The Drug Treatment of Mild Hypertension in the Multiple Risk Factor Intervention Trial: A Review

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Summary

The Multiple Risk Factor Intervention Trial was a long term study on the benefit of lowering risk factors for coronary heart disease mortality in middle-aged men. Study participants were randomised to either 'special intervention' or 'usual care'. Intensive intervention for special intervention men involved cholesterol lowering dietary advice, behaviour modification for cigarette smoking and a stepped care pharmacological approach to lower blood pressure.

Overall, at 6 years, there was a 7.1% lower coronary heart disease mortality in special intervention compared with usual care men, a statistically non-significant difference (Confidence Interval +25 to -15%). Subgroup analysis revealed that special intervention men who were hypertensive at baseline and who had resting ECG abnormalities experienced a higher coronary heart disease mortality than the comparable usual care group. Within group Cox regression analysis, with coronary heart disease mortality as the dependent variable, revealed an interaction between diuretic use and resting ECG abnormalities in special intervention men. Additional analyses of clinics revealed a higher special intervention/usual care mortality in those clinics that used mainly hydrochlorothiazide in special intervention hypertensives. Results of the Multiple Risk Factor Intervention Trial raise important questions concerning the treatment of mild hypertension, and the clinical significance of metabolic alterations of antihypertensive drugs.

A great deal of progress has been made concerning the recognition of risks associated with high blood pressure and its pharmacological treatment. Several large scale clinical trials have been conducted that, when viewed collectively, strongly support the pharmacological treatment of hypertension (HDFP 1979a,b, 1982a,b; Report by the Management Committee 1980). However, the optimal treatment of 'mild' hypertension remains controversial, especially the benefit of treatment for preventing atherosclerotic end-points. The Hypertension Detection and Follow-up Program and the Australian Trial in Mild Hypertension have both reported results which support the active pharmacological treatment of hypertension, including mild hypertension (diastolic blood pressure 90-105mm Hg). The Multiple Risk Factor Intervention Trial, a trial on the benefit of risk factor low-
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ering which included intervention to influence blood pressure, blood cholesterol, and cigarette smoking has recently published its results and although many of the results are consistent with other trials, including the Hypertension Detection and Follow-up Program and Australian Trials, this study has also reported at least some results on blood pressure treatment that are discrepant with other studies. These results have generated much discussion and several editorials (Fries 1982; Grimm 1984; Kaplan 1983; McAlister 1983; Ram 1984). This article reviews some of the major blood pressure results of the Multiple Risk Factor Intervention Trial with a discussion of the possible implications of these findings including directions for additional areas of research.

1. Methods

The Multiple Risk Factor Intervention Trial was a collaborative study examining the benefit of risk factor lowering in men aged 35 to 57 identified at higher risk for coronary heart disease (MRFIT 1982). The primary purpose was to study if lowering risk factors (diastolic blood pressure, blood cholesterol, cigarette smoking) would result in a reduced incidence of coronary heart disease. Middle-aged men (aged 35-57 years) were screened and those identified in the upper 10 to 15% of risk for coronary heart disease (based on Framingham risk coefficients), who were free of overt evidence of the disease were randomised to 1 of 2 groups, special intervention or usual care. Special intervention men (n = 6428) underwent intensive intervention designed to lower the major cardiovascular risk factors. Usual care men (n = 6438) were referred to the regular source of medical care. They were not given any advice concerning intervention. After an initial 10-week intensive intervention phase, special intervention men were then seen at least every 4 months in ‘maintenance intervention’. Both the special intervention and usual care groups were seen annually. The annual visits included a set of questionnaires, standardised measurement of blood pressure, cholesterol, and cigarette smoking (serum thiocyanate, a biochemical measure of smoking).

A drug history was taken on all participants at annual examinations and was also collected on special intervention men at the intervening 4-monthly visits. Blood pressure measures were defined in this study as the average of 2 random-zero sphygmomanometer readings taken from the right arm with the participant in the seated position. Blood pressures were measured after a rest period of 5 minutes.

Participants were considered hypertensive at entry into the programme if their baseline diastolic pressure was 90mm Hg or higher (baseline pressure being the average of the random-zero readings at the second and third screening visits) or if a man reported that he was already taking antihypertensive medication at the second screening visit.

2. Intervention Programme

Intensive intervention for special intervention men involved both group session and individual counselling. Participants were instructed on cholesterol lowering eating habits. Cigarette smoking cessation was the goal of the smoking intervention which was carried out using behavioural modification techniques. Blood pressure lowering was accomplished primarily by a standardised stepped care pharmacological approach which initially involved attempts at weight loss (table I). Once a special intervention man was determined to be hypertensive, an individualised goal blood pressure was set for him by subtracting 10 from the average diastolic pressure at the second of 2 visits or 89mm Hg, whichever value was lower. Those with diastolic blood pressure less than 90mm Hg, who at entry into the study were already taking antihypertensive medication, were assigned a goal pressure of 80mm Hg. The average goal blood pressure for special intervention hypertensive men was 85mm Hg.

Stepped care therapy was initiated with a diuretic. Either hydrochlorothiazide or chlorothalidone at an initial dose of 50mg daily could be used at the discretion of the study physician. If after 6 weeks, the diastolic blood pressure failed to fall below the individual’s goal, the dose of diuretic was