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COOPERATIVE STUDIES

Fifteen Year Mortality in Coronary Drug Project Patients: Long-Term Benefit With Niacin

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The Coronary Drug Project was conducted between 1966 and 1975 to assess the long-term efficacy and safety of five lipid-influencing drugs in 8,341 men aged 30 to 64 years with electrocardiogram-documented previous myocardial infarction. The two estrogen regimens and dextrothyroxine were discontinued early because of adverse effects. No evidence of efficacy was found for the clofibrate treatment. Niacin treatment showed modest benefit in decreasing definite nonfatal recurrent myocardial infarction but did not decrease total mortality.

With a mean follow-up of 15 years, nearly 9 years after termination of the trial, mortality from all causes in each of the drug groups, except for niacin, was similar to that in the placebo group. Mortality in the niacin group was 11% lower than in the placebo group (52.0 versus 58.2%; p = 0.0004). This late benefit of niacin, occurring after discontinuation of the drug, may be a result of a translation into a mortality benefit over subsequent years of the early favorable effect of niacin in decreasing nonfatal reinfarction or a result of the cholesterol-lowering effect of niacin, or both.

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The Coronary Drug Project, a long-term study of lipid-influencing drugs in male survivors of myocardial infarction, was concluded as planned in early 1975 (1). Three of the five lipid-influencing regimens studied were discontinued early because of adverse effects. Treatment with the remaining two agents, clofibrate and niacin, did not show convincing evidence of benefit compared with placebo for the primary end point of total mortality during an average period of observation of 6 years. In 1980, the Coronary Drug Project coordinating center systematically began to follow up those patients still alive at the conclusion of the trial. The primary purpose was to determine whether any long-term *adverse* effects were evident in cause-specific mortality several years after the end of the study. This follow-up study was prompted by a possible excess mortality due to cancer in the Coronary Drug Project low dose estrogen group (2,3) and excess mortality from all causes in the clofibrate regimen of the World Health Organization Clofibrate Trial (4). The findings of this follow-up study are presented in this report.

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Methods

Design and methods of the Coronary Drug Project. The background, design and organization of the Coronary Drug Project have been described in detail (1,5,6). The primary objective was to test efficacy and safety of several lipid-influencing drugs in the long-term therapy of coronary heart disease in men with proved previous myocardial infarction. The 53 project clinical centers, located in the United States and Puerto Rico, recruited 8,341 patients who were randomly assigned to six treatment groups: conjugated estrogens at two dosage levels, clofibrate, dextrothyroxine sodium, niacin and a lactose placebo. The allocation schedule was designed to ensure approximately five patients in the placebo group for every two patients in any other group (Fig. 1).

The patients were men aged 30 through 64 years at entry, with verified evidence of one or more myocardial infarctions, categorized in class I or II of the New York Heart Association functional classification (7) and free from a specified list of diseases and conditions (5). All patients

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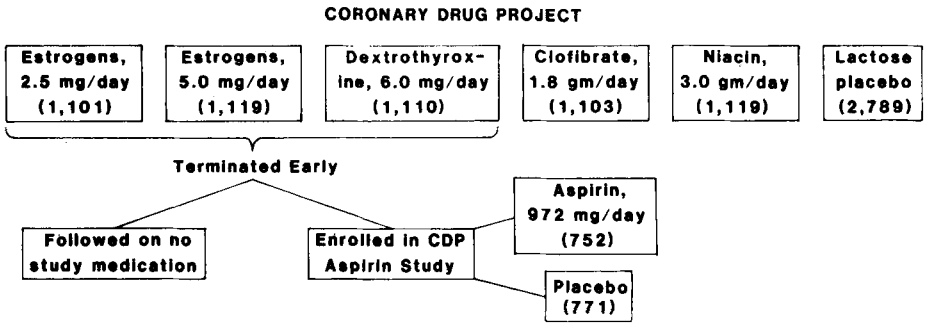


Figure 1. Treatment scheme in the Coronary Drug Project (CDP) and Coronary Drug Project Aspirin Study. Numbers of patients are given in parentheses.

were at least 3 months beyond their most recent myocardial infarction and free of recent worsening of coronary disease or other major illnesses. The study protocol was approved by the human experimentation committees of the coordinating center and all clinical centers' institutions.

The first patient was randomly allocated to treatment in March 1966, and the last in October 1969. Patients were followed up in double-blind fashion with visits every 4 months. Patient follow-up and data collection for the main trial were completed in February 1975. All surviving patients were followed up for at least 4.5 years, and 96% for at least 5 years. The maximal follow-up time was 8.5 years for the participants recruited earliest; the mean follow-up time was 6.2 years. The primary end point was mortality from all causes. Secondary end points included mortality from coronary heart disease, sudden death and incidence of recurrent nonfatal myocardial infarction (5).

The two estrogen regimens and the dextrothyroxine regimen were discontinued before the scheduled end of the trial. High dose estrogen treatment was terminated in 1970 (mean follow-up 1.5 years) because of a significant increase in definite nonfatal myocardial infarction and an unfavorable trend in total mortality (8). Dextrothyroxine was stopped in 1971 (mean follow up 3.0 years) because of increased total mortality, with particularly unfavorable mortality rates in certain patient subgroups (9). Low dose estrogen was terminated in 1973 (mean follow-up 4.7 years) because of an increase in cancer deaths compared with deaths in those receiving placebo and an unfavorable trend in total mortality (2).

Three treatment groups—clofibrate, niacin and placebo—were continued to the scheduled end of the trial (mean follow-up 6.2 years). The clofibrate group showed no benefit with respect to mortality or nonfatal cardiovascular events (1). Niacin had no statistically significant effect on total mortality; however, patients in the niacin group had a significantly lower incidence of definite nonfatal myocardial infarction compared with patients in the placebo group (1).

Coronary Drug Project Aspirin Study. About half the patients in the three groups that were terminated early (1,529 of the 3,330 patients originally assigned to the dextrothyroxine and two estrogen groups) were enrolled between November 1972 and April 1974 in a trial (called the Coronary Drug Project Aspirin Study) comparing aspirin and placebo (Fig. 1). These patients were followed up for a minimum of 10 and a maximum of 28 months (mean 22). Patient follow-up and data collection terminated in February 1975. A difference found in overall mortality between the aspirin and placebo groups was "suggestive of a beneficial effect for aspirin in the treatment of post-myocardial infarction men but not large enough to be conclusive" (10).

Design and methods of the Coronary Drug Project Mortality Follow-up Program. In June 1981, the Coronary Drug Project coordinating center was awarded a contract by the National Heart, Lung, and Blood Institute for mortality follow-up of Coronary Drug Project patients who were alive at the end of the trial. The primary objectives were to determine vital status, at least 5 years after the end of the trial, of all 6,008 Coronary Drug Project patients alive in February 1975, and to relate the findings to previous study treatment group.

Vital status was ascertained by a variety of means—information from study investigators; letters (first regular mail and later certified mail) and telephone calls to the patients; telephone calls to the patients' relatives, neighbors, physicians and employers; National Death Index search; Social Security Administration file search; Veterans Administration file search and utilization of the services of a national search agency. (Details concerning these various procedures can be obtained from the senior author.) For all deaths ascertained, attempts were made to obtain death certificates from state offices of vital records so that cause of death could be determined. Other patient information for this post-trial period, such as occurrence of nonfatal cardiovascular events or cardiovascular surgery or use of cholesterol-lowering drugs, was not systematically collected.

Statistical methods. Treatment group comparisons of mortality rates were made by the ordinary test of two proportions (11). This test yields z values defined as the drug-placebo difference in proportions of events divided by the standard error of the difference. A z value exceeding $\pm$ 1.96 is generally considered statistically significant at the 5% level of significance; however, adjustment for five drug-placebo comparisons requires a z value on the order of $\pm$ 2.58 for statistical significance. Further conservatism is generally considered appropriate in evaluating treatment effects

Table 1. Vital Status Information by Treatment Group in the Coronary Drug Project and Coronary Drug Project Aspirin Study

Vital Status Information	Coronary Drug Project							Coronary Drug Project Aspirin Study		
	Low Dose Estrogen	High Dose Estrogen	Clofibrate	Dextro-thyroxine	Niacin	Placebo	All	Aspirin	Placebo	All
Number of patients originally enrolled	1,101	1,119	1,103	1,110	1,119	2,789	8,341	758	771	1,529
Deaths reported before end of study in early 1975	317	324	311	308	292	781	2,333	48	71	119
Number of patients in CDP Mortality Follow-up Program	784	795	792	802	827	2,008	6,008	710	700	1,410
Deceased	340 (1)*	328 (1)	326 (1)	325 (0)	290 (1)	842 (1)	2,451 (5)	255 (0)	269 (1)	524 (1)
Alive	432	461	447	467	523	1,137	3,467	446	423	869
"Assumed alive"†	10	5	13	9	8	21	66	7	8	15
No vital status information	2	1	6	1	6	8	24	2	0	2

*Number of unconfirmed deaths (see text for definition); †as determined from Social Security or Veterans Administration files.

in subgroups. Homogeneity of treatment effects between two categories of a given baseline characteristic was assessed by means of a log odds ratio procedure (11). Adjustment of drug-placebo differences in event rates for baseline covariates was made using multiple linear regression (12). Survival curves were estimated using the Littell method (13), and compared using the log rank test (14).

Results

Ascertainment of vital status (Table 1). Of the 8,341 patients originally enrolled in the Coronary Drug Project, 2,333 were known to have died by the end of the trial in February 1975. Information on vital status as of at least March 1980 was obtained on 5,984 (99.6%) of the other 6,008 patients. For 66 patients, the only information available was "assumed alive" according to either Social Security Administration records as of early 1983 (61 patients) or Veterans Administration records as of early 1985 (5 patients). A total of 3,041 patients were reported by the Social Security Administration as "assumed alive," but 98 (3.2%) of these were found from other sources to be deceased. Thus, it is possible that a small number of the patients for whom the only information is "assumed alive" are actually deceased.

Death certificates have been obtained for 2,227 (91%) of the 2,451 patients identified by one or more of the preceding mechanisms as having died after February 1975. For another 130, death reports were received from two or more independent sources, and for 89 the information concerning the death (including a date of death and often a place of death) was deemed to provide adequate confirmation of the death, even though death certificates could not be obtained. The remaining five identified deaths could not be confirmed (Table 1). These five patients with unconfirmed death are assumed dead for purposes of this report.

Follow-up period. The mortality findings represent a mean patient follow-up period of about 15 years—6.2 years on the Coronary Drug Project treatment regimen (or less for those in the three treatment groups stopped prematurely) and 8.8 years after termination of the study. The 8.8 years correspond to the interval from August 1974 (midpoint of the period in which the Coronary Drug Project treatment regimen was terminated) to June 1983 (when the Social Security Administration records were searched, identifying the vast majority of the deaths). For patients enrolled in the Coronary Drug Project Aspirin Study, the total follow-up period is 10.2 years—1.8 years on the study regimen and 8.4 years after termination of the study. The mortality findings for patients in the two estrogen and the dextrothyroxine groups—the groups terminated early—include the mortality during the 1.8 years (average) of participation in the Coronary Drug Project Aspirin Study, assigned with equal probability to either aspirin or placebo regimens.

The annual death rates for all six treatment groups combined were 5.1, 4.5 and 4.4%, respectively, for the first 3 years, with a slight but steady increase each year thereafter to 7.1% for the 15th year. The slightly higher rate for the first year may reflect the relative proximity to the qualifying myocardial infarction. The qualifying infarction preceded entry into the study by as little as 3 months and a median of 23 months (5). The rates for the first, second and third 5 year periods were 21.6, 25.0 and 29.5%, respectively, and the cumulative 15 year mortality rate was 58.6%.

Findings in the estrogen, clofibrate and dextrothyroxine groups (Table 2). The mortality follow-up of Coronary Drug Project patients was performed primarily to assess long-term findings in the groups—high and low dose estro-

Table 2. All-Cause Mortality (%) for a Mean Follow-up Period of 15 Years in the Estrogen, Clofibrate, Dextrothyroxine and Placebo Groups

	Drug		Placebo		
Lipid-Lowering Drug	n	%	n	%	z Value
Low dose estrogen	1,101	59.7	2,789	58.2	0.84
High dose estrogen	1,119	58.3	2,789	58.2	0.04
Clofibrate	1,103	57.8	2,789	58.2	−0.25
Dextrothyroxine	1,110	57.0	2,789	58.2	−0.67

gen, dextrothyroxine and clofibrate—found in the Coronary Drug Project or the World Health Organization Clofibrate Trial to have adverse effects. For these four groups, the mortality rate from all causes for a mean follow-up period of 15 years ranged from 57.0% in the dextrothyroxine group to 59.7% in the low dose estrogen group, compared with 58.2% in the placebo group. Mortality in each treatment group was within ± 1.5% of the placebo group mortality, a relative difference of ± 2.6%; none of the drug-placebo differences was statistically significant.

The Coronary Drug Project low dose estrogen group, terminated prematurely because of excess cancer mortality, continues to show a moderate excess of cancer deaths compared with such deaths in the placebo group (5.9 versus 4.4%; z = 1.90, p = 0.057) (Table A2 in Appendix A). However, if cancer deaths before the end of the treatment phase in August 1974 (Table A1) are excluded, the subsequent cancer mortality rate since conclusion of the trial is only slightly higher for the low dose estrogen group (3.9%) than for the placebo group (3.5%). The high dose estrogen group and the clofibrate group both had a somewhat lower cancer mortality rate (3.7 and 3.4%, respectively) than did the placebo group (4.4%) over 15 years (Table A2).

Findings in the aspirin group. The Coronary Drug Project Aspirin Study concluded with a mortality rate from all causes of 5.8% in the aspirin group compared with 8.3% in the placebo group (z = 1.90; p = 0.057), a 30% reduction in mortality (10). An additional 8.4 years after termination of the study, the mortality rate from all causes was 40.0% in the aspirin group and 44.1% in the placebo group (z = −1.63; p = 0.10), a 9% reduction in mortality. Thus, the absolute difference in mortality has subsequently widened somewhat, but the relative difference and degree of statistical significance are diminished.

Findings in the niacin group (Tables 3 to 5). Cumulative mortality from all causes for a mean follow-up period of 15 years was 52.0% in the niacin group compared with 58.2% in the placebo group (Table 3). There were 69 (11%) fewer deaths in the niacin group than expected on the basis of placebo group mortality. The z value for the niacin-placebo difference in mortality from all causes was −3.52, corresponding to a two-sided p value of 0.0004. Survival curves for mortality from all causes are shown for patients in the niacin and placebo groups in Figure 2; the median survival time from entry into the Coronary Drug Project was 13.03 years for patients in the niacin group compared with 11.40 years for those in the placebo group (p = 0.0012). The survival benefit in the niacin group is primarily evident for death caused by coronary heart disease, with small beneficial trends for each of cerebrovascular, other cardiovascular, cancer, noncardiovascular and noncancer causes of death.

The beneficial effect of niacin on mortality is present in all subgroups of 12 entry characteristics except for probable or definite cardiomegaly, where there is a 0.1% excess mortality in the niacin group (Table 4). There is no statistically significant lack of homogeneity between the niacin treatment effect and the levels of any of these entry characteristics (that is, the niacin-placebo difference in one subgroup is not significantly different from that difference in the complementary subgroup). The largest trend (z = 1.93) toward lack of homogeneity was a greater beneficial effect on mortality in the niacin group compared with placebo in the subgroup with a serum cholesterol level of 250 mg/dl or greater at entry than in those with lower levels.

A multiple linear regression analysis using the niacin treatment variable plus the 12 entry variables given in Table 4 in the model, with total mortality as the dependent variable, yielded an adjusted z value for the niacin effect on total mortality (−3.53), about the same as the unadjusted value reported earlier.

Mortality from all causes in relation to occurrence of

Table 3. Mortality (%) by Cause for a Mean Follow-up Period of 15 Years in the Niacin and Placebo Groups

Cause of Death	Niacin	Placebo	z Value
All causes	52.0	58.2	−3.52
Coronary heart disease	36.5	41.3	−2.80
Cerebrovascular causes	1.4	1.6	−0.34
Other cardiovascular	4.5	4.8	−0.45
Cancer	4.0	4.4	−0.59
Other causes	2.9	3.0	−0.16
Unknown or not coded	2.7	3.0	−0.56
No. of patients	1,119	2,789	

Table 4. All-Cause Mortality by Findings at Entry for Niacin and Placebo Groups

Entry Characteristic	Niacin		Placebo		z Value
	No. Men	% Deaths	No. Men	% Deaths	
Age (yr)					
<55	614	43.2	1,590	49.6	−2.70
≥55	505	62.6	1,199	69.3	−2.71
Cigarette smoker					
No	709	47.2	1,731	53.9	−2.99
Yes	409	59.9	1,056	64.9	−1.77
No. of previous myocardial infarctions					
1	909	48.8	2,231	53.8	−2.54
≥2	209	65.1	555	75.0	−2.72
New York Heart Association class					
I	538	45.2	1,295	49.7	−1.78
II	580	58.1	1,492	65.3	−3.04
Cardiomegaly on chest X-ray film					
No	943	47.9	2,281	54.7	−3.49
Probable or definite	176	73.3	508	73.2	0.02
Diuretic usage					
No	940	48.7	2,321	54.6	−3.04
Yes	179	68.7	468	75.2	−1.67
Serum cholesterol (mg/dl)					
<250	577	53.2	1,481	56.2	−1.22
≥250	541	50.5	1,306	60.2	−3.84
Serum triglycerides (mEq/liter)					
<5	528	51.9	1,375	57.3	−2.13
≥5	590	51.9	1,412	58.8	−2.85
Serum uric acid (mg/dl)					
<7	633	50.2	1,553	55.6	−2.30
≥7	485	54.0	1,234	61.1	−2.69
Plasma fasting glucose (mg/dl)					
<100	630	48.6	1,564	53.5	−2.10
≥100	488	56.1	1,223	63.9	−2.96
Systolic blood pressure (mm Hg)					
<130	526	44.3	1,353	53.4	−3.56
≥130	592	58.6	1,434	62.4	−1.60
Diastolic blood pressure (mm Hg)					
<85	700	49.0	1,763	55.9	−3.11
≥85	418	56.7	1,024	61.7	−1.77

definite nonfatal myocardial infarction during the trial is given for the niacin and placebo groups in Table 5. At the conclusion of the Coronary Drug Project, the incidence of definite nonfatal myocardial infarction was 10.4% for patients in the niacin group and 14.7% for patients in the placebo group. The findings in Table 5 suggest that this beneficial effect of niacin with respect to definite nonfatal myocardial infarction may account for approximately 10 of the 69 fewer deaths in the niacin treatment group. The reasoning for this is as follows: If we assume that the placebo group incidence (14.7%) of definite nonfatal recurrent myocardial infarction had applied to the niacin group of 1,119 men, we would have observed 164 men in the niacin group with such an event, instead of the 116 actually observed. If we then apply the niacin group death rate (81 of 116, or 69.8%) given one or more myocardial infarctions to this group of 164 men, we find that 114 deaths would have been expected. Similar calculations for the noninfarct groups yield a total of 570 deaths expected in the niacin group compared with 560 deaths actually observed.

The percent decrease in mean serum cholesterol from baseline to year 1 was 10.1% in the niacin group (Table 6). Treatment with niacin proved to be the best lipid-lowering regimen among the five Coronary Drug Project treat-

Table 5. All-Cause Mortality by Occurrence of Definite Nonfatal Myocardial Infarction During the Trial in the Niacin and Placebo Groups

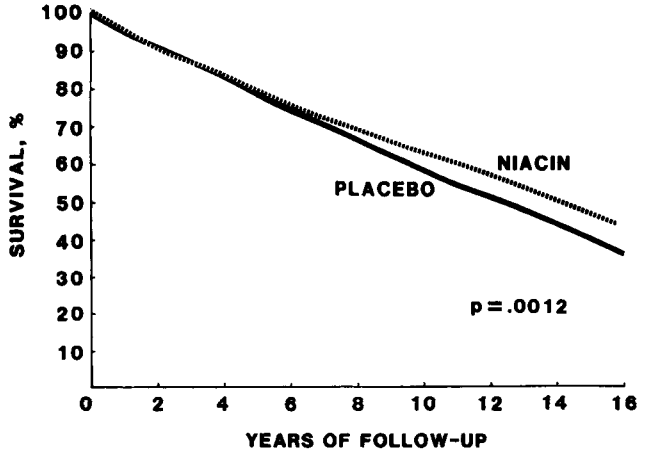
No. of Definite Nonfatal Myocardial Infarctions During Trial	Niacin			Placebo		
	No. Men	No. Deaths	% Deaths	No. Men	No. Deaths	% Deaths
None	1,003 (89.6%)*	479	47.8	2,380 (85.3%)	1,285	54.0
One or more	116 (10.4%)	81	69.8	409 (14.7%)	282	68.9
All	1,119	560	50.0	2,789	1,567	56.2
Applying placebo group incidence of definite nonfatal myocardial infarction to niacin group						
None	955 (85.3%)	456	47.8			
One or more	164 (14.7%)	114	69.8			
All	1,119	570†	51.0			

*Percent of men in the particular subgroup given in parentheses; †570 expected deaths minus 560 observed deaths equals 10 niacin deaths saved due to reducing the incidence of definite nonfatal myocardial infarction. Note that deaths that occurred both during the trial (except those before the first Coronary Drug Project follow-up visit, that is, before a nonfatal myocardial infarction could have been reported) and during the period of subsequent follow-up reported in this review are included in this table.

ment regimens. Also, within the niacin group, patients with the largest decrease in serum chlesterol at 1 year experienced a lower subsequent mortality than did those with an increase in serum cholesterol. There was no significant correlation between change in serum triglyceride level and mortality in the niacin group.

As reported earlier by the Coronary Drug Project Research Group (1), niacin therapy was associated with statistically significant increases in serum glutamic oxaloacetic transaminase, serum alkaline phosphatase, plasma fasting and 1 hour glucose and serum uric acid levels, and decreases in plasma urea nitrogen levels and systolic and diastolic blood pressure. Analyses of these response variables in the niacin group failed to demonstrate any correlation between change in values from baseline to 1 year and subsequent mortality.

Figure 2. Survival curves for niacin and placebo treatment groups.



Discussion

Ascertainment of vital status. The Coronary Drug Project Mortality Follow-up Program has been successful in locating and determining vital status of participants in the Coronary Drug Project 9 years after conclusion of the trial. Definite information concerning vital status was obtained on 98.9% of the 8,341 Coronary Drug Project patients; for 0.8%, death was reported but not confirmed or the patient was "assumed alive"; no information on vital status was obtained for the remaining 0.3% of the patients.

Findings in the estrogen, clofibrate, dextrothyroxine and aspirin groups. The 15 year mortality findings for the two estrogen, the dextrothyroxine, the clofibrate and the aspirin groups compared with the placebo group do not substantially differ qualitatively from those initially reported for each of these treatment groups (1–3, 8–10). There is no evidence of long-term adverse effects in the estrogen- and dextrothyroxine-treated patients beyond those reported at the time these regimens were discontinued. Neither is there evidence of long-term adverse effects of clofibrate. Although the initial findings of the World Health Organization Clofibrate Trial (4) revealed excess mortality from all causes in the patients treated with clofibrate, follow-up data covering a 7.9 year post-trial period showed a moderate attenuation of this excess mortality after the end of treatment (15).

Findings in the niacin group. We are aware of only two randomized placebo-controlled trials of niacin in which

Table 6. Serum Lipid Levels at Baseline and Year 1 for the Treatment and Placebo Groups

Mean Lipid Level	Low Dose Estrogen	High Dose Estrogen	Clofibrate	Dextrothyroxine	Niacin	Placebo
Cholesterol (mg/dl)						
Baseline	250	251	252	250	253	249
Year 1	247	245	239	226	227	254
% change	−1.3	−2.3	−5.1	−9.7	−10.1	+1.9
Triglycerides (mEq/liter)						
Baseline	6.0	6.1	6.1	5.7	6.4	6.2
Year 1	6.4	7.1	4.3	5.0	4.7	6.3
% change	+6.9	+17.2	−23.1	−12.1	−26.9	+2.1

an attempt was made to assess the efficacy and safety of niacin with respect to mortality. Both studies were of survivors of acute myocardial infarction. The Veterans Administration study (16) of lipid-lowering agents showed, after 3.2 years of follow-up, a slight excess in total mortality in the 77 patients receiving niacin alone compared with the 143 placebo-treated patients. In the Stockholm Ischemic Heart Disease Study (17–19), effects of niacin were confounded with those of clofibrate. The 5 year mortality rate from all causes (21.9%) in 279 patients receiving 2 g/day of clofibrate plus 3 g/day of niacin was 29% lower than that (30.7%) in 267 control group patients ($p = 0.036$).

In the Coronary Drug Project, the 5 year mortality rate in the niacin group was 21.2%, slightly higher than in the placebo group (20.9%) (1). At the scheduled conclusion of the trial, with a mean follow-up period 6.2 years, mortality in the niacin group was 4% lower than in the placebo group (24.8 versus 25.9%) (Table A1). The published life tables (1) showed that the niacin and placebo mortality rates were almost identical throughout the first 68 months of follow-up, but started to diverge at month 72. Life table curves for definite nonfatal myocardial infarction showed that the niacin group began to diverge in the beneficial direction at about month 28.

The significant benefit in 15 year mortality from all causes in the niacin group in the Coronary Drug Project Mortality Follow-up Program was found even though, during the treatment phase, nearly 30% of the niacin-treated patients adhered poorly to the treatment regimen (that is, took less than 60% of the protocol amount of drug) over the follow up period (1). Thus, therapeutic benefit may have been derived from less than optimal doses of the drug.

Explanations for survival benefits of niacin. The unanticipated finding of a significant long-term survival benefit with niacin may be explained in part by the earlier decrease in definite nonfatal myocardial infarction. However, a more likely explanation stems from the cholesteral-lowering effect of niacin, which was superior to that of the other drugs studied in the Coronary Drug Project. In the niacin group, patients with the largest decrease in serum cholesterol at 1 year had a lower subsequent mortality than did those with an increase in serum cholesterol. Analyses relating mortality or other outcomes to variables that are themselves affected by the treatment are fraught with hazards and can lead to invalid conclusions (20). Nonetheless, these findings lend support to the suggestion that the cholesterol-lowering effect of niacin may be partly responsible for the reduced mortality. Thus, it is possible that a 10% reduction in serum cholesterol, maintained over 5 to 8 years, may have significantly slowed the progression of coronary atherosclerosis.

Time lag in development of a beneficial trend. While a time lag in development of a beneficial trend in mortality as a consequence of lowering serum cholesterol and slowing coronary atherosclerosis (21) is to be expected, it seems surprising that this lag—for niacin treatment—is of the magnitude of 6 years or more. Both the niacin data during the Coronary Drug Project and the cholestyramine data from the Lipid Research Clinics Coronary Primary Prevention Trial (22) show about a 2 to 3 year delay before the development of a beneficial trend in nonfatal myocardial infarction. Because the atherosclerotic processes underlying nonfatal and fatal myocardial infarction presumably are similar, with the availability of emergency medical services and life support measures often making the difference between a fatal and a nonfatal event, it is puzzling that an additional 3 years of serum lipid-lowering seems to be required for a beneficial trend in *mortality*. However, it is possible that initially, niacin prevents primarily milder, nonlife-threatening infarction. This is suggested by unpublished data from the Coronary Drug Project: among patients with interim nonfatal myocardial infarction, those in the niacin group had greater subsequent mortality during the treatment phase of the trial than did patients in the placebo group. Thus, although patients receiving niacin experienced nonfatal myocardial infarction less frequently than did patients receiving placebo, their nonfatal infarctions were more severe than those of the placebo group, suggesting that milder myocardial infarction may have been prevented by niacin. Then, as the favorable lipid-lowering effect of niacin on the coronary arteries increased over time, more severe life-threatening infarction may have been prevented.

As an alternative explanation for the 6 year lag, there may have been counterbalancing adverse effects of niacin while patients were taking the drug; the beneficial lipid-lowering effect may be manifest only after the drug is discontinued. The significantly higher incidence of atrial fibrillation and other cardiac arrhythmias in the niacin group (1) may be a possible mechanism for this explanation.

Other explanations for the beneficial effect of niacin. Did patients in the niacin group receive more aggressive medical or surgical treatment of their coronary heart disease after the Coronary Drug Project trial was completed than did patients in the placebo and other treatment groups? No post-trial data are available to answer this question. However, during the Coronary Drug Project trial, patients in the niacin group had a nearly 50% *lower* incidence of cardiovascular surgery than did placebo-treated patients; also, most categories of cardiac medications were prescribed *less* frequently for niacin than for placebo-treated patients during the trial (1). There is no reason to expect these patterns to have changed drastically after the trial was over; thus, such an explanation of the niacin findings seems most improbable.

It is possible that *part* of the observed effect is due to incomplete ascertainment of vital status. However, if the mathematically worst possible scenario occurred (that is, all 6 patients in the niacin group without vital status information and all 8 patients designated as "assumed alive" by Social Security or Veterans Administration information were actually deceased and all 8 and 21 corresponding patients in the placebo group were alive), the z value for the niacin-placebo difference in total mortality would change from -3.52 to -2.81, still a significant difference. Therefore, imcomplete ascertainment of vital status does not explain the beneficial effect of niacin.

Conclusion. Follow-up data on patients who participated in the Coronary Drug Project suggest that niacin administered after recovery from myocardial infarction may confer a long-term survival benefit, averaging 1.6 additional years of life. These data are derived from men recovered from myocardial infarction who were prescribed 3 g of niacin daily for an average of 6.2 years, then presumably stopped taking the drug. The maximal difference in survival was attained at about 12 years after initiation of niacin therapy, or an average of about 5.8 years after termination of that regimen. The available data relate only to the use of niacin for 5 to 8 years in survivors or myocardial infarction. There is no information on whether longer-term niacin usage might be helpful or harmful, whether the drug is effective in *women* after myocardial infarction or whether the drug has any value in the *primary* prevention of coronary heart disease. However, in the context of all other information that is available from both epidemiologic and clinical trial sources, the results may indeed be applicable to populations not included in the Coronary Drug Project.

The valuable information obtained from the Coronary Drug Project Mortality Follow-up Program, and especially the totally unexpected findings in the niacin group, suggest the potential usefulness of "reopening the books" on other completed clinical trials to assess long-term treatment effects on mortality.

Appendix A

Detailed Data on Cause-Specific Mortality

Final in-trial cause-specific mortality. The mortality results in the clofibrate, niacin and placebo groups for the treatment phase of the Coronary Drug Project were published in 1975 (1). After that report, a few additional deaths that occurred before August 31, 1974 were brought to the attention of the study investigators. In addition, the cause-specific mortality data reported in 1975 were based on the death reports received from the clinical centers. The coding of all deaths by a Mortality Classification Committee using uniform criteria and without knowledge of treatment assignment was completed subsequently. Table A1 presents this final, committee-coded, detailed cause-specific mortality for the treatment phase of the Coronary Drug Project (that is, all deaths up to the time of the termination of the study treatment in the summer of 1974 or up to August 31, 1974 for patients who dropped out of the study). This table includes patients originally in the two estrogen and dextrothyroxine groups who were subsequently enrolled in the Coronary Drug Project Aspirin Study, as well as patients in those groups not in the Coronary Drug Project Aspirin Study. Thus, the data in Table A1 represent a mean follow-up period of 1.5 years on the high dose estrogen regimen and 4.7 years off this regimen, with 50% of the patients participating in the Coronary Drug Project Aspirin Study for a mean of 1.7 of these years. For dextrothyroxine, there was a mean follow-up on treatment of 3.0 years and 3.2 years off treatment, with 53% of these patients in the Coronary Drug Project Aspirin Study for a mean of 1.7 years. For low dose estrogen, the mean follow-up on treatment was 4.7 years and 1.5 years off treatment, with 35% of these patients participating in the Coronary Drug Project Aspirin Study for a mean of 0.5 years. Finally, the data in Table A1 for the clofibrate, niacin and placebo groups reflect a mean follow-up on study treatment regimen of 6.2 years.

In-trial plus post-trial cause-specific mortality. Table A2 gives cause-specific mortality for the six treatment groups for both the treatment phase covered in Table A1 and the post-trial phase of a mean of 8.8 years. Some difficulties were encountered in attempting to combine cause of death categories used by the Mortality Classification Committee with International Classification of Diseases (ICD) codes used to classify deaths reported during the post-trial follow-up period. The biggest difficulty related to coronary heart disease deaths. The Mortality Classification Committee, using detailed descriptions of the terminal event, carefully classified coronary deaths into those with a recent or acute cardiac event (for example, sudden unexpected death or recent myocardial infarction) and those without a recent or acute cardiac event (for

Table A1. Cause-Specific Mortality During the Coronary Drug Project Treatment Phase

Cause of Death	Low Dose Estrogen (n = 1,101) No. (%)	High Dose Estrogen (n = 1,119) No. (%)	Clofibrate (n = 1,103) No. (%)	Dextrothyroxine (n = 1,110) No. (%)	Niacin (n = 1,119) No. (%)	Placebo (n = 2,789) No. (%)
All causes	294 (26.7)	301 (26.9)	288 (26.1)	287 (25.9)	277 (24.8)	723 (25.9)
Cardiovascular	265 (24.1)	279 (24.9)	259 (23.5)	262 (23.6)	250 (22.3)	660 (23.7)
Coronary—acute	230 (20.9)	242 (21.6)	221 (20.0)	225 (20.3)	215 (19.2)	583 (20.9)
Coronary—chronic	20	20	19	26	23	49
Cerebrovascular	5	10	14	6	6	14
Pulmonary embolism	1	1	1	1	2	2
Other cardiovascular	9	6	4	4	4	12
Cancer	22 (2.0)	13 (1.2)	11 (1.0)	15 (1.4)	14 (1.3)	27 (1.0)
Lung	8	7	3	4	9	12
Gastrointestinal	5	0	2	3	1	2
Pancreatic	2	3	1	2	0	2
Liver, gallbladder	1	0	1	1	0	0
Genitourinary	2	2	1	1	3	5
Blood, lymph	0	0	2	0	0	3
Other cancer	4	1	1	4	1	3
Other noncardiovascular	6 (0.5)	6 (0.5)	12 (1.1)	9 (0.8)	13 (1.2)	31 (1.1)
Infection	1	0	2	2	1	4
Lung disease	0	0	1	0	2	5
Gastrointestinal	1	1	1	2	0	5
Pancreatitis	1	1	0	0	0	1
Liver, gallbladder	0	3	2	0	1	0
Genitourinary	0	0	1	0	1	0
Blood	0	0	0	0	0	0
Endocrine, metabolic	0	0	0	0	0	0
Central nervous system	0	0	0	0	0	0
Nonmedical*	3	1	5	5	8	15
Other	0	0	0	0	0	1
Unknown	1 (0.1)	3 (0.3)	6 (0.5)	1 (0.1)	0 (0.0)	5 (0.2)

*Includes accidents, homicide and suicide.

example, congestive heart failure). It is much more difficult, if not impossible, to make such a distinction using ICD codes. A death certified as "cardiac arrest due to atherosclerotic coronary heart disease," and thus coded 414.0, is more than likely a sudden unexpected cardiac death. However, a death certified as "chronic congestive heart failure due to atherosclerotic coronary heart disease" is also coded 414.0. For purposes of Table A2, all ICD codes 410 to 414 except 414.8 ("chronic myocardial ischemia") plus ICD code 429.2 ("arteriosclerotic cardiovascular disease") were counted as "coronary—acute." Codes 414.8 and 428 were counted as "coronary—chronic."

During the treatment phase (Table A1), 91% of deaths were from cardiovascular causes, while 75% of post-trial deaths were cardiovascular. This highly significant difference ($p = 10^{-48}$) is likely a result of the fact that individuals with serious noncardiovascular disease at the outset were not enrolled in the study.

Appendix B

The key bodies of the Coronary Drug Project Mortality Follow-up Program and the senior staff members are as follows:

Steering and Editorial Review Committee. Jeremiah Stamler, MD (Chairman), Kenneth Berge, MD, Henry Blackburn, MD, William Friedewald, MD, Lawrence Friedman, MD, Adrian Hainline, Jr., PhD, Christian Klimt, MD, DrPH, Charles Laubach, Jr., MD, Ronald Prineas, MB, BS, PhD, Nanette Wenger, MD.

Coordinating Center. Paul Canner, PhD (Principal Investigator), Sandra Forman, MA (Co-Investigator), Joseph Canner; Martha Canner, MS, Rosemary Giro, Elizabeth Heinz, Mary Keiser, Christian Klimt, MD, DrPH, Delores Seldon.

National Heart, Lung, and Blood Institute Staff. William Friedewald, MD, Lawrence Friedman, MD.

Principal Investigators, Clinical Centers. Kenneth Berge, MD, Nicholas Galluzzi, MD, Paul Geller, MD, James Schoenberger, MD, Samuel Baer, MD, Henry Schoch, MD, Ronald Gillilan, MD, Robert Kohn, MD, Bernard Lewis, MD, Richard Jones, MD, Philip Frost, MD, Dean Emanuel, MD, David Morgan, MD, David Berkson, MD, William Bernstein, MD, Ernst Greif, MD, Richard Pyle, MD, Ephraim Donoso, MD, Jacob Haft, MD, Gordon Maurice, MD, Ralph Lazzara, MD, Irving Liebow, MD, Marvin Segal, MD, Charles Moore, MD, John Morledge, MD, Olga Haring, MD, Robert Schlant, MD, Joseph Wagner, MD, Ward Laramore, MD, Donald McCaughan, MD, Robert Oblath, MD, Peter Gazes, MD, Bernard Tabatznik, MD, Richard Hutchinson, MD, Raphael Sobrino, MD, J. Edward Pickering, MD, Robert Grissom, MD, Ralph Scott, MD, Frank Canosa, MD, Charles Laubach, Jr., MD, Ralph Cole, MD, Thaddeus Prout, MD, Jerome Cooper, MD, Ernest Theilen, MD, C. Basil Williams, MD, Edward Michals, MD, Fred Gilbert, Jr., MD, Sidney Levine, MD, Louis Matthews, Jr., MD, Irving Ershler, MD, Elmer Cooper, MD, Allan Barker, MD, Paul Samuel, MD.

Table A2. Cause-Specific Mortality During and After the Coronary Drug Project Treatment Phase

	Low Dose Estrogen (n = 1,101)		High Dose Estrogen (n = 1,119)		Clofibrate (n = 1,103)		Dextrothyroxine (n = 1,110)		Niacin (n = 1,119)		Placebo (n = 2,789)	
Cause of Death	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
All causes	657	(59.7)	652	(58.3)	637	(57.8)	633	(57.0)	582	(52.0)	1,623	(58.2)
Cardiovascular	527	(47.9)	540	(48.3)	533	(48.3)	525	(47.3)	474	(42.4)	1,331	(47.7)
Coronary—acute	455	(41.3)	460	(41.1)	466	(42.2)	452	(40.7)	408	(36.5)	1,153	(41.3)
Coronary—chronic	28		32		24		32		26		67	
Cerebrovascular	17		24		24		18		16		44	
Pulmonary embolism	2		2		1		1		3		5	
Other cardiovascular	25		22		18		22		21		62	
Cancer	65	(5.9)	41	(3.7)	37	(3.4)	47	(4.2)	45	(4.0)	124	(4.4)
Lung	23		21		13		16		23		53	
Gastrointestinal	14		6		4		13		6		17	
Pancreatic	8		5		4		2		4		8	
Liver, gallbladder	2		0		1		1		1		2	
Genitourinary	7		5		4		5		5		12	
Blood, lymph	3		0		6		3		0		12	
Other cancer	8		4		5		7		6		20	
Other noncardiovascular	38	(3.5)	34	(3.0)	36	(3.3)	32	(2.9)	33	(2.9)	85	(3.0)
Infection	6		7		7		7		2		10	
Lung disease	7		4		5		5		7		23	
Gastrointestinal	6		5		1		4		1		8	
Pancreatitis	1		1		0		0		1		2	
Liver, gallbladder	2		4		5		1		2		5	
Genitourinary	1		1		1		2		3		4	
Blood	0		1		1		0		0		1	
Endocrine, metabolic	4		3		5		2		3		6	
Central nervous system	2		1		0		3		2		1	
Nonmedical*	8		6		11		8		12		24	
Other	1		1		0		0		0		1	
Unknown	27	(2.5)	37	(3.3)	31	(2.8)	29	(2.6)	30	(2.7)	83	(3.0)

*Includes accidents, homicide and suicide.

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