherence rate. We should not let our disappointment with the lack of uniformly excellent treatment results lead us to speculate and theorize to the point of drastically changing our approach to management. The newer agents—the angiotensin converting enzyme inhibitors and calcium blockers—are welcome and useful additions to our therapeutic armamentarium and can be used appropriately as initial therapy for mild to moderately severe hypertension in special treatment groups (e.g., patients with vascular disease, angina, recurrent gout, asthma). I do not believe, however, that sufficient data are available to advocate the use of these agents as initial therapy in the majority of hypertensive patients.

References

- Zusman RM. Alternatives to traditional antihypertensive therapy [Editorial]. *Hypertension* 1986;8:837-842
- Veterans Administration Cooperative Study Group on Anti-hypertensive Agents. Effects of treatment on morbidity in hypertension: II. Results in patients with diastolic blood pressure averaging 90 through 114 mm Hg. *JAMA* 1970;213:1143-1152
- Berglund G, Andersson O. Beta blockers or diuretics in hypertension? A six-year follow-up blood pressure and metabolic side effects. *Lancet* 1981;1:744-777
- Medical Research Council Working Party. MRC trial of treatment of mild hypertension: principal results. *Br Med J* 1985;291:97-104
- Veterans Administration-National Heart, Lung, and Blood Institute Cooperative Study on Antihypertensive Therapy. Mild hypertension: serum lipoprotein levels during chlorthalidone therapy. *JAMA* 1980;244:1691-1695
- Systolic Hypertension in the Elderly Program. Antihypertensive efficacy of chlorthalidone. *Am J Cardiol* 1985;56:913-920
- Williams WR, Schneider K, Borhani NO, et al. The relationship between diuretics and serum cholesterol in Hypertension Detection and Follow-up Program participants. *Am J Prev Med* 1986;2:248-255
- The Oslo Study. Treatment of mild hypertension: a five-year controlled drug trial. *Am J Med* 1980;69:725-732
- Multiple Risk Factor Intervention Trial: risk factor changes and mortality results. *JAMA* 1982;248:1465-1477
- Wilhelmsen L, Berglund G, Elmfeldt D, et al. Beta-blockers versus diuretics in hypertensive men: main results from the HAPPY trial. *J Hypertens* 1987;5:561-572
- Miall W, Greenberg G. Mild hypertension: is there pressure to treat? An account of the MRC trial. New York: Cambridge University Press, 1987
- Holland OB, Nixon JV, Kuhnert I. Diuretic-induced ventricular ectopic activity. *Am J Med* 1981;70:762-768
- Hollifield JW, Slaton PE. Thiazide diuretics, hypokalemia and cardiac arrhythmias. *Acta Med Scand [Suppl]* 1981;647:67-73
- Caralis P, Perez-Stable E, Materson B. Ventricular ectopy and diuretic-induced hypokalemia in hypertensive patients [Abstract]. *Clin Res* 1981;29:832A
- Madias JR, Madias NE, Gavras HP. Nonarrhythmogenicity of diuretic-induced hypokalemia: its evidence in patients with uncomplicated hypertension. *Arch Int Med* 1984;144:2171-2176
- Papademetriou V, Fletcher R, Khatri IM, et al. Diuretic-induced hypokalemia in uncomplicated systemic hypertension: effect of plasma potassium correction in cardiac arrhythmias. *Am J Cardiol* 1983;52:1017-1022
- Leif PD, Beligon I, Mates J, et al. Diuretic-induced hypokalemia does not cause ventricular ectopy in uncomplicated essential hypertension [Abstract]. *Kidney Int* 1984;24:203
- Hypertension Detection and Follow-up Program Cooperative Group. Five-year findings of the Hypertension Detection and Follow-up Program: I. Reduction in mortality of persons with high blood pressure, including mild hypertension. *JAMA* 1979;242:2562-2571
- European Working Party on High Blood Pressure in the Elderly. Morbidity and mortality results. *Lancet* 1985;1:1349-1354
- Day JL, Simpson N, Metcalfe J, et al. Metabolic consequences of atenolol and propranolol in treatment of essential hypertension. *Br Med J* 1979;1:77-80
- Beta-Blocker Heart Attack Trial Research Group. A randomized trial of propranolol in patients with acute myocardial infarction: I. Mortality results. *JAMA* 1982;247:1707-1714
- 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 Hypertens* 1985;3:379-392
- Wikstrand J, Warnold I, Olsson G, et al. Primary prevention with metoprolol in patients with hypertension: mortality results from the MAPHY study. *JAMA* 1988;259:1976-1982
- Report of the Management Committee. The Australian Therapeutic Trial in Mild Hypertension. *Lancet* 1980;1:1261-1267
- Shulman NB, Martinez B, Brogan C, et al. Financial cost as an obstacle to hypertension therapy. *Am J Public Health* 1986;76:1105-1108

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