Rationale Against the Drug Treatment of Marginal Diastolic Systemic Hypertension

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The Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure[1] does not recommend drug treatment for uncomplicated hypertension when the diastolic blood pressure (BP) is in the range of 90 to 94 mm Hg (marginal hypertension). They advise instead nonpharmaceutical therapy with periodic examinations to detect possible progression of hypertension. Most physicians, however, still use 90 mm Hg as the level at which they will begin treatment with drugs if necessary and at least 2 authorities[2,3] emphasize the importance of decreasing BP using drug treatment when needed in all hypertensive patients, including those with diastolic levels as low as 90 mm Hg. This report will review some of the background data concerning the effectiveness of treatment of patients with diastolic BP in the range of 90 to 94 mm Hg. The question is of considerable importance because patients with diastolic BP in this marginal range comprise approximately 40% of the hypertensive population.[4,5]

Level of diastolic blood pressure and coronary heart disease mortality: The leading cause of death in marginal hypertension is coronary heart disease, which is 3 times greater than stroke, the second leading cause. However, cardiovascular risk is lower in marginal hypertensive patients compared to patients with higher levels of diastolic BP.[6]

The curve relating diastolic BP and coronary heart disease mortality increases steeply at levels above 100 mm Hg.[6] Anderson,[7] using 1978 data from the Framingham study, pointed out that the curve flattened out at diastolic BP levels between 70 and 90 mm Hg; that is, there was no increase in coronary heart disease mortality between 70 and 90 mm Hg. No such inflection or "dogleg" in the curve was seen with respect to systolic BP where coronary heart disease mortality increased continuously from the lowest levels. This inflection in the diastolic curve was not recognized before because of the previous practice of drawing a smooth linear regression curve, which will never disclose a dogleg. This author has been informed by Dr. A. D'Agastino of the Framingham study that their most recent, still unpublished data also show a dogleg or J-shaped diastolic curve. Furthermore, 4 other epidemiologic studies[8] also show in the unsmoothed curves relating diastolic BP and coronary disease mortality an inflection in the range of 95 to 105 mm Hg diastolic BP (Figure 1). The relatively flat portion of the dogleg in all of the studies included the range of marginal hypertension, suggesting that the risk of coronary heart disease is no greater in marginal hypertensive patients than in the normotensive population.

Evidence for a dogleg or even J-shaped curve also has been reported for treated hypertensive patients. The inflection occurs at approximately 90 mm Hg with an increasing incidence of coronary heart disease deaths at progressively lower levels of diastolic BP.[9,10] Cruickshank[10] reported that this phenomenon occurred only in patients with evidence of preexisting ischemic heart disease. He suggests that in patients with narrowed coronary arteries, myocardial perfusion, which occurs mainly in diastole, may become critical at a diastolic BP of approximately 85 mm Hg.[10] Other groups, however, have noted a J-shaped curve[11-13] in the absence of clinically evident coronary heart disease. One study in the elderly found a J-shaped curve[14] while another did not.[15]

Because the epidemiologic studies described before found J-shaped or dogleg curves, it is not surprising that the same phenomenon is seen when the diastolic BP is decreased to <90 mm Hg by treatment. Although final proof is still lacking, the recent evidence suggests that diastolic BP possibly should not be decreased to <90 mm Hg.

Effect of drug treatment on heart disease mortality in marginal hypertension: Most multiclinic trials (Table I) indicate that antihypertensive drug treatment has not been effective in preventing coronary heart disease morbidity-mortality.[16-22]

Opposed to 7 negative trials, only 2 found that treatment was effective in preventing coronary heart disease, the relatively small European Working Party on Hypertension in the Elderly Trial[15] and the Hypertension Detection and Follow-up Program.[23] However, the latter was not a controlled trial in the accepted sense because the general care of the control group was quite different from that of the treatment group.

The 2 most definitive trials from the point of view of adequate numbers and appropriate design were the Australian[16] and Medical Research Council[19] (MRC) trials. Their overall results indicated no significant protection against major coronary heart disease events from the use of antihypertensive drugs. These negative results are supported by the 5 remaining trials listed in Table I.[17,18,20-22]

Effect of drug treatment on stroke prevention: It is generally agreed that antihypertensive therapy decreases stroke morbidity and mortality.

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TABLE I Effect of Treatment on Major Coronary Heart Disease Events: Summary of Trials

Trial	No. of Subjects	Entry DBP (mm Hg)	Incidence CHD Events: Treatment	Incidence CHD Events: Control	% Difference
Showing no or negative benefit					
VA	380	90 to 114	11	13	13
USPHS	389	90 to 115	7	6	−17
Oslo	785	90 to 109	20	13	−54
Australian	3,427	95 to 109	33	33	0*
MRFIT	7,012	90+	115	124	5
MPPCDM	1,222	95+	19	9	−111
MRC	17,354	90 to 109	222	234	12
Showing benefit					
EWPHE	840	90 to 119	7	16	56
HDFP	7,825	90 to 104	86	107	20

Includes either mortality alone or morbidity plus mortality when data for both are given.
* Intention to treat.
CHD = coronary heart disease; DBP = diastolic blood pressure; EWPHE = European Working Party High Blood Pressure in the Elderly, HDFP = Hypertension Detection and Follow-up Program, MPPCDM = Multifactorial Primary Prevention of Cardiovascular Diseases in Middle-Aged Men, MRC = Medical Research Council; MRFIT = Multiple Risk Factor Intervention Trial, USPH = United States Public Health Service; VA = Veterans Administration

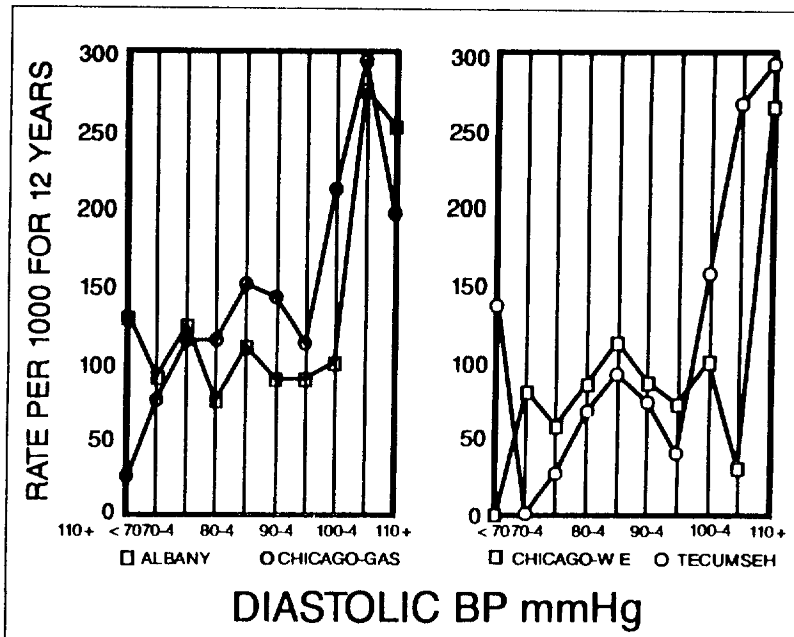
In marginal hypertension, however, the risk of stroke is relatively low. The MRC trial[19] found that treatment for 1 year protected against stroke in only 1 in 850 patients with a diastolic BP of 90 to 109 mm Hg. However, in patients with a baseline diastolic BP of 90 to 99 mm Hg, the incidence of stroke was only one-third or less than in the 105 to 109 mm Hg range (Table II). Therefore, the number of milder hypertensive patients required to be under treatment in order to prevent a single stroke must have been considerably >1 in 850. These results further call into question the cost-effectiveness of treatment of marginal hypertensive patients even for the prevention of stroke.

Adverse effects and cost of drug treatment: Although most patients tolerate antihypertensive drugs quite well, moderate to severe adverse effects may occur in a few. In the Veterans Administration trial,[24] for example, of 180 actively treated patients, 2 were withdrawn because of presumed toxic reactions, and side effects such as lethargy, weakness and nasal stuffiness were significantly more frequent in the treated patients as compared to the placebo control subjects. The MRC trial[25] reported that in men, adverse effects with bendroflumethiazide or propranolol were significantly increased as compared to placebo.

The cost of lifelong treatment for such a large number of patients is also a major consideration. This cost is magnified by the current trend to prescribe new, quite expensive drugs such as calcium antagonists and converting enzyme inhibitors in place of the less costly, older agents such as generic thiazide diuretics, propranolol and reserpine. Drug treatment for the 20 million marginal hypertensive subjects could total, therefore, several billion dollars per year.

The course of untreated marginal hypertension: In the Australian trial,[26] 1,943 placebo-treated patients had diastolic BP for the 3 initial visits averaging between 95 and 109 mm Hg and remaining at ≥95 mm Hg at the third visit. The investigators also followed, without active treatment, 325 patients whose diastolic

FIGURE 1. Coronary heart disease death rates/1,000 patient years for 12 years recorded in 4 epidemiologic studies (Albany, Chicago Gas, Chicago Western Electric and Tecumseh) related to diastolic blood pressure (DBP). Graphic representation of tabular data as presented by ~~Cruickshank~~ et al.[16] The 4 curves all showed a dogleg inflection with a relatively flat portion between <70 and ≥95 mm Hg DBP. Mortality rates then increased steeply beginning at levels of DBP ≥100 mm Hg. DBP, therefore, correlated directly with rates of coronary heart disease only at levels ≥100 mm Hg. Mortality rates were no higher in the marginal hypertensive range than in the normal range of DBP.



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BP averaged <95 mm Hg during the 3 initial visits. After 3 years, 48% of the total untreated patients had reverted to normal BP without treatment.

Many physicians regard 3 visits as being sufficient to characterize the average BP. The Australian trial indicated that the BP of some patients will require ≥4 months to decrease to normal.

None of the patients with initial diastolic BP <95 mm Hg at baseline developed elevation >109 mm Hg over 3 years of follow-up, whereas 94 of the patients exhibiting baseline diastolic BP levels between 105 and 109 mm Hg increased to >109 mm Hg during the trial. Thus, marginal hypertensive subjects rarely exhibit severe acceleration of BP over 3 years, whereas moderately severe hypertensive subjects often do. A lesser increase of 95 to 109 mm Hg occurred in some of the marginal patients (Table III). However, these more moderate increases can be safely managed by 6-month visits when they would be detected and treated before the BP reached a high-risk level.

The placebo group who remained in the range of 90 to 94 mm Hg throughout the trial, that is, the untreated marginal hypertensive subjects, exhibited no significantly greater rate of trial end points than the placebo patients who maintained normotensive levels of diastolic BP of 85 to 89 mm Hg (Table IV). These data further suggest the low risk associated with untreated marginal hypertension. By contrast, in the placebo patients maintaining higher levels of 95 to 99 mm Hg, the event rate per year nearly doubled as compared to the marginal hypertensive subjects and then increased more steeply with a diastolic BP >100 mm Hg. At similar levels of diastolic BP, the treated patients in general had higher rates of trial end points than the placebo patients.

Marginal hypertension combined with systolic hypertension: Systolic hypertension is defined as a systolic BP of 160 mm Hg or higher. Although often associated, there are important differences between systolic and diastolic hypertension.[27] The latter is characterized by constriction of arterioles while systolic hypertension results from loss of compliance of the aorta causing a steep systolic increase during cardiac ejection. Diastolic BP may remain normal if the arterioles are not constricted.

Systolic hypertension in the presence of normal or marginal diastolic hypertension often occurs in the aged. Under the stress of the first 1 or 2 medical examinations, these individuals may have an increased cardiac output, resulting in systolic hypertension. This response is amplified by impaired baroreceptor moderation of the BP elevation with aging. During subsequent visits, as elderly patients become accustomed to the clinic environment, the increased cardiac output often moderates and the systolic BP reverts to normal. Systolic hypertension, however, may persist in many other patients.

Epidemiologic studies indicate that systolic hypertension poses as great or greater a risk as diastolic hypertension.[28] However, there are presently no data from controlled clinical trials for determining the effectiveness of drug treatment in isolated systolic hypertension. It is, therefore, uncertain whether treatment will be beneficial or at what level to begin. Some physicians initiate drug treatment of persistent systolic hypertension on the reasonable but unproven assumption that such treatment will prevent stroke and heart failure, which are both prevalent in aged hypertensive patients.

Conclusions: Few patients with uncomplicated marginal hypertension require drug treatment. However, other hygienic measures such as weight reduction if needed, salt and alcohol restriction, regular exercise, cessation of cigarette smoking and especially dietary restriction of saturated fats and cholesterol are indicated. Also, antihypertensive drug treatment is advisable in marginal hypertensive subjects with diabetes mellitus or with renal impairment from other causes or congestive heart failure or with moderate to severe left ventricular hypertrophy or other evidence of organic changes secondary to hypertension. Aside from these exceptions, most of which are infrequent among marginal hypertensive subjects, there is little evidence that these patients will achieve enough benefit to justify the costs and adverse effects of antihypertensive drug treatment.

TABLE II MRC Trial: Stroke Rates/1,000 Patient Years in Relation to Average Entry Diastolic Blood Pressure

	Average Entry DBP (mm Hg)			
Strokes/1,000 Pt Yrs	<95	95 to 99	100 to 104	105 to 109
Active treatment	0.3	1.8	1.4	1.4
Placebo	1.4	2.3	3.1	4.4
Difference				
"Strokes prevented"	1.1	0.5	1.7	3.0

DBP = diastolic blood pressure.
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TABLE III Australian Trial—Placebo Group: Average Diastolic Blood Pressure After 3 Years Compared to Average Diastolic Blood Pressure at Entry

Average DBP After 3 Yrs (mm Hg)	Average DBP First 3 Visits (mm Hg)			
	<95	95 to 99	100 to 104	105 to 109
>109	0	4%	13%	40%
95 to 109	19%	30%	41%	35%
<95	75%	58%	38%	16%

DBP = diastolic blood pressure.
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TABLE IV Data from Australian Trial—Trial End Points: Rates by Average Diastolic Blood Pressure Throughout the Study for Active and Placebo Subjects

Average DBP (mm Hg) Throughout the Trial	TEP Rates/1,000 Yrs	
	Active	Placebo
<85	12.3	11.8
85 to 89	13.4	18.8
90 to 94	29.7	16.2
95 to 99	75.8	28.7
>100	84.5	60.4

DBP = diastolic blood pressure; TEP = trial end points.

REFERENCES

1. Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure. The 1988 Report. *Arch Intern Med 1988;148:1023–1038.*

2. Gifford RW. Essential hypertension: cost-effective evaluation and treatment. *Am J Med 1986;81(suppl C):C-23–C-37.*

3. Moser M. Is drug treatment indicated for mild hypertension with diastolic blood pressure 90 mm Hg to 100 mm Hg? An affirmative view. *J Fam Pract 1988;26:449–459.*

4. United States Department of Health and Human Services. Public Health Service. Health, United States with prevention profile. *Washington DC: Government Printing Office, 1981:35(DHHS publication no (PHS) 81-1232):35–39.*

5. Hypertension Detection and Follow-up Program Cooperative Group. The Hypertension Detection and Follow-up Program. A progress report. *Circ Res 1977;40(suppl I):I-106–I-109.*

6. The Pooling Project Research Group. Relationship of blood pressure, serum cholesterol, smoking habit, relative weight and ECG abnormalities to incidence of major coronary events: final report of the pooling project. *J Chronic Dis 1978;31:201–306.*

7. Anderson TW. Re-examination of some of the Framingham blood pressure data. *Lancet 1978;2:1139–1141.*

8. McGee D, Gordon T. The results of the Framingham Study applied to four other U.S.-based epidemiological studies of cardiovascular disease. Section 31: The Framingham Study: an epidemiological investigation of cardiovascular disease. In: Kannel WB, Gordon T, eds. *Washington DC, U.S. Department of Health, Education and Welfare, 1976 NIH Publication 76-1,083.*

9. Stewart JMcDG. Relation of reduction in pressure in first myocardial infarction in patients receiving treatment for severe hypertension. *Lancet 1979;1:861–865.*

10. Cruickshank JM, Thorp JM, Zacharias FJ. Benefits and potential harm of lowering high blood pressure. *Lancet 1987;1:581–584.*

11. Waller PC, Isles CG, Lever AF, Murray GD, McInnis GT. Does therapeutic reduction in blood pressure cause death from coronary artery disease? *J Human Hypertension 1988;2:7–10.*

12. Fletcher AE, Beeners DG, Bulpitt CJ, Butler A, Coles EC, Hunt D, Munro-Faure AD, News MR, O'Riordan PW, Petrie JC, Ratagoplan B, Rylance PB, Twallin G, Webster J, Dollery CT. The relationship between a low treated blood pressure and IHD mortality; a report from DHSS Hypertension Care Computing Group (DHCCP). *J Human Hypertension 1988;2:11–15.*

13. Samuelson O, Wilhelmson I, Anderson OK, Peunert K, Berglund G. Cardiovascular mortality in blood pressure and serum cholesterol levels in treated hypertension. Results from the Primary Prevention Trial in Goteborg. *JAMA 1987;258:1768–1776.*

14. Coope J, Warrender TS. Lowering blood pressure. *Lancet 1987;1:1380.*

15. Amery A, Birkenhager W, Brixko P, Bulpitt C, De Schaepdryver A, Dollery C, Fogard R, Forette F, Forte J, Handy R, Henry JF, Joossens JV, Leonetti G, Lund-Johansen P, O'Malley K, Petrie J, Strasser T, Tuomilehto J, Williams B. Mortality and morbidity results from European Working Party on High Blood Pressure in the Elderly Trial. *Lancet 1985;1:1349–1354.*

16. Report by the Management Committee. The Australian therapeutic trial in mild hypertension. *Lancet 1980;1:1261–1267.*

17. Veterans Administration Cooperative Study Group on Antihypertensive Agents. Effects of treatment on morbidity in hypertension. II. Results of patients with diastolic blood pressure averaging 90 through 114 mm Hg. *JAMA 1970;213:1143–1151.*

18. Smith WM for the U.S. Public Health Service Hospitals Cooperative Study Group. Treatment of mild hypertension. Results of a ten-year intervention trial. *Circ Res 1977;40(suppl I):I-98–I-105.*

19. Medical Research Council Working Party On Mild Hypertension. MRC trial of treatment of mild hypertension: principal results. *Br Med J 1985;291:97–104.*

20. Helgeland A. Treatment of mild hypertension: a five-year controlled drug trial. The Oslo study. *Am J Med 1980;69:725–732.*

21. Miettinen TA, Huttunen JK, Naukkarinen V, Strandberg T, Mittilla S, Kumlin T, Sarna S. Multifactorial primary prevention of cardiovascular diseases in middle-aged men. Risk factor changes, incidence and mortality. *JAMA 1985;254:2097–2102.*

22. Multiple Risk Factor and Intervention Trial Research Group. Multiple Risk Factor Intervention Trial. Risk factor changes and mortality results. *JAMA 1982;248:1465–1477.*

23. 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.*

24. Veterans Administration Cooperative Study Group on Antihypertensive Agents. III. Influence of age, diastolic blood pressure and prior cardiovascular disease; further analysis of side effects. *Circulation 1972;45:991–1004.*

25. Medical Research Council Working Party on Mild to Moderate Hypertension. Adverse reactions to bendrofluazide and propranolol for the treatment of mild hypertension. *Lancet 1981;2:539–543.*

26. Management Committee of the Australian Therapeutic Trial in Mild Hypertension. Untreated mild hypertension. *Lancet 1982;1:185–191.*

27. Gifford RW. Isolated systolic hypertension in the elderly. Some controversial issues. *JAMA 1982;247:781–785.*

28. Kannel WB. Role of blood pressure in cardiovascular morbidity and mortality. *Prog Cardiovasc Dis 1974;18:5–23.*