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Original Contributions

Multiple Risk Factor Intervention Trial

Risk Factor Changes and Mortality Results

Multiple Risk Factor Intervention Trial Research Group

• **The Multiple Risk Factor Intervention Trial was a randomized primary prevention trial to test the effect of a multifactor intervention program on mortality from coronary heart disease (CHD) in 12,866 high-risk men aged 35 to 57 years. Men were randomly assigned either to a special intervention (SI) program consisting of stepped-care treatment for hypertension, counseling for cigarette smoking, and dietary advice for lowering blood cholesterol levels, or to their usual sources of health care in the community (UC). Over an average follow-up period of seven years, risk factor levels declined in both groups, but to a greater degree for the SI men. Mortality from CHD was 17.9 deaths per 1,000 in the SI group and 19.3 per 1,000 in the UC group, a statistically nonsignificant difference of 7.1% (90% confidence interval, −15% to 25%). Total mortality rates were 41.2 per 1,000 (SI) and 40.4 per 1,000 (UC). Three possible explanations for these findings are considered: (1) the overall intervention program, under these circumstances, does not affect CHD mortality; (2) the intervention used does affect CHD mortality, but the benefit was not observed in this trial of seven years' average duration, with lower-than-expected mortality and with considerable risk factor change in the UC group; and (3) measures to reduce cigarette smoking and to lower blood cholesterol levels may have reduced CHD mortality within subgroups of the SI cohort, with a possibly unfavorable response to antihypertensive drug therapy in certain but not all hypertensive subjects. This last possibility was considered most likely, needs further investigation, and lends support to some preventive measures while requiring reassessment of others.**

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BACKGROUND

THE YEARS subsequent to World War II saw increasing evidence of the importance of arteriosclerosis and its complications as the leading cause of death in the United States. Scientific studies in the laboratory, clinic, and in population groups pointed to the contributing roles of diet, hypertension, cigarette smoking, diabetes, and other risk factors in the genesis of coronary heart disease (CHD). Yet convincing demonstrations of the favorable effect of risk factor modification on CHD morbidity and mortality were not at hand by the 1960s.

For editorial comment see p 1501.

In July 1970, the National Heart and Lung Institute (NHLI) convened a Task Force on Arteriosclerosis specifically to develop a broad long-range plan for the study, control, and possible prevention of arteriosclerosis.[1] The Task Force concluded that the time had come for vigorous application of existing knowledge for the purpose of determining whether CHD could be prevented. Among its final recommendations were (1) the advice not to institute a large-scale national diet-heart trial because of excessive cost and uncertain feasibility, and (2) a proposal that multiple risk factor intervention trials be undertaken to ascertain whether modification of elevated serum cholesterol levels, hypertension, and cigarette smoking in persons at increased risk of death from heart attacks would result in reduction of coronary death rates. With acceptance of the latter proposal, the NHLI prepared and distributed requests for participation of clinical and support centers in the Multiple Risk Factor Intervention Trial (MRFIT).

METHODS

Organization

In 1972 and 1973, awards from the NHLI (later the National Heart, Lung, and Blood Institute, or NHLBI) were made to 22 clinical centers, a coordinating center, a laboratory center, a laboratory standardization center, and two electrocardiography centers. A policy advisory board, whose members had no formal association with any of the other participating units of the trial, was appointed by the Institute to provide advice on the overall course of the trial and to monitor the effects of intervention.[2] A steering committee comprised of investigators from the clinical and support centers and NHLBI staff was responsible for the scientific leadership of the trial.[3]

Design

The MRFIT design called for the recruitment of at least 12,000 men aged 35 to 57 years who were at increased risk of

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death from CHD, but had no clinical evidence of CHD. Persons were designated at "increased risk" if their levels of three risk factors—cigarette smoking, serum cholesterol, and blood pressure (BP)—were sufficiently high at a first screening visit to place them in the upper 15% of a risk score distribution based on data from the Framingham Heart Study.[4] After about one third of the screening was completed and success in recruitment had been demonstrated, the 15% was changed to 10% to increase the average risk level of the eligible men. As an example of the application of this criterion, a man whose diastolic BP was 90 mm Hg and who reported smoking 30 cigarettes per day was risk-eligible at the 10% level if his serum cholesterol level was at least 295 mg/dL. The study was restricted to men because of their much higher risk of premature heart attack compared with women.

The men were to be randomized into two groups of approximately equal size. One group received a "special intervention" (SI) program aimed at cessation of cigarette smoking and reduction of elevated serum cholesterol and BP levels. Men in the other group, "usual care" (UC), were referred to their personal physicians or other community medical facility for such treatment of their risk factors as was considered individually appropriate.

Recruitment

As a first step in identifying at least 12,000 men eligible for the trial, 361,662 men were recruited for a first screening visit to determine CHD risk eligibility and to apply several exclusion criteria. Various recruitment techniques were used, with the most common procedure being to offer voluntary screening to industry or government employee groups. The number recruited for screening at each center ranged from 11,435 to 30,465. The men were informed at the first as well as at subsequent screening visits of the randomized nature of the trial.

Eligibility Criteria

Eligibility was determined at three successive screening visits (S_1, S_2, and S_3). At S_1, to determine risk for CHD, systolic and diastolic BPs were measured, the number of cigarettes smoked daily was ascertained, and a sample of blood was drawn for determination of the serum cholesterol level. Men were excluded from further screening on the basis of low risk, history of a heart attack, diabetes mellitus requiring medication, expected geographic mobility, a serum cholesterol level of 350 mg/dL or higher, or diastolic BP of 115 mm Hg or higher. The last two exclusions were made because of their special clinical features and therapeutic requirements. Of the men seen at S_1, 25,545 (7.1%) qualified and were invited to return for S_2.

The second screening visit, S_2, followed a 12-hour fast and included among other tests (1) a medical history and physical examination; (2) four BP determinations; (3) a locally read resting ECG; (4) a fasting blood sample for measurement of cholesterol, triglyceride, lipoprotein cholesterol, serum thiocyanate, and potassium levels, as well as a blood sample drawn one hour after a 75-g glucose load; (5) pulmonary function tests; (6) a posterior-anterior chest film; (7) an assessment of willingness and ability to adhere to the proposed intervention program; and (8) a detailed explanation of the purposes of the trial and requirements for participation.

Reasons for excluding men at this visit included body weight greater than or equal to 150% of desirable weight; angina pectoris as determined by the Rose questionnaire[5]; history or ECG evidence of myocardial infarction; untreated symptomatic diabetes; diets incompatible with the MRFIT food pattern; treatment with guanethidine, hydralazine, insulin, oral hypoglycemic agents, or lipid-lowering agents; illnesses or disabilities likely to impair full participation in the trial; and diastolic BP of 120 mm Hg or higher. Of the 22,080 men seen at the S_2 visit, 15,791 men (71.5%) were invited to return for the third and final screening visit.

The third screening visit, S_3, included (1) a resting and exercise ECG, (2) a detailed smoking questionnaire, and (3) a 24-hour dietary recall. A brief medical review and examination determined whether any major change in cardiovascular status had occurred since S_2. The purpose and scope of the trial were again explained, and men who then signed the consent form were randomized by the coordinating center into either the SI or UC group. The randomization assignment was obtained by the local clinic coordinator who telephoned the coordinating center after eligibility and willingness to enter the trial had been established. Allocation to SI or UC was stratified by clinic and balanced in blocks of four or six, providing two groups of nearly equal size at each clinic, with 6,428 assigned studywide to SI and 6,438 to UC. Of the 14,111 men seen at S_3, 12,866 were randomized into the trial, constituting a yield of 3.6% of men seen at S_1. The first man was randomized in December 1973; the last randomization occurred on Feb 28, 1976.

Intervention Program

No intervention program was offered to the UC men who continued to be followed by their usual source of medical care, but they were invited to return once a year for a medical history, physical examination, and laboratory studies as listed herein. The results of the screening and annual examinations were provided to their personal physicians, who were informed as to the scientific objectives of the study.

The detailed components of the SI program have been reported earlier[6-9] and are summarized here. The initial phase of intervention was an intensive integrated effort to lower the three major risk factors. Immediately after randomization to the SI group, each cigarette smoker was counseled individually by a study physician in an effort to achieve cessation of smoking at that time. Shortly thereafter, each SI man was invited with his spouse or friend to a series of weekly group discussions addressing all three risk factors; uniformity of structure and content was sought by the use of common protocols and educational materials. Each group included about ten men and met for about ten sessions.

After the initial intensive intervention phase, individual counseling, planned and executed by an intervention team usually headed by a behavioral scientist and including nutritionists, nurses, physicians, and general health counselors, became the general approach in all three modalities. Participants in the SI group were seen every four months, and more often as needed for intervention purposes. The course of every SI participant was monitored to assess changes in risk factor status, the ultimate objective being to reach specific goals established for each individual.

Hypertension.—Hypertension was considered present if the man reported having antihypertensive medication prescribed for him by his personal physician (regardless of BP level), or if an untreated man was found to have a diastolic BP of at least 90 mm Hg on two consecutive monthly visits during the trial. The reading at the second of these visits was used to establish a goal BP of either a 10 mm Hg reduction or 89 mm Hg, whichever was lower; men who had a diastolic BP of 90 mm Hg or less who were already taking antihypertensive drugs prescribed by a personal physician were assigned a goal of 80 mm Hg. Before drug prescription, weight reduction was attempted for overweight men. Drugs were prescribed according to a stepped-care protocol beginning with the use of either hydrochlorothiazide or chlorthalidone. Reserpine, hydralazine, guanethidine, or certain alternate drugs were sequentially added if goal BP had not been achieved.[9] The protocol also included a provision for mild sodium restriction. Participants in the SI group who had been treated with BP medication by nonstudy physicians were usually transferred, with the permission of their private physicians, to the care of an MRFIT clinician.

Nutrition.—The nutrition intervention program sought to encourage the development of lifelong shopping, cooking, and eating patterns rather than to specify a

structured diet.[7] Individual intervention goals for lowering serum cholesterol levels by an amount dependent on the entry level were established. Initially, eating patterns were recommended that reduced saturated fat intake to less than 10% of calories and dietary cholesterol intake to less than 300 mg/day, and increased polyunsaturated fat intake to 10% of calories. In 1976, the nutrition pattern was changed to specify that saturated fat be less than 8% of calories and dietary cholesterol less than 250 mg/day. Weight reduction was sought for men whose weight was 115% or greater of desirable weight by recommending reductions in caloric intake and increases in moderate forms of physical activity.

Smoking.—The smoking intervention program urged those SI participants who smoked cigarettes to quit; no systematic effort was made to alter the smoking habits of persons who smoked only pipes and cigars.[8] Dosage reduction, including switching to cigarettes low in tar and nicotine, was recommended only as an intermediate step to cessation. Conventional behavioral modification techniques were used throughout the trial; aversive techniques and hypnosis were used in selected instances during the final years. Particularly successful intervention approaches were the ten-week group sessions at the beginning of the trial and the five-day quit clinics during the final years.

Data Collection Methods

On or about each anniversary of randomization, participants in both the SI and UC groups returned for assessment of risk factor levels and morbidity status. Data collected at these annual visits, at screening, intervention, and four-month visits were sent to the coordinating center for processing and analysis. Serum cholesterol concentration obtained at S_1, the first screening visit, for risk eligibility purposes was determined at one of 14 local laboratories established for this purpose and monitored by the Centers for Disease Control (CDC) Lipid Standardization Laboratory and the coordinating center. All subsequent analyses of blood samples for levels of cholesterol, triglycerides, lipoproteins, creatinine, potassium, glucose, uric acid, SGOT, and thiocyanate were determined by the central laboratory using techniques previously described.[10,11]

Except for the ECG taken at S_2 and read locally for exclusion purposes, cassette tapes of all ECGs were sent to the ECG Center in Halifax, Nova Scotia, for computer processing and interpretation. A paper tracing produced from the cassette was then forwarded to the ECG Reading Center in Minneapolis for visual classification according to the Minnesota code. Major ECG abnormalities included major Q wave findings, ST segment elevations and depressions, negative T waves, frequent ventricular premature beats (VPBs) (≥10% of recorded beats), complete atrioventricular (AV) and bundle-branch block, and supraventricular tachycardia. Minor ECG abnormalities included high R waves, left axis deviation, and less frequent VPBs (<10% of recorded beats). The treadmill exercise test at S_3 was done according to a modified Bruce protocol.[12]

Cigarette smoking was measured in two ways: (1) a participant interview for smoking behavior; and (2) thiocyanate-adjusted smoking and quit rates using serum thiocyanate level as an objective measure of smoking behavior.[13]

For analyses in this report, baseline BP is defined as the average of the two random-zero manometer readings at S_2 and S_3; BP at each follow-up visit is the average of the two random-zero readings at the visit. A participant was considered hypertensive at entry if his baseline diastolic BP was 90 mm Hg or higher or if he reported at S_2 having antihypertensive drugs prescribed for him. No attempt was made before randomization to alter antihypertensive medication for those already receiving such agents.

Serum cholesterol concentration was determined at S_1 and each annual follow-up visit using automated methods with periodic quality control developed by the CDC Lipid Standardization Laboratory.[11] Plasma cholesterol and triglyceride concentrations were obtained at S_2 and each annual visit except at 12 months. The cholesterol content of each lipoprotein fraction, estimated after heparin/manganese precipitation, was obtained at S_2 and at 24, 48, and 72 months.[11] All lipid determinations were performed on serum or plasma specimens collected after an overnight fast except for the serum cholesterol at the first screening visit.

Twenty-four hour dietary recalls were obtained at S_3 and at 12, 24, 36, 60 (SI men only), and 72-month visits through interview by an MRFIT nutritionist. Recalls were coded by a Nutrition Coding Center (NCC) with nutrient calculations made using version VI of the NCC food table.[14]

Sample Size and Statistical Power

In planning for the MRFIT, four key endpoints were identified: (1) death from CHD (the primary endpoint); (2) death from cardiovascular disease (CVD); (3) death from any cause; and (4) the combination of fatal CHD and nonfatal myocardial infarction. Data on the first three endpoints are presented in this report on mortality; morbidity data will be included in a subsequent report. Application of the logistic function with coefficients estimated from Framingham data to the observed risk factor combinations of the men randomized projected a six-year CHD death rate for UC men of 29.0 deaths per thousand men. With a sample size of 12,866 (the number eventually randomized into the trial), a reduction in CHD mortality among SI men to 21.3 per thousand (26.6% reduction) could be detected with a probability of .88 using a one-sided test for a difference in proportions at a .05 level of significance. This reduction was determined by using the following anticipated intervention effects (and corresponding potential risk reductions): (1) a 10% reduction of serum cholesterol level if 220 mg/dL or higher—otherwise no change; (2) a 10% reduction of diastolic BP if 95 mm Hg or higher—otherwise no change; and (3) graded reductions in cigarette smoking as follows: 25% reduction for smokers of 40 or more cigarettes per day, 40% for smokers of 20 to 39 per day, and 55% for smokers of less than 20 per day. These anticipated differential intervention effects were based on experience in earlier smoking cessation programs.[15]

In addition, it was assumed that the corresponding groups of UC smokers at entry would have reductions during the course of the trial of 5%, 10%, and 15%, respectively, but that there would be no change in serum cholesterol or BP level in the UC group. Further allowances were incorporated for nonadherence by SI men (estimated to increase progressively to 50% by the end of six years), and for time to achieve maximum potential benefit of risk factor change (estimated to be a "lag" of three years). A similar calculation for the endpoint of death from any cause gave an estimate of power of .92. Statistical aspects of the design have been reported elsewhere.[3,4]

During the trial, subgroup hypotheses relative to mortality outcome were formulated by MRFIT investigators blinded to interim mortality data with the realization that power would be lower for their testing than for comparisons based on all SI and UC men. These hypotheses were based on the recognition that, in such a group of men at increased risk of coronary disease, a proportion would have advanced coronary atherosclerosis at entry even after excluding those with clinical evidence of CHD (history of myocardial infarction or angina, or ECG evidence of myocardial infarction). One of these hypotheses, that the intervention program would be especially effective in lowering CHD mortality for men with normal baseline resting ECGs, is referred to in this article.

Mortality Ascertainment

All participants were followed for a minimum of six years, with an average period of observation of seven years. Deaths were ascertained by clinic staff through contact with family or friends of the deceased, routine follow-up of missed clinic visits, response to postcards request-

Table 1.—Mean Values of Selected Variables at Entry for MRFIT SI and UC Men*

	SI (n=6,428)	UC (n=6,438)
Screen 1		
Age, yr	46.2	46.1
Serum cholesterol, mg/dL	253.8	253.5
Diastolic BP, mm Hg	99.2	99.2
Cigarette smokers, %	63.8	63.5
Cigarettes smoked by smokers, No. per day	33.7	34.2
Black participants, %	7.2	7.2
Framingham 6-yr risk of CHD death, %	3.12	3.15
Screen 2		
Plasma cholesterol, mg/dL	240.3	240.6
Plasma LDL cholesterol, mg/dL	159.8	160.3
Plasma HDL cholesterol, mg/dL	42.0	42.1
Plasma triglycerides, mg/dL	194.7	193.9
Weight, lb	189.3	189.1
Serum thiocyanate, μmole/L	131.0	131.1
Screen 3		
Minnesota codes 1.1-1.2.7 (definite myocardial infarction), %†	0.36	0.36
Minnesota codes 1.1-1.3 (definite or possible myocardial infarction), %	1.29	1.57
Major ECG abnormalities, %‡	4.4	4.6
Major or minor ECG abnormalities, %	28.4	27.5
Ischemic response to exercise, %§	12.5	11.9
Dietary data (24-hr recall)		
Energy, kcal	2,497	2,478
Saturated fatty acids, % of calories	14.0	14.0
Polyunsaturated fatty acids, % of calories	6.4	6.4
Alcohol, % of calories	7.3	7.6
Cholesterol, mg	454	448
Baseline		
Systolic BP, mm Hg	135.7	135.5
Diastolic BP, mm Hg	91.0	90.9
Hypertensive (baseline diastolic BP ≥90 mm Hg or on antihypertensive drugs at screen 2), %	62.5	62.0

*MRFIT indicates Multiple Risk Factor Intervention Trial Research Group; SI, special intervention; UC, usual care; CHD, coronary heart disease; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

†These men, who had been judged free of ECG evidence of myocardial infarction by clinic physicians in order to be eligible for randomization, were subsequently assigned these Minnesota codes by the ECG Center.

‡For detailed listing of Minnesota codes, see Table 7.

§Based on computer measurement of the ST depression integral.

ing change-of-address information sent twice yearly to UC participants, and searches of publicly accessible files of deceased persons.

To determine survival status as of Feb 28, 1982 (six years after the last day of randomization), a telephone or mail contact was attempted with each man not previously known to be deceased. The status of men not located by this procedure was sought using the files of the Social Security Administration and the service of a commercial firm specializing in methods of follow-up. The 15 SI and 15 UC men whose survival status remained unknown as of July 1, 1982, are included in the analyses as survivors to Feb 28, 1982.

Cause of death was assigned by a Mortality Review Committee, a three-member panel of cardiologists not associated with any MRFIT center and not privy to interim trial results. This committee, without knowledge of study group membership of the deceased, reviewed clinic records, hospital records, next-of-kin interviews, death certificates, and reports of autopsies performed (31% of SI decedents, 33% of UC). Deaths ascribed to CHD were subclassified as (1) myocardial infarction (documented by clinical or autopsy evidence), with death occurring within 30 days of onset of symptoms or during hospitalization for acute myocardial infarction; (2) sudden death (within 24 hours of symptom onset and without documented myocardial infarction); (3) congestive heart failure due to CHD; or (4) death during hospitalization for surgery for CHD or from complications of such an operation.

Statistical Methods

Differences in baseline characteristics and in risk factor levels at annual follow-up visits between men randomly allocated to the SI and UC groups were tested for statistical significance using Student's t (two-sided) or the 2×2 χ^2 test without adjustment for multiple comparisons.

Risk factor changes over time are presented as mean values for all participants who attended each visit. (Results based on cohort analysis and data imputation procedures for missing values, such as substitution of either baseline or previous annual visit risk factor levels, did not differ from these in any substantial way.) Mortality results are presented as life-table functions using the Kaplan-Meier product limit method[16] and as the proportion of deaths as of Feb 28, 1982, among SI and UC participants. Significance testing of mortality results is limited to the key endpoints for the entire cohort. For the three key mortality endpoints, differences between all SI and UC participants are summarized using the log rank test.[17] For the primary endpoint of CHD death, a 90% confidence interval (CI) for the percentage difference,[18] ([UC−SI]/UC)×100, between all SI and all UC men in the proportion of deaths at the end of follow-up is given since the design of the trial was based on a one-sided test at the .05 probability level. For other comparisons, the more conventional 95% CI for the percentage difference is given.

The analysis of subgroups of men is, unless otherwise noted, restricted to groups defined by baseline characteristics. Men are classified, regardless of degree of adherence, as SI or UC based on the allocation at randomization.

RESULTS

Comparison of SI and UC Groups at Entry

The effectiveness of the randomization process in establishing two comparable groups at baseline is demonstrated by the excellent agreement in prerandomization levels of numerous risk factor and risk factor-related variables (Table 1). None of these differences is statistically significant at the .05 level.

Follow-up Visit Record

The missed visit rates (the number of men alive at the time of the specified annual visit but who did not attend, divided by the number of men randomized) were 4.5% for SI and 5.2% for UC men at 12 months; these increased only slightly each year and, although somewhat higher for the UC group at each visit, remained below 10% through six years for both groups. Participants who were randomized early in the recruitment period came to the clinic for annual visits beyond the sixth; however, data on risk factor change is presented in this report only through the sixth, the last visit that the entire surviving cohort could have attended.

Risk Factor Reduction

A necessary intermediate goal of

the trial was to obtain adequate reductions, through intervention, of the three major modifiable CHD risk factors (Fig 1). For each of these, highly statistically significant ($P<.01$) differences between the SI and UC groups were observed at each annual visit.

The mean diastolic BP at the first screening visit, S_1, for men subsequently randomized was 99.2 mm Hg. Baseline diastolic pressure, defined as the average of S_2 and S_3 random-zero readings, was 91.0 mm Hg, with regression to the mean probably accounting for much of the decrease from S_1. By 12 months, average reductions from baseline of 6.3 mm Hg for SI men and 2.5 mm Hg for UC men were observed (Table 2). By 72 months, these reductions were 10.5 mm Hg and 7.3 mm Hg, respectively. Of the men randomized, 19% reported at baseline being prescribed antihypertensive medication; at six years, 58% of SI men and 47% of UC men reported such prescription. Of SI men treated for hypertension, 88% had diastolic pressures lower than 90 mm Hg at six years. The average percent reduction from baseline to 72 months among all SI men with S_1 diastolic pressure of 95 mm Hg or higher was 12%, a figure exceeding design expectations; however, the corresponding reduction for UC men (unanticipated in the design) was 8%. The SI-UC difference in diastolic BP averaged over annual visits was 4%, approximately 75% of the design goal used for sample size calculations. Among the 22 clinical centers, differences in mean diastolic BP at 72 months for SI and UC participants ranged from 0.2 to 5.1 mm Hg.

At the time of randomization, 59% of all men reported themselves as current cigarette smokers (Table 2). For men who reported smoking at S_1, stated quit rates at 12 months were 43% for SI men and 14% for UC men; at 72 months, these were 50% and 29%. Thiocyanate-adjusted quit rates at 12 months were 31% for SI men and 12% for UC; at 72 months, these were 46% and 29%, respectively. The reported and the thiocyanate-adjusted SI-UC differences, stated in terms of mean change in number of cigarettes smoked per day for all participants, exceeded design goals by 122% and 45%, respectively. At 72 months, the SI-UC differences in

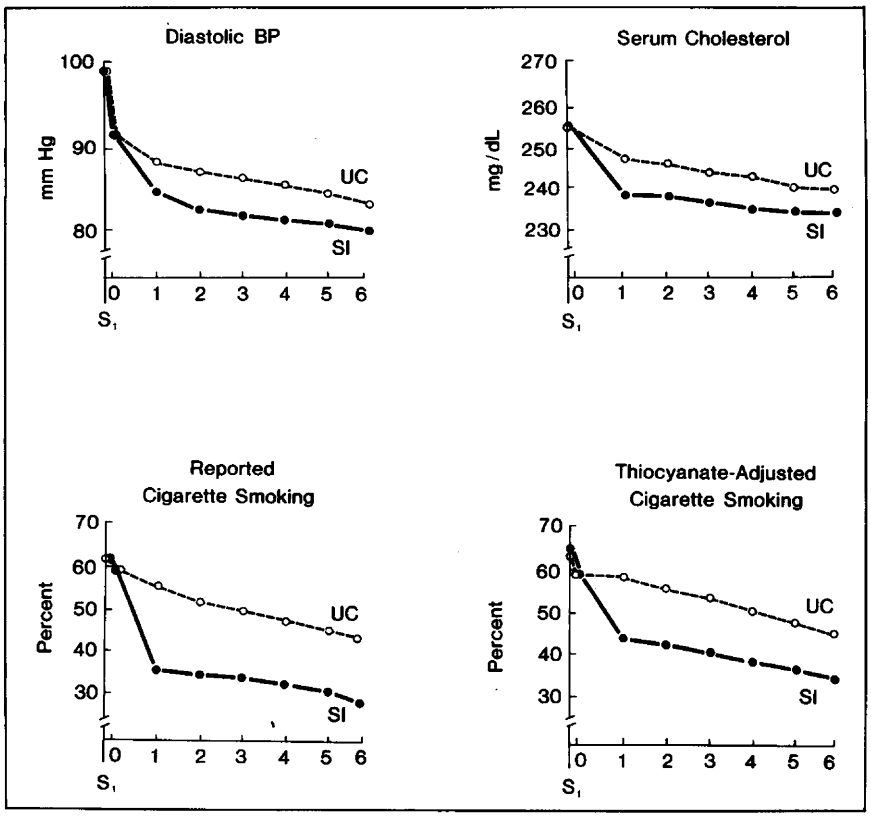

Fig 1.—Mean risk factor levels by year of follow-up for Multiple Risk Factor Intervention Trial Research Group participants. SI indicates special intervention; UC, usual care; S_1, first screening visit.

Table 2.—Mean Risk Factor Levels at Screening and Annual Visits for MRFIT SI and UC Men*

	Screening		Annual Visits, mo					
	S_1	S_2/S_3	12	24	36	48	60	72
			Diastolic BP, mm Hg†					
SI	99.2	91.0‡	84.7	82.5	82.0	81.6	81.2	80.5
UC	99.2	90.9‡	88.4	86.9	86.3	85.6	84.6	83.6
			Reported Cigarette Smoking, %					
SI	63.8	59.3	35.9	35.2	35.1	33.9	32.6	32.3
UC	63.5	59.0	55.6	52.2	50.5	48.2	46.7	45.6
			Serum Cholesterol, mg/dL§					
SI	253.8	...	238.4	238.2	236.9	235.4	234.9	235.5
UC	253.5	...	246.8	246.0	244.2	243.4	240.6	240.3
			Plasma Cholesterol, mg/dL§					
SI	...	240.3	...	229.9	228.1	227.2	226.6	226.2
UC	...	240.6	...	237.2	235.1	234.7	232.3	233.1
			Plasma LDL Cholesterol, mg/dL					
SI	...	159.8	...	150.7	...	148.1	...	148.7
UC	...	160.3	...	157.3	...	154.5	...	152.9
			Plasma HDL Cholesterol, mg/dL					
SI	...	42.0	...	42.8	...	42.8	...	41.7
UC	...	42.1	...	43.3	...	43.0	...	41.9
			No. of Participants at Each Visit					
SI	6,428	6,428	6,112	5,995	5,883	5,791	5,682	5,754
UC	6,438	6,438	6,080	5,919	5,793	5,711	5,615	5,639

*MRFIT indicates Multiple Risk Factor Intervention Trial Research Group; SI, special intervention; UC, usual care; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

†All readings except S_1 are by the random-zero manometer.

‡The average of S_2 and S_3 BP readings is defined as baseline and given here.

§Both serum and plasma cholesterol level determinations were made; the latter were consistently lower as reported by others.[33]

Table 3.—Number of Deaths and Cumulative Mortality (per 1,000) by Year of Follow-up for MRFIT SI and UC Men*

	No. of Deaths						Cumulative Mortality, Deaths per 1,000 Men					
	CHD		CVD		All Causes		CHD		CVD		All Causes	
Year	SI	UC	SI	UC	SI	UC	SI	UC	SI	UC	SI	UC
1	11	9	14	10	19	17	1.7	1.4	2.2	1.6	3.0	2.6
2	11	20	14	23	22	31	3.4	4.5	4.4	5.1	6.4	7.5
3	16	18	17	20	29	37	5.9	7.3	7.0	8.2	10.9	13.2
4	16	16	18	18	34	39	8.4	9.8	9.8	11.1	16.2	19.3
5	21	15	25	19	52	41	11.7	12.2	13.8	14.0	24.3	25.6
6	17	26	24	33	55	54	14.4	16.3	17.5	19.2	32.8	34.0
6-yr Total†	92	104	112	123	211	219	...	...	...	...	...	...
As of 2/28/82‡	115	124	138	145	265	260	17.9	19.3	21.5	22.5	41.2	40.4

*MRFIT indicates Multiple Risk Factor Intervention Trial Research Group; SI, special intervention; UC, usual care; CHD, coronary heart disease; CVD, cardiovascular disease.

†All men had at least six years of follow-up.

‡Mortality rates as of Feb 28, 1982, the last day of follow-up for all men, are simple proportions; for years 1 through 6, life table rates are given.

Table 4.—Frequency Distribution of Deaths by Cause for MRFIT SI and UC Men*

	Special Intervention		Usual Care	
Cause of Death	n	% of Total	n	% of Total
Coronary heart disease (CHD)	115	43.4	124	47.7
Myocardial infarction (MI)†	38	14.3	35	13.5
Sudden death (without documented MI)				
Within 60 min of being seen alive	54	20.4	58	21.5
Within 24 hr, but more than 60 min of being seen alive	18	6.8	25	9.6
Congestive heart failure due to CHD‡	1	0.4	4	1.5
Coronary surgery death§	4	1.5	4	1.5
Other cardiovascular disease	23	8.7	21	8.1
Stroke	13	4.9	11	4.2
Hypertension with left ventricular failure	0	0.0	1	0.4
Pulmonary embolus	3	1.1	3	1.2
Other	7	2.6	6	2.3
Noncardiovascular disease	116	43.8	109	41.9
Neoplasia	81	30.6	69	26.5
Lung	34	...	28	...
Colorectal	8	...	6	...
Other GI	20	...	11	...
Other	19	...	24	...
Liver disease	4	1.5	4	1.5
Lung disease	2	0.8	2	0.8
Suicide	7	2.6	8	3.1
Homicide	5	1.9	5	1.9
Accident	10	3.8	14	5.4
Other	7	2.6	7	2.7
Unknown cause of death	11	4.2	6	2.3
Total	**265**	**100.0**	**260**	**100.0**

*MRFIT indicates Multiple Risk Factor Intervention Trial Research Group; SI, special intervention; UC, usual care; GI, gastrointestinal tract.

†Myocardial infarction, documented by clinical or autopsy evidence, with death occurring within 30 days of onset of symptoms or during hospitalization for acute MI.

‡Without documented MI.

§Death from hospitalization for surgery for coronary heart disease or from complications of such an operation.

thiocyanate-adjusted quit rates for the 22 centers ranged from 5% to 24%.

Mean plasma cholesterol level at S_2 (relatively free of regression to the mean because, unlike the cholesterol level at S_1, it was not used as an eligibility criterion to select men at high risk) was 240 mg/dL. After two years there were reductions of 10.4 mg/dL for SI men and 3.4 mg/dL for UC men; after six years the mean levels were 12.1 mg/dL and 7.5 mg/dL below baseline for SI and UC men, respectively. These reductions, which primarily represent changes in low-density lipoprotein (LDL)-cholesterol and not high-density lipoprotein (HDL)-cholesterol (Table 2), amount to an SI-UC difference in total cholesterol of 4.6 mg/dL, or 2%. With the less-than-anticipated reduction among SI men and the unexpected decline among UC men, the SI-UC difference was about 50% of goal. Differences among the 22 centers in mean plasma cholesterol levels varied from −1.6 to 10.4 mg/dL at 72 months.

Several approaches were used to estimate the combined risk factor reductions. Incorporating the observed changes for the three risk factors into an expression for the relative odds (SI/UC) of CHD death using a Framingham risk function yielded an estimated relative odds 30% short of goal at 12 months, 10% short at 48 months, and nominally at goal at 72 months. This convergence to design goal largely reflects the design prediction of larger initial differentials followed by increasingly poor adherence, whereas the data show long-term maintenance of more modest initial differences. An analysis based on averaging calculated CHD risks for each participant over the six years of follow-up, indicated a potential net CHD mortality lowering of 22.2% rather than the 26.6% considered possible at the design stage; thus, this computation implies achievement of 83% of the SI-UC risk factor difference initially assumed in the design.

Mortality, All SI and UC Participants

As of Feb 28, 1982, after an average period of follow-up of seven years, there were 260 deaths among UC men, of which 124 were ascribed to CHD and 145 to cardiovascular causes (including CHD). Of 265 SI deaths, 115 were ascribed to CHD and 138 to CVD (Tables 3 and 4). The key mortality endpoints of CHD and CVD were 7.1% and 4.7% less, respectively, in the SI compared with the UC group, while the death rate for all causes was 2.1% higher for the SI men. The corresponding life table (log rank) Z values for the endpoints are

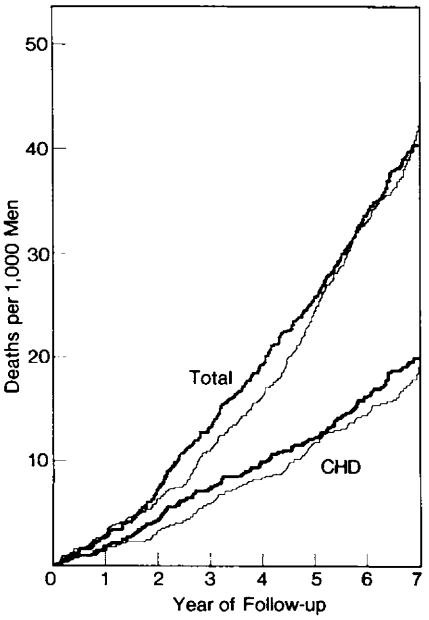

Fig 2.—Cumulative coronary heart disease (CHD) and total mortality rates for Multiple Risk Factor Intervention Trial Research Group participants. Heavy line indicates men receiving usual care (UC); thin line, men receiving special intervention (SI). Number of men alive with follow-up of seven years or longer: 3,117 UC and 3,118 SI.

Table 5.—Number of CHD and Total Deaths and Mortality Rate (per 1,000) by Baseline Risk Factor Levels*

	No. of Participants		CHD Deaths		Total Deaths	
	SI	UC	SI	UC	SI	UC
Nonhypertensive†						
Nonsmokers at S, Serum cholesterol						
<250 mg/dL	102	128	1(9.8)	1(7.8)	3(29.4)	2(15.6)
≥250 mg/dL	415	432	3(7.2)	4(9.3)	5(12.0)	6(13.9)
Smokers at S, Serum cholesterol						
<250 mg/dL	846	844	16(18.9)	11(13.0)	36(42.6)	30(35.5)
≥250 mg/dL	1,046	1,041	15(14.3)	29(27.9)	47(44.9)	53(50.9)
Hypertensive‡						
Nonsmokers at S, Serum cholesterol						
<250 mg/dL	620	627	2(3.2)	11(17.5)	14(22.6)	25(39.9)
≥250 mg/dL	1,188	1,160	23(19.4)	19(16.4)	42(35.4)	37(31.9)
Smokers at S, Serum cholesterol						
<250 mg/dL	1,388	1,369	30(21.6)	28(20.5)	68(49.0)	66(48.2)
≥250 mg/dL	823	837	25(30.4)	21(25.1)	50(60.8)	41(49.0)
Subtotals						
Nonhypertensive	2,409	2,445	35(14.5)	45(18.4)	91(37.8)	91(37.2)
Hypertensive	4,019	3,993	80(19.9)	79(19.8)	174(43.3)	169(42.3)
Serum cholesterol						
<250 mg/dL	2,956	2,968	49(16.6)	51(17.2)	121(40.9)	123(41.4)
≥250 mg/dL	3,472	3,470	66(19.0)	73(21.0)	144(41.5)	137(39.5)
Nonsmokers at S,	2,325	2,347	29(12.5)	35(14.9)	64(27.5)	70(29.8)
Smokers at S,	4,103	4,091	86(21.0)	89(21.8)	201(49.0)	190(46.4)
Total	6,428	6,438	115(17.9)	124(19.3)	265(41.2)	260(40.4)

*For Multiple Risk Factor Intervention Trial Research Group participants. SI indicates special intervention; UC, usual care; CHD, coronary heart disease.

†Baseline diastolic BP (average of two R-Z readings at S_2 and S_3) less than 90 mm Hg and not receiving antihypertensive treatment at S_2.

‡Baseline diastolic BP ≥90 mm Hg or receiving antihypertensive treatment at S_2.

Table 6.—Number of CHD and Total Deaths and Mortality Rate (per 1,000) by Hypertensive Status at Baseline*

	No. of Participants		CHD Deaths		Total Deaths	
	SI	UC	SI	UC	SI	UC
Nonhypertensive†	2,409	2,445	35(14.5)	45(18.4)	91(37.8)	91(37.2)
Hypertensive‡	4,019	3,993	80(19.9)	79(19.8)	174(43.3)	169(42.3)
Receiving treatment at S_2	1,261	1,227	28(22.2)	26(21.2)	59(46.8)	54(44.0)
Not receiving treatment at S_2, mm Hg						
90-94§	1,157	1,181	17(14.7)	12(10.2)	47(40.6)	31(26.2)
95-99§	830	846	19(22.9)	19(22.5)	43(51.8)	39(46.1)
≥100§	771	739	16(20.8)	22(29.8)	25(32.4)	45(60.9)
Total	6,428	6,438	115(17.9)	124(19.3)	265(41.2)	260(40.4)

*For Multiple Risk Factor Intervention Trial Research Group participants. SI indicates special intervention; UC, usual care; CHD, coronary heart disease.

†Baseline diastolic BP (average of two R-Z readings at S_2 and S_3) less than 90 mm Hg and not receiving antihypertensive treatment at S_2.

‡Baseline diastolic BP ≥90 mm Hg or receiving antihypertensive treatment at S_2.

§Baseline diastolic BP.

+0.6, +0.4, and −0.2. None of these is statistically significant. A slight mortality advantage of the SI group, as shown by the separation of the cumulative mortality curves beginning at about two years, waned by year 5 (Fig 2). Of the 22 clinical centers, 11 had more CHD deaths among UC men than among SI; for total mortality, ten centers had more UC than SI deaths.

The number of deaths from noncardiovascular causes was also similar in the two groups (116 SI *v* 109 UC). There were 81 cancer deaths in the SI group and 69 in the UC, resulting from lung cancer (34 SI *v* 28 UC), colorectal cancer (8 SI *v* 6 UC), other gastrointestinal neoplasms (20 SI *v* 11 UC), and other neoplasia (19 SI *v* 24 UC).

The number of deaths in the UC group was substantially short of expectation for the six complete years of follow-up as well as for the average follow-up period of seven years. Based on design risk factor change assumptions and Framingham risk functions, 442 deaths (including 187 from CHD) were expected by the end of six years of follow-up among the 6,438 UC men; only 219 (including 104 from CHD) occurred. By the end of follow-up for all men, the total of 260 UC deaths (including 124 from CHD) was still well below the number expected for the six-year follow-up period. The approximate 90% CI for the percentage change in CHD mortality attributable to MRFIT intervention is therefore large, ranging from a 25% decrease to a 15% increase.

Mortality in Baseline-Defined Subgroups

Comparisons of mortality rates for SI and UC men within subgroups defined by prerandomization characteristics preserve the comparability provided by the randomization but

Table 7.—Number of CHD and Total Deaths and Mortality Rate (per 1,000) by Hypertensive Status at Baseline and by Presence of Resting ECG Abnormalities*

	No. of Participants		CHD Deaths		Total Deaths	
	SI	UC	SI	UC	SI	UC
Nonhypertensive						
Resting ECG abnormalities†						
Absent	1,817	1,862	24(13.2)	30(16.1)	71(39.1)	63(33.8)
Present	592	583	11(18.6)	15(25.7)	20(33.8)	28(48.0)
Total	2,409	2,445	35(14.5)	45(18.4)	91(37.8)	91(37.2)
Hypertensive						
Resting ECG abnormalities†						
Absent	2,785	2,808	44(15.8)	58(20.7)	100(35.9)	122(43.4)
Present	1,233	1,185	36(29.2)	21(17.7)	74(60.0)	47(39.7)
Total	4,018	3,993	80(19.9)	79(19.8)	174(43.3)	169(42.3)

*For Multiple Risk Factor Intervention Trial Research Group participants. SI indicates special intervention; UC, usual care; MC, Minnesota Code.

†Abnormalities include high R waves in the precordial leads (MC, 3.1,3.3,3.4; N=1,410), negative T waves (MC, 5.1-5.3; N=511); R-R′ pattern (MC, 7.5; N=488); ectopic ventricular premature beats (MC, 8.1; N=452); left axis deviation ≤−30°. (N=380); incomplete RBBB (MC, 7.3; N=359); ST depression (MC, 4.1-4.3; N=237); ST elevation (MC, 9.2; N=240); major Q waves (MC, 1.1-1.3; N=184); short P-R (MC, 6.5; N=109); first degree atrioventricular block (MC, 6.3; N=66); supraventricular tachycardia (MC, 8.4; N=38); right axis deviation ≥+120° (N=17); and other rare conditions (N=36).[34]

Table 8.—Number of CHD and Total Deaths and Mortality Rate (per 1,000) by Baseline Risk Factor Levels for the Subgroup of MRFIT SI and UC Participants Without Resting ECG Abnormalities at Entry*

	No. of Participants		CHD Deaths		Total Deaths	
	SI	UC	SI	UC	SI	UC
Nonhypertensive†						
Nonsmokers at S, Serum cholesterol						
<250 mg/dL	78	93	1(12.8)	1(10.8)	3(38.5)	2(21.5)
≥250 mg/dL	324	340	1(3.1)	3(8.8)	3(9.3)	3(8.8)
Smokers at S, Serum cholesterol						
<250 mg/dL	616	635	11(17.9)	8(12.6)	28(45.5)	21(33.1)
≥250 mg/dL	799	794	11(13.8)	18(22.7)	37(46.3)	37(46.6)
Hypertensive†						
Nonsmokers at S, Serum cholesterol						
<250 mg/dL	439	445	1(2.3)	7(15.7)	9(20.5)	17(38.2)
≥250 mg/dL	851	852	13(15.3)	15(17.6)	23(27.0)	27(31.7)
Smokers at S, Serum cholesterol						
<250 mg/dL	928	922	21(22.6)	21(22.8)	45(48.5)	49(53.1)
≥250 mg/dL	567	589	9(15.9)	15(25.5)	23(40.6)	29(49.2)
Subtotals						
Nonhypertensive	1,817	1,862	24(13.2)	30(16.1)	71(39.1)	63(33.8)
Hypertensive	2,785	2,808	44(15.8)	58(20.7)	100(35.9)	122(43.4)
Serum cholesterol						
<250 mg/dL	2,061	2,095	34(16.5)	37(17.7)	85(41.2)	89(42.5)
≥250 mg/dL	2,541	2,575	34(13.4)	51(19.8)	86(33.8)	96(37.3)
Nonsmokers at S,	1,692	1,730	16(9.5)	26(15.0)	38(22.5)	49(28.3)
Smokers at S,	2,910	2,940	52(17.9)	62(21.1)	133(45.7)	136(46.3)
Total	4,602	4,670	68(14.8)	88(18.8)	171(37.2)	185(39.6)

*MRFIT indicates Multiple Risk Factor Intervention Trial Research Group; SI, special intervention; UC, usual care; CHD, coronary heart disease.

†Baseline diastolic BP (average of two R-Z readings at S_2 and S_3) less than 90 mm Hg and not receiving antihypertensive treatment at S_2.

‡Baseline diastolic BP ≥90 mm Hg or receiving antihypertensive treatment at S_2.

have less precision as a result of the reduced sizes of the groups. There is also the increased likelihood of over-interpreting nominally significant differences resulting from the examination of multiple comparisons, some of which were defined post hoc. However, the subgroup findings need exploration, especially to provide insight into the overall result and to indicate areas for further investigation.

The relationship of mortality to baseline levels of the three risk factors is shown in Table 5, where numbers of deaths by cause together with corresponding mortality rates are given for SI and UC men. The mortality rates for smokers, for hypercholesterolemic (≥250 mg/dL) and for hypertensive men are given as subtotals in the lower rows. For each of these three groups, the mortality rates are similar for SI and UC men. However, it must be remembered that subgroups defined by the presence or absence of one of the three major risk factors are not otherwise comparable; for example, because of the selection procedure used, nonsmokers have on the average higher blood cholesterol and BP levels than smokers. Despite this complexity, it may be noted in the subtotals that CHD mortality, and in most cases total mortality, tends to be higher in smokers, in participants with hypercholesterolemia, and in those with hypertension, supporting the risk factor status of these variables within this cohort.

Among the group of all nonhypertensive men at baseline, there was a 21% lower CHD death rate (CI, −22% to 50%) for the SI group compared with UC men, but no comparable difference in deaths from all causes. Of the four substrata of men not hypertensive at baseline, the largest, consisting of cigarette smokers who were hypercholesterolemic, is of particular interest for its resemblance to the group of men in the Oslo primary prevention trial that recently reported positive findings (see Comment). The CHD mortality rate is 49% lower (CI, 8% to 75%) for the SI group compared with the UC group (15 SI deaths *v* 29 UC deaths), with a smaller difference observed for total mortality. Given the presence of both cigarette smoking and hypercholesterolemia, BP levels of men in this substratum of those not hypertensive at baseline were lower than those for the other three substrata, as a result of the risk-selection criteria; consequently, a relatively small percentage of the SI men in this substratum subsequently became hypertensive and received antihypertensive treatment.

Of the four substrata of hypertensive men, only in the smallest, consisting of nonsmokers who were not

hypercholesterolemic, was the CHD rate lower for SI men. With only one of the three risk factors present, this group, to meet the MRFIT risk-eligibility criteria, was necessarily made up of men with more severe degrees of hypertension.

A more detailed breakdown by hypertensive status at entry is given in Table 6. Among hypertensive men not receiving treatment at entry, the differences in SI and UC CHD and total mortality rates differ by level of baseline diastolic BP. The percentage differences in CHD mortality rates are −45% (17 SI CHD deaths *v* 12 UC), −2% (19 SI CHD deaths *v* 19 UC), and +30% (16 SI CHD deaths *v* 22 UC), respectively, for participants with baseline diastolic BP levels of 90 to 94, 95 to 99, and 100 mm Hg or higher. The corresponding differences for total mortality are −55% (47 SI deaths *v* 31 UC), −12% (43 SI deaths *v* 39 UC), and +47% (25 SI deaths *v* 45 UC).

Analyses related to one of the formal subgroup hypotheses (see Methods) suggested a possible explanation for the results observed in hypertensive men. Abnormalities on the baseline resting ECG seemed to be associated with an excess of CHD mortality in the SI compared with the UC group, with the effect limited to hypertensive persons (Table 7). For the group of hypertensive men without ECG abnormalities, a 24% lower death rate was noted in the SI group (44 SI CHD deaths *v* 58 UC). This difference is similar to the 21% found for normotensive men with or without ECG abnormalities (35 SI CHD deaths *v* 45 UC). For the group of hypertensive men with ECG abnormalities, there were 15 more SI deaths than UC (36 SI CHD deaths *v* 21 UC). This percentage difference (−65%) is larger than, and in the opposite direction from, the corresponding difference for hypertensive men without ECG abnormalities. Similar findings, though not as pronounced, are found for total mortality (Table 7).

With this possibility that participants with abnormal ECG at baseline reponded adversely to MRFIT intervention, the mortality results are retabulated by baseline risk factors for the 72% of men with a normal baseline resting ECG (Table 8). Such analyses are complicated because of the previously mentioned reciprocal and overlapping relationships of risk factor levels among the participants. For each subgroup listed in the lower half of Table 8, the SI men experienced fewer CHD deaths than did the corresponding UC group. A comparison of the results in Table 8 for men without ECG abnormalities at baseline with those for the total cohort in Table 5 reveals that for nearly all risk factor combinations there were fewer SI CHD deaths than UC for this large subgroup. There is a difference in CHD mortality of 24% (CI, −13% to 49%) for hypertensives without ECG abnormalities, and a 32% difference (CI, −3% to 57%) for those with cholesterol levels of 250 mg/dL or higher and without ECG abnormalities. The lower CHD mortality for SI compared with UC men in these subgroups, consisting of a large majority of the total MRFIT cohort, is similar to the mortality reduction expected based on the design of the trial.

Table 9.—Number of CHD and Total Deaths and Mortality Rate (per 1,000) for Smokers at Entry S, by Smoking Status at 12 Months and Amount Smoked at Entry*

	No. of Participants		CHD Deaths		Total Deaths	
	Quit†	Did Not Quit	Quit†	Did Not Quit	Quit†	Did Not Quit
Special intervention						
1-29 cigarettes/day Reported at S_1	454	806	6(13.2)	19(23.6)	13(28.6)	34(42.2)
≥30 cigarettes/day Reported at S_1	537	2,036	5(9.3)	39(19.2)	16(29.8)	99(48.6)
Usual care						
1-29 cigarettes/day Reported at S_1	159	1,021	3(18.9)	23(22.5)	8(50.3)	44(43.1)
≥30 cigarettes/day Reported at S_1	215	2,435	1(4.7)	47(19.3)	7(32.6)	101(41.5)

*For Multiple Risk Factor Intervention Trial Research Group participants. CHD indicates coronary heart disease. Deaths during the first year of follow-up are excluded.

†Quitters are S_1 smokers who reported quitting at 12 months with serum thiocyanate levels (at 12 months) lower than 100 μmole/L.

Mortality in Subgroups Defined After Randomization

Since the smoking intervention was the most successful relative to the risk factor design goals, yet the CHD mortality differences between SI and UC men who had been smokers at baseline were modest (Tables 5 and 8), the relationship between smoking cessation and mortality was examined further. In men who quit smoking during the first year, subsequent death rates were compared with the rates in those who continued to smoke, controlling for the reported number of cigarettes per day at baseline (Table 9). It must be emphasized that this kind of analysis does not preserve the randomized controlled design of the MRFIT, and must be interpreted with regard for the possibility of confounding by many factors. In both the SI and the UC groups, those who quit smoking had significantly lower rates of CHD and, for the most part, total mortality. Multivariate analyses controlling for critical variables, including the other major risk factors, have consistently supported the relationship between smoking cessation and CHD mortality.

COMMENT

Strengths and Limitations of the Data

This large and complex trial was operationally successful. The recruitment phase was completed in a 28-month period and, in numbers recruited, exceeded the design goal. Randomization proceeded without incident, the two randomized groups being well balanced on numerous relevant characteristics. The completeness of follow-up exceeded expectations, with 91% of those alive returning for the sixth annual visit. For mortality endpoints, requirements of thorough documentation of all deaths and "blinded" classification of causes of death were met.

Intervention accomplishments in the SI group, which have been reported in detail,[6,9] were substantial: smoking cessation was much more successful than had been expected, the BP reduction in the SI group exceeded the desired drop in diastolic BP, and the effect on cholesterol lowering was considerable but less

than had been sought. A notable achievement of the intervention program was a continued decline in mean risk factor levels after the substantial drop in the first year.

Risk factor changes were also observed in the UC group, though to a lesser degree. Whereas it had been projected on the basis of the best information available ten years ago that this group would exhibit over six years no important changes in BP and serum cholesterol levels, and only minimal change in smoking habits, the actual findings were very different. Sizable reductions occurred in the levels of all three risk factors for UC men. Thus, over six years, reported cigarette smoking declined from 59% to 46%, the diastolic BP from a baseline value of 90.9 to 83.6 mm Hg, and plasma cholesterol levels from 241 to 233 mg/dL. Also, 47% of the UC men were receiving antihypertensive medication at the end of the sixth year compared with 19% at baseline.

The cause of these unanticipated changes in the UC group is speculative. Contributing elements to the risk factor reductions may include the psychological impact on the UC men of enrollment in a trial limited to persons at high risk of heart attacks, the possibility that persons volunteering for a six-year trial are unusually health conscious and motivated to change, sensitization of the UC men to their risk factor status resulting from annual visits to the clinical centers, and the broad influence of health education in the United States aimed at modifying all of the three risk factors. The physicians of the UC men may well have instituted their own preventive programs. Ethical considerations prompted notification of these physicians of the findings from each annual visit, although the MRFIT centers made no recommendation regarding intervention for UC men.

The risk factor changes in the UC group may be relevant to one of the assumptions on which the power of the trial was based and that has been shown to be inaccurate. The number of deaths in the UC group was substantially short of expectation. By the end of follow-up (an average of 7.0 years) for all men, the total of 260 UC deaths (including 124 from CHD) was still slightly less than two thirds the number expected for the six-year follow-up period.

Several factors may have contributed to the lower-than-expected UC mortality: (1) the recent reduction in CHD mortality in the United States, the reasons for which are still not totally understood[19]; (2) exclusion criteria applied to the MRFIT screened group that may have been more stringent than those applied to data from the Framingham cohort during the design phase of MRFIT, resulting in the selection of men with a lower than expected mortality in both the SI and UC groups; (3) the phenomenon of lower-than-expected mortality in almost all clinical trials involving human volunteers; and (4) finally, the substantial risk factor changes made by UC men, as mentioned previously. The latter possibility can be entertained only if one assumes that risk-factor modification is effective in reducing mortality in high-risk men aged 35 to 57 years, the question the trial was designed to test.

The lower-than-predicted mortality for the UC group has the important effect of lowering the power from .88 to .75 for detecting the 26.6% SI-UC difference in mortality specified in the design. Furthermore, if the risk model based on Framingham data were accurate in predicting potential risk reduction, the unexpected decreases in UC risk-factor levels would also affect the power unfavorably. The power, based on the observed UC mortality rate, for detecting the 22% difference in CHD mortality predicted by the risk factor difference actually achieved, is about 0.6.

Interpretation of Mortality Results

The finding of percentage differences of only +7%, +5%, and −2% for CHD, CVD, and all-cause mortality rates, respectively, deserves careful examination. At least three possible explanations for these results must be considered: (1) such an intervention program is without benefit in terms of substantial decreases in mortality; (2) the intervention program does affect CHD mortality, but the benefit was not observed in this study; or (3) one or more constituents in the intervention program may have had an unfavorable effect on survival in some subgroups offsetting beneficial effects of others.

The first possibility, of ineffectiveness on CHD, CVD, and total mortality of programs to reduce cigarette smoking, treat hypertension with drugs, and lower elevated serum cholesterol levels by diet, seems inconsistent with most published scientific data: clinical, pathological, animal experimental, and epidemiologic.[19] The trial was of course initiated to test this question in high-risk middle-aged men. Only one controlled trial limited solely to testing the benefit of reduction in or cessation of cigarette smoking has been executed; its results were inconclusive, but showed a favorable trend for CHD mortality.[20] A large body of scientific data supports the conclusion that cigarette smokers who reduce the amount of smoking or give it up entirely have improved life expectancy.[21] It is not clear, however, how long it takes after modification of smoking—especially heavy smoking—for favorable alterations of mortality rates to occur, and it may take longer than the seven-year duration of this trial to be clearly demonstrated.[22] Somewhat contrary to the possibility of a delayed effect is the observation that CHD mortality within the SI group subsequent to the first year of follow-up diverges sharply depending on smoking status at the 12-month visit. The rate in quitters who had smoked at least 30 cigarettes per day is approximately half that of those who continue smoking. Such within-group analyses, however, do not make use of the randomized control design of a clinical trial, and the results, while suggestive, leave open the possibility of confounding by other factors.

Regarding hypertension, a beneficial impact of drug treatment by a "stepped-care" protocol, as contrasted with "referred care," on total mortality has been described in a population of 10,940 men and women by the Hypertension Detection and Follow-up Program (HDFP).[23] For persons in the age group 30 to 49 years at entry, the difference in total mortality was 5.7%; for persons aged 50 to 59 years it was 25.3%.[24] The Australian National Blood Pressure Study, a placebo-controlled primary prevention trial in 3,427 men and women with mild hypertension, reported significantly fewer morbid and fatal events, including significantly fewer deaths from cardiovascular disease, in persons aged 30 to 69 years

who were treated with antihypertensive medication, but the corresponding percentage difference for all endpoints in the subgroup of men aged 30 to 49 years, though similar in magnitude, lacked statistical significance.[25] The earlier classic report from the Veterans Administration Cooperative Study concluded that treatment was effective in preventing congestive heart failure and stroke, but no statistically significant benefit for CHD mortality (six in the treated group, 11 in the placebo group) was found.[26]

In the area of lipid-lowering diet, some controversy has existed for years as to precise benefits, although most scientific including public health groups have concluded that benefits do indeed exist.[27-29] For example, the Los Angeles Veterans Administration Study, in a population of 846 institutionalized men aged 55 years and older, demonstrated significant reduction in mortality from atherosclerotic diseases, but not in total mortality.[30] The recently concluded Oslo trial in 1,232 high-risk nonhypertensive men aged 40 to 49 years combining lipid-lowering dietary intervention with smoking cessation showed statistically significant reductions in sudden coronary death and in CHD incidence, and substantial, though nonsignificant, reductions in CHD and total mortality. In the Oslo study, differential quit rates for cigarette smoking were less than those achieved in the MRFIT, but serum cholesterol differences were appreciably greater.[31] An overall impression from this partial review, particularly of recent clinical trials, is that the interventions used in the MRFIT would be expected to have a beneficial effect. However, sufficient differences from MRFIT exist in study design and related factors that firm conclusions are not possible.

The second possible explanation for the nonsignificant mortality outcome in the MRFIT is that the hypothesis received a less than definitive test, and the observed differences in mortality represent chance deviations from a larger effect that this intervention program has in the population. We have noted earlier that the power of the trial was lower than projected. One way to consider this problem, now that the trial has been completed, is through the 90% CI for CHD mortality. This ranged from a favorable effect of 25% to a harmful effect of 15%, an interval that includes the 22% benefit projected from the observed risk factor changes. A related approach is to compute the probability of observing a CHD mortality rate differential of 7.1% or less, given the observed mortality rate in the UC (19.3 deaths per 1,000) and the mortality reduction projected from the observed risk factor reduction (22%). This probability is .12, indicating that the observed result is not inconsistent with a hypothesized 22% mortality differential; however, it suggests that an effect of this magnitude is unlikely.

The third possible explanation, that some aspect of the intervention program has a deleterious effect on mortality in some subgroups, has been extensively investigated. Thus, we observed that the men who stopped smoking cigarettes were considerably less successful in weight control than were men who continued to smoke,[8] yet against any important negative influence was the finding that weight reduction was greater, overall, for SI than UC men.[7] Also, diuretics seem to increase the level of plasma cholesterol, and men who took such drugs (including nearly all hypertensive men in the SI group) had a blunting of the dietary hypocholesterolemic effect such that they achieved only about half of the cholesterol-lowering seen in men not receiving these drugs and a modest elevation of plasma triglyceride levels.[32] While it might be reasonable to conclude that a lessened lipid-lowering might mean a lessened improvement in CHD, CVD, and total mortality, one could hardly conclude that this effect actually increased mortality.

Another possibility, namely, that other aspects of drugs used in the treatment of hypertension in MRFIT contributed to an increased mortality, was explored. It was noted that among those hypertensive at baseline (and therefore most likely to have antihypertensive drug therapy), intervention did not result in an appreciable difference in number of deaths from CHD in the two groups (80 SI deaths and 79 UC deaths). When examined further, it seemed that the largest percentage increase in CHD mortality for SI compared with UC occurred in men with hypertension at entry whose baseline resting ECGs showed signs of abnormalities. These findings are not conclusive, but the possibility that the use of pharmacologic therapy in these subgroups is associated with an increased CHD mortality warrants further investigation.

In some contrast with the ambiguous but disquieting results in those with hypertension are the findings in other subgroups. Here again, we mention that such subgroup data are cited with awareness of their limitations and to indicate trends and avenues for future study. Among those not hypertensive at baseline, but of course possessing other risk factors, there were 35 deaths from CHD in the SI men and 45 deaths in the UC group. Furthermore, examination of the mortality data for men with serum cholesterol values of 250 mg/dL or more at the first screening visit, but without hypertension, revealed 18 deaths from CHD in the SI group and 33 in the UC group. Similarly, among those who were cigarette smokers at baseline but were not hypertensive, there were 31 coronary deaths in the SI category and 40 among the UC men. There is therefore a pattern, at least for CHD mortality, suggesting that among those MRFIT men free of hypertension at baseline, life-style changes may result in favorable reductions in mortality.

Thus, of the possible interpretations of the mortality results, the last discussed—a combination of favorable and unfavorable effects of the intervention program—seems most plausible. Even with the unexpected sizable risk factor reduction among the UC men, the lower-than-expected UC mortality, and the duration of intervention averaging only seven years, the likelihood that these factors resulted in missing an overall positive effect is relatively low. The data suggest that, except for some groups of hypertensive persons, particularly those with resting ECG abnormalities, the MRFIT intervention is apparently associated with a lower CHD mortality in the SI group.

CONCLUSION

In conclusion, we have shown that it is possible to apply an intensive long-term intervention program against three coronary risk factors with considerable success in terms of

risk factor changes. The overall results do not show a beneficial effect on CHD or total mortality from this multifactor intervention. These results are accompanied by an apparent heterogeneity of effects among sizable subgroups, but there must be caution in reaching conclusions from such subgroup data. It may be relevant that multifactor intervention received a less than optimal test owing, in part, to unexpected declines in risk factor levels and, in part, to lower-than-expected mortality in the UC group. In regard to the former, the UC men thus constituted to a considerable extent a "treated" group.

The SI-UC comparisons indicate that among men with normal baseline ECGs, the MRFIT intervention program may have had a favorable effect on CHD mortality. The data also suggest that men with hypertension, primarily those with resting ECG abnormalities, had no favorable, and possibly an unfavorable response to intervention. More study is required to clarify this issue and its possible relation to antihypertensive treatment. Findings also include the within-group observation that men who stopped cigarette smoking had lower CHD and total mortality than those who continued to smoke.

The results of this trial do not address the possible effects of risk-factor intervention carried out over time periods of a decade or more or those begun before middle age. Future publications will address the morbidity results of the trial, subgroup hypotheses, and the role of other major variables.

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