Test of Effect of Lipid Lowering by Diet on Cardiovascular Risk

The Minnesota Coronary Survey

Ivan D. Frantz Jr., Emily A. Dawson, Patricia L. Ashman, Laël C. Gatewood, Glenn E. Bartsch, Kanta Kuba, and Elizabeth R. Brewer

The Minnesota Coronary Survey was a 4.5-year, open enrollment, single end-time, double-blind, randomized clinical trial that was conducted in six Minnesota state mental hospitals and one nursing home. It involved 4393 institutionalized men and 4664 institutionalized women. The trial compared the effects of a 39% fat control diet (18% saturated fat, 5% polyunsaturated fat, 16% monounsaturated fat, 446 mg dietary cholesterol per day) with a 38% fat treatment diet (9% saturated fat, 15% polyunsaturated fat, 14% monounsaturated fat, 166 mg dietary cholesterol per day) on serum cholesterol levels and the incidence of myocardial infarctions, sudden deaths, and all-cause mortality. The mean duration of time on the diets was 384 days, with 1568 subjects consuming the diet for over 2 years. The mean serum cholesterol level in the pre-admission period was 207 mg/dl, falling to 175 mg/dl in the treatment group and 203 mg/dl in the control group. For the entire study population, no differences between the treatment and control groups were observed for cardiovascular events, cardiovascular deaths, or total mortality. A favorable trend for all these end-points occurred in some younger age groups.
(Arteriosclerosis 9:129–135, January/February 1989)

The institutions chosen for the trial were the Minnesota state mental hospitals at Anoka, Fergus Falls, Hastings, Moose Lake, St. Peter, and Willmar and the nursing home at Oak Terrace. Before initiation of the experimental phase, the populations were observed for a 3-year period, during which their suitability for a long-term dietary trial was studied. The feeding program began in the Willmar State Hospital in November, 1968. The program was phased in to the other institutions in succession over the following 15 months. The trial was an outgrowth of the National Diet-Heart Feasibility Study.[1]

Methods

Ethical Considerations

The project was approved by the Clinical Research Committee of the University and, after extensive discussion with the relevant institutional committees, by each of the collaborating hospitals. No consent forms were required on the grounds that the two diets were both acceptable as house diets and the tests all contributed to better patient care. Before initiation of the study in each hospital, all the residents and staff were invited to a meeting at which the investigators explained the project. Samples of the foods were served at these meetings. There was a question and answer period, and the residents were invited to make appointments for one-to-one further explanations if they wished. They were allowed to decline to participate or to discontinue their participation at any time. Nonparticipants were served the control diet, which was similar to the pre-study institutional diets. Blood was not drawn from nonparticipants, and electrocardiograms were not recorded. Participation was nearly 100% with fewer than a dozen refusals throughout the trial.

Experimental Plan

The original population was initially stratified into 512 cells on the basis of eight variables. These were: age, sex, length of stay in the hospital, weight, blood pressure, diabetes, cigarette smoking, and evidence by electrocardiogram of a previous myocardial infarction. When new subjects were admitted later, they were divided among four cells, based on only age and sex.

Two diets were served. The control diet involved little departure from the institutional diet served before the trial. The treatment diet represented a compromise between the B and C diets of the National Diet-Heart Study, with target values of 45% of calories from fat, a polyunsaturated/saturated fat (P/S) ratio of 2.5, and less than 150 mg of cholesterol daily.

Both diets were served in a single line. As a participant entered the line, he or she was handed a label bearing his or her name and a code number that was incomprehensible to the uninitiated but easily interpreted by the food servers to determine which diet was to be served. A new set of 21 labels was prepared by computer each week for each participant based on changes in the population during that week. The label served multiple purposes.

From the Departments of Medicine, Biometry, and Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, Minnesota.

This work was supported by Grant No. HE 09686 from the National Heart, Lung, and Blood Institute.

Address for reprints: Ivan D. Frantz Jr., M.D., Division of Epidemiology, School of Public Health, University of Minnesota, 611 Beacon Street S.E., Minneapolis, MN 55455.

Received March 25, 1987; revision accepted August 30, 1988.

Table 1. Specification and Values for Experimental Diets Averaged over 4 Years

Diet group	Total fat (% calories)	Saturated fat (% calories)	Polyunsaturated fat (% calories)	Cholesterol (mg/day)	P/S
Specified					
Control	42.4	18.6	4.3	602	0.2
Treatment	44.9	8.0	19.8	137	2.5
Achieved					
Control	39.1	18.3	5.2	446	0.3
Treatment	37.8	9.2	14.7	166	1.6

Analyses of foods were performed by Woodson-Tenent Laboratories, Memphis, Tennessee.
P/S=polyunsaturated/saturated fat ratio.

One was to sound a personal note with the subject, one of the many positive influences which our study had on the hospitals. The label also enabled the food service worker to serve the proper tray without compromising the blind design, and the labels remaining on the sheet provided the basis for the daily tally of missed meals. Each month the hospital technicians transferred the missing meals data to a "Port-o-Punch card." These cards were read by the computer and at the end provided a correlation between adherence and cholesterol response.

Fasting blood was drawn from every patient on admission to the hospital, and at 6-month intervals thereafter. The serum was frozen and analyzed at a later date to avoid doing analyses on patients who remained in the hospital for too short a time to contribute significantly to the results. All sera from all subjects who remained in the study on either diet for at least 1 year, from every subject who died or had a cardiovascular event, and from a set of additional subjects matched on age and sex who did not have an event were analyzed. When a subject left the hospital and then returned, blood for the cholesterol determination was drawn after he had been back on the diet for 3 weeks.

Dietary Procedures

Traditional American foods were used for the control diet, and foods high in polyunsaturated fat and low in saturated fat and cholesterol were used for the experimental diet. Baseline dietary data were obtained by chemical analysis of composites of a 21-day food collection conducted at all hospitals during the pre-diet period. The experimental diet goal was to provide 18% to 20% of calories from polyunsaturated fat, to limit saturates to less than 9%, and to maintain the ratio of polyunsaturated to saturated fats at more than 2:1. Cholesterol was to be as low as could be achieved without sacrificing palatability (150 mg per day or less). Specifications and 4-year average values are shown in Table 1. Figures 1 and 2 are plots of seven hospital averages of the P/S ratio and the dietary cholesterol content, respectively, measured at yearly intervals over a 4-year period. Table 2 shows the content of the diets for some of the more important nutrients and minerals.

Procurement of suitable foods for the treatment diet, (with the desired polyunsaturated fat, which were yet palatable, stable, and indistinguishable from the corresponding components of the control diet) presented a great challenge. It was achieved through cooperation of the study nutritionists, the hospital dietitians, manufacturers of food products, and the Food Inspection Division of the Minnesota Department of Agriculture. Products that proved particularly useful were filled milk and ice cream, a whole egg substitute, soft margarine, whipped topping, filled cheese, low fat ground beef with added vegetable oil, and filled sausage products.

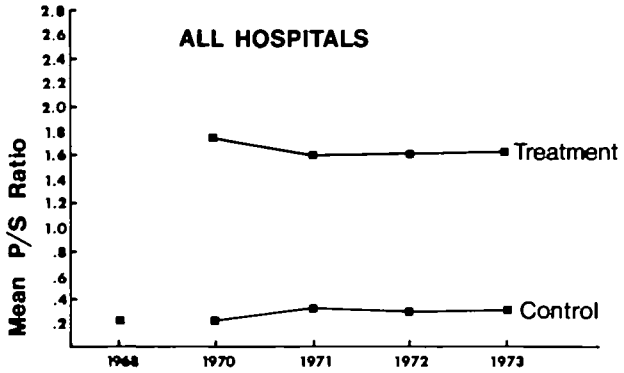

Figure 1. Mean P/S ratio of treatment and control diets. The ratios are averages for all seven hospitals determined by chemical analysis. The point for 1968 is the value for the hospital diets before the intervention trial. P=polyunsaturated fat and S=saturated fat.

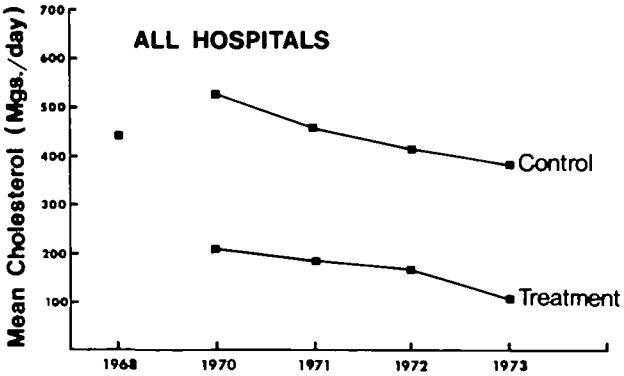

Figure 2. Mean daily cholesterol content (mgs/day) of the treatment and control diets. The values are averages for all seven hospitals determined by chemical analysis. The point for 1968 is the value for the hospital diets before the intervention trial.

Laboratory Methods

Blood was drawn under fasting conditions. The serum was sealed in glass ampules under nitrogen, and stored at −20°C. Analyses were carried out for total cholesterol and triglycerides by the standard protocol of the Lipid Research Clinics.[2] The laboratory was standardized and monitored by the Centers for Disease Control in Atlanta.

Table 2. Comparison of Mean Daily Diet Composition for All Hospitals

Diet Composition	RDA*		Mean for all hospitals†	
	Men	Women	1971	1972
Protein (g)	65	55	97.9	95.7
Calcium (g)	0.8	0.8	1.2	1.2
Iron (mg)	10	18	14.5	15.5
Vitamin A (IU)	5000	5000	8128	7910
Thiamine (mg)	1.3	1.0	1.4	1.5
Riboflavin (mg)	1.7	1.5	2.2	2.3
Niacin equivalents (mg)	17	13	26.3	25.3
Ascorbic acid (mg)	60	55	95.0	84.5

*Recommended Daily Dietary Allowances from the National Research Council, 1968 revision.
†Handbook analysis values are for the control diet. All modified foods (whole egg substitute, filled dairy products, and filled processed meats) were formulated to provide nutrient levels comparable to the standard products.

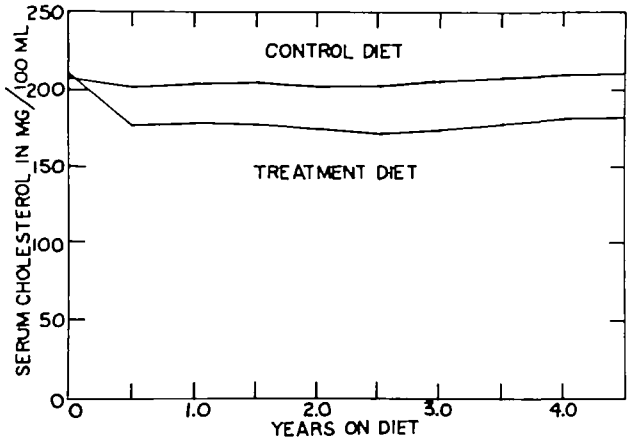

Figure 3. Average serum cholesterol concentrations (mg/100 ml).

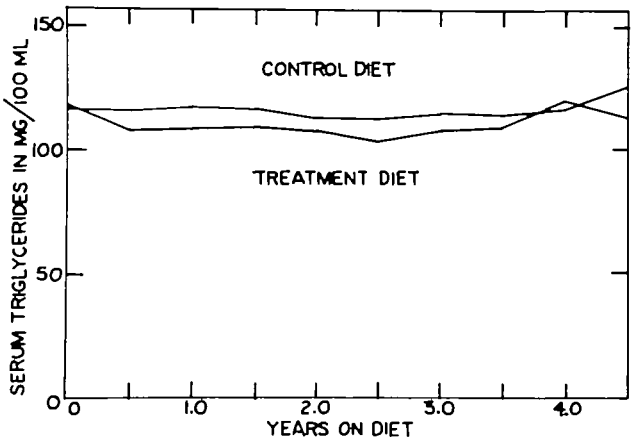

Figure 4. Average serum triglyceride concentrations (mg/100 ml).

Heat-stable lactate dehydrogenase was measured in the laboratory of Paul E. Strandjord.[3]

Electrocardiograms were read by Naip Tuna (Chief of Electrocardiography at the University of Minnesota Hospitals) and also by technicians in the Laboratory of Physiological Hygiene who were supervised by Henry Blackburn. Any discrepancies between the two readings were resolved by consultation between readers. The records were classified according to the Minnesota Code.[4]

Table 3. Total Participants by Age and Sex

Age	Treatment		Control	
	Men	Women	Men	Women
<30	520	410	509	426
30 to 34	194	210	197	157
35 to 39	152	187	147	195
40 to 44	156	211	146	208
45 to 49	138	226	150	236
50 to 54	168	202	163	209
55 to 59	210	221	216	229
60 to 64	198	195	199	180
65 to 69	139	154	147	163
≥70	322	328	322	317
Totals	2197	2344	2196	2320

Ascertainment of Cardiovascular Events

Three electrocardiograms were recorded on days 1, 3, and 7 after every suspected event. Blood was drawn at 1, 2, 3, and 4 days for measurement of total and heat-stable lactic dehydrogenase. Historical data were recorded by our technicians after consultation with the attending physician. In addition, an electrocardiogram was recorded routinely on all subjects on admission to the hospital and at intervals of 6 months for the detection of silent myocardial infarctions. When subjects returned after an absence from the hospital, an electrocardiogram was recorded if more than 6 months had elapsed since the last tracing. The autopsy percentage was maintained as high as possible. The overall percentage for persons in the trial was 57.1%. The reasons for failure to perform autopsies was almost always refusal by relatives or inability to contact relatives. The aorta, heart, and brain were fixed at the institution and were sent for study according to protocol by cardiac and neuropathologists at the University.

The principal investigator visited each of the institutions at frequent intervals and reviewed under masked conditions the hospital charts, the records kept by the trial technicians, the autopsy reports, and the laboratory data (but not the lipid analyses) on all patients who had died or who had had a suspected cardiovascular event since his last visit. He consulted with the responsible physician, if

Table 4. Primary End-points (Acute and Silent Myocardial Infarctions and Sudden Deaths)

Time in hospital (yrs)	Men		Women		Total	
	Treatment	Control	Treatment	Control	Treatment	Control
<1	81.9(42)	88.0(47)	55.6(35)	27.6(16)	67.4 (77)	56.6 (63)
≥1	13.9(27)	14.8(27)	15.5(27)	17.4(31)	14.7 (54)	16.1 (58)
≥2	8.8(14)	11.4(17)	11.3(16)	10.5(15)	10.0 (30)	11.0 (32)
≥3	4.3 (5)	7.0 (8)	8.9(10)	4.3 (5)	6.6 (15)	5.6 (13)
≥4	1.2 (1)	1.3 (1)	1.3 (1)	0.0 (0)	1.3 (2)	0.6 (1)
Total	28.1(69)	31.4(74)	26.2(62)	19.9(47)	27.2(131)	25.7(121)

These data include people of all ages. Values are the rates per 1000 person-years with numbers of persons in parentheses.

necessary, and then classified the event according to the International Classification of Diseases.[5]

Data Management

Fifteen forms were devised for recording the data from the hospitals and laboratories. The data were transferred to magnetic tape to facilitate day-to-day management of the project and for later analysis.

Results

Figure 3 shows the average serum cholesterol concentrations at 6-month intervals over the duration of the study. The abscissa represents time on diet, rather than calendar months. More persons are included, therefore, at the shorter time intervals. The average fall in cholesterol for the control group was 0.7%, and for the treatment group, 14.5%. The difference between the two groups was virtually constant from 6 months onward. Figure 4 shows the smaller, but definite, difference in plasma triglycerides.

The monitoring of missed meals was effective, as indicated by the relationship between adherence and missed meals. Persons assigned to the treatment diet who missed fewer than 5% of their meals during the 3 weeks before their semi-annual blood sample showed an average decrease in plasma cholesterol of 15.4% compared with their control measurement. If more than 5% of meals were missed, the decrease was 11.4% and it deteriorated progressively to 8.9% and 6.2%, respectively, if 20% or 50% of meals were missed. When persons failed to go through the serving line, they presumably ate elsewhere, although some routinely skipped breakfast.

The total number of participants in the study categorized by age and sex is shown in Table 3. The total number of hospital stays was 11 920. The average length of each hospital stay was 292 days. The average total time in the hospital for each participant, including multiple admissions, was 384 days. Hospital stays totaled 6005 for

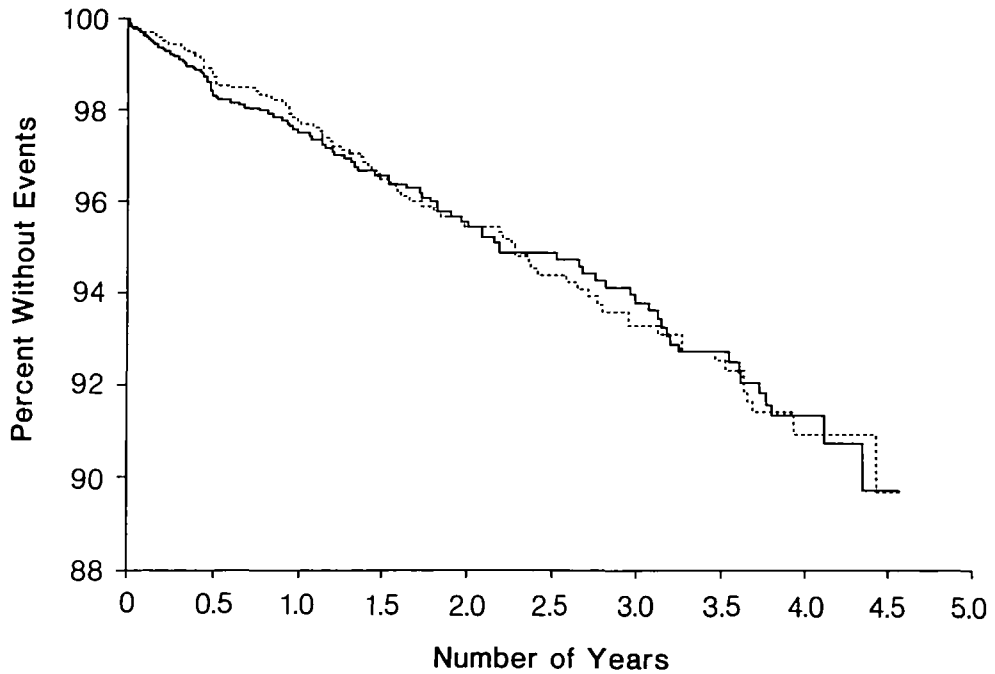

Figure 5. Life-table presentation of percent of men and women of all ages without cardiovascular events. Treatment (—), and control, (- -).

Table 5. All Deaths

Time in hospital (yrs)	Men		Women		Total	
	Treatment	Control	Treatment	Control	Treatment	Control
<1	193.0 (99)	191.0(102)	89.0 (56)	89.8(52)	135.7(155)	138.4(154)
≥1	30.4 (59)	28.0 (51)	31.7 (55)	24.2(43)	31.0(114)	26.1 (94)
≥2	15.8 (25)	18.2 (27)	23.4 (33)	18.2(26)	19.4 (58)	18.2 (53)
≥3	7.8 (9)	8.7 (10)	15.2 (17)	12.1(14)	11.4 (26)	10.4 (24)
≥4	1.2 (1)	1.3 (1)	1.3 (1)	1.2 (1)	1.3 (2)	1.3 (2)
Total	64.4(158)	64.9(153)	46.9(111)	40.3(95)	55.8(269)	52.6(248)

These data include persons of all ages. Values are the rates per 1000 person-years with numbers of persons in parentheses.

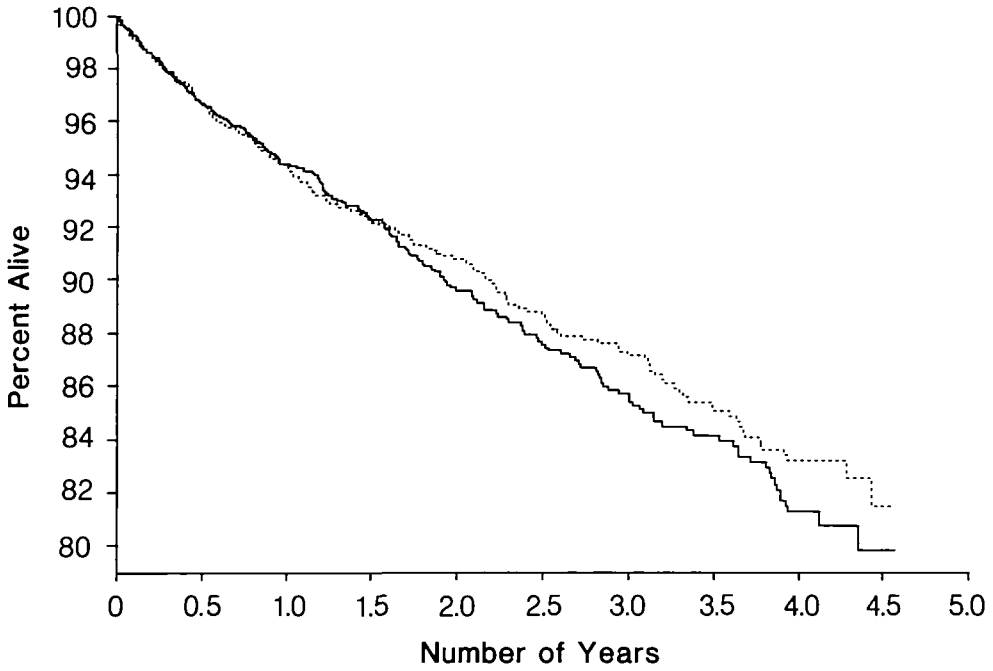

Figure 6. Life-table presentation of percent of men and women of all ages still living. Treatment, (—) and Control, (- -).

the treatment group and 5915 for the controls. Of these, only 2668 were for more than 1 year. The number of person-years of observation was 9538, with 5903 of these for persons in the hospital continuously for more than 2 years and 2495 for more than 4 years.

Table 4 shows the number of occurrences of the primary end-points—acute myocardial infarctions, sudden deaths, and silent myocardial infarctions—for men and women of all ages, classified according to time in hospital. A few more events occurred in the treated group. The data are presented in life table form in Figure 5. The similarity of the two curves is striking. Similar data for deaths from all causes are presented in Table 5 and Figure 6. The small difference between the two life tables is in an unfavorable direction.

When the study was initiated, we suspected that any favorable outcome would be confined to the younger participants in most of whom severe atherosclerosis would not yet be present. It also seemed likely that a fair length of time would be required for the diet to exert an effect. In two recently reported drug trials, the Lipid Research

Table 6. Trends in Persons on Diets More than 2 Years

	Events	
	Acute MI, sudden death, and silent MI	All deaths
Ages 35 to 39		
Men		
Treatment group	5.4(4)	5.4(4)
Control group	9.8(7)	7.0(5)
Women		
Treatment group	3.2(2)	9.8(6)
Control group	6.6(4)	6.6(4)
Ages 45 to 55 years		
Men		
Treatment group	0.0(0)	6.1(2)
Control group	16.7(6)	11.1(4)
Women		
Treatment group	3.8(1)	3.8(1)
Control group	14.2(4)	14.2(4)

Values are events or deaths per 1000 person-years with numbers of persons in parentheses.
MI=myocardial infarction.

Table 7. Causes of Death

Causes	Men		Women	
	Treatment	Control	Treatment	Control
Arteriosclerotic heart disease	18	13	12	11
Vascular lesions of central nervous system	13	11	9	10
Cardiac arrest, heart block	21	21	10	9
Chronic brain syndrome, general atherosclerosis, senility	30	40	22	16
Hypertensive heart and renal disease, other hypertensive disease, congestive heart failure	4	3	0	4
Other circulatory disease including rheumatic heart disease	1	3	1	3
Pulmonary embolism and infarction	5	3	11	10
Malignant neoplasm	16	12	7	8
Infectious diseases including influenza and pneumonia	4	4	4	1
Other diseases of central nervous system	6	10	14	5
Pulmonary disease including empyema, lung abscess, and emphysema	6	5	2	0
Gastrointestinal disease	4	7	3	3
Genitourinary disease including pyelonephritis and calculi	4	4	4	0
Diabetes mellitus	3	1	0	1
External causes including fractures, drug reactions, burns, foreign bodies, extraction of tooth, freezing, heat stroke, drowning, and suicide	21	14	12	14
Congenital malformations	2	2	0	0
Totals	158	153	111	95

Clinics Primary Prevention Trial[6,7] and the Helsinki Heart Study,[8] 2 years were required before favorable trends appeared. Therefore, it is of some interest to look for trends in persons on the diets for at least 2 years who fell in the age ranges chosen for those studies (35 to 59 and 45 to 55 years old, respectively). Such an analysis is presented in Table 6. If total time in hospital including multiple admissions is counted in arriving at the numbers on the diets for more than 2 years, only one more death and no more cardiovascular events are identified in the 35 to 59 year age group. In men younger than 50 years, there were three events and two deaths in the treatment group. In the control group, there were 11 events and 12 deaths.

Table 7 shows the causes of death for all participants who died during the study.

Discussion

The data were viewed in many other ways. For example, persons who had a poor cholesterol response or whose initial electrocardiogram showed evidence of a previous myocardial infarction were omitted from the study. Other combinations of end-points were examined. Subsequent events after the initial one in a given subject were disregarded. None of these maneuvers changed the conclusions.

Although this study did not show a statistically significant reduction in cardiovascular events or total deaths from the treatment diet, the authors suspect that it might have shown such a reduction if the period of treatment had been longer in persons in the age range likely to benefit. We included persons of all ages, both men and women, with an average cholesterol concentration of 207 mg/dl, compared to about 290 mg/dl for the participants in the Helsinki and Lipid Research Clinics trials. When the study was first proposed, very lengthy stays in mental hospitals were common. By the end of the initial 3-year pre-treatment observation period, the practice of vigorous drug treatment and early discharge to the community was in full swing.

Table 6, in which the analysis is confined to persons on diet for at least 2 years and in the age groups chosen

for recent drug trials, shows some favorable trends, but the numbers are far too small to achieve statistical significance.

Acknowledgments

The authors thank the medical directors, hospital administrators, business managers, dietitians, directors of nursing, and project technicians of the seven hospitals. They also thank the University of Minnesota pathologists, cardiologists, and neuropathologists who assisted in the survey.

References

1. **National Diet Heart Study Research Group.** The National Diet Heart Study Final Report. Circulation 1968;37(suppl I): I-419
2. **Lipid Research Clinics Program.** Manual of laboratory operations, vol 1. Lipid and lipoprotein analysis. DHEW publication no (NIH) 1974:75-628
3. **Strandjord PE, Clayson KJ, Freier EF.** Heat stable lactate dehydrogenase in the diagnosis of myocardial infarction. JAMA 1962;182:1099–1102
4. **Blackburn H, Keys A, Simonson E, Rautaharju P, Punsar S.** The electrocardiogram in population studies. A classification system. Circulation 1960;21:1160–1175
5. **International classification of diseases.** Adapted for indexing hospital records by diseases and operations. DHEW publication no (PHS) 1962:719
6. **Lipid Research Clinics Program.** The Lipid Research Clinics Coronary Primary Prevention Trial results. I. Reduction in incidence of coronary heart disease. JAMA 1984; 251:351–364
7. **Lipid Research Clinics Program.** The Lipid Research Clinics Coronary Primary Prevention Trial results. II. The relationship of reduction in incidence of coronary heart disease to cholesterol lowering. JAMA 1984;251:365–374
8. **Frick MH, Elo O, Haapa K, et al.** Helsinki Heart Study: Primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. N Engl J Med 1987;317:1237–1245

Index Terms: cardiovascular risk • lipid lowering by diet • plasma cholesterol

Arteriosclerosis, Thrombosis, and Vascular Biology

JOURNAL OF THE AMERICAN HEART ASSOCIATION

Test of effect of lipid lowering by diet on cardiovascular risk. The Minnesota Coronary Survey.

I D Frantz, Jr, E A Dawson, P L Ashman, L C Gatewood, G E Bartsch, K Kuba and E R Brewer

Arterioscler Thromb Vasc Biol. 1989;9:129-135
doi: 10.1161/01.ATV.9.1.129
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 1079-5642. Online ISSN: 1524-4636