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INFLUENCE OF ADHERENCE TO TREATMENT AND RESPONSE OF CHOLESTEROL ON MORTALITY IN THE CORONARY DRUG PROJECT

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Abstract The Coronary Drug Project was carried out to evaluate the efficacy and safety of several lipid-influencing drugs in the long-term treatment of coronary heart disease. The five-year mortality in 1103 men treated with clofibrate was 20.0 per cent, as compared with 20.9 per cent in 2789 men given placebo ($P = 0.55$). Good adherers to clofibrate, i.e., patients who took 80 per cent or more of the protocol prescription during the five-year follow-up period, had a substantially lower five-year mortality than did poor adherers to clofibrate (15.0 vs. 24.6 per cent; $P = 0.00011$). However, similar findings were noted in the placebo group, i.e., 15.1 per cent mortality for good adherers and 28.3 per cent for poor adherers ($P = 4.7 \times 10^{-16}$). These findings and various other analyses of mortality in the clofibrate and placebo groups of the project show the serious difficulty, if not impossibility, of evaluating treatment efficacy in subgroups determined by patient responses (e.g., adherence or cholesterol change) to the treatment protocol after randomization. (N Engl J Med. 1980; 303:1038-41.)

MANY pitfalls are encountered in the analysis of data from clinical trials. This is true even of trials that are properly randomized, controlled, and double blind. Among these pitfalls are the following: repeated analysis of the data as they accrue over the course of the trial[1,2]; "fishing" through many end points, subgroups, and life-table intervals for maximal treatment effects[3-5]; and exclusion of certain groups of patients or events (or both) from analysis.[6]

Another pitfall is considered in this paper. Participants in a clinical trial will vary in adherence to the treatment regimen and in physiologic, biochemical, or behavioral response to the treatment or intervention. Accordingly, there is often temptation to evaluate the treatments with respect to mortality and morbidity in only the patients who adhered to the treatment regimen. Similarly, there is temptation to confine analysis to patients who manifested the desired effect of the intervention on some intermediate response (such as lowering of cholesterol or glucose, or suppression of platelet aggregation or cardiac arrhythmia).

However, such analyses are unreliable or misleading because of the manner in which patients are selected or select themselves into groups that are good or poor with respect to adherence or response. Data from the Coronary Drug Project for the clofibrate and placebo groups clearly document such problems.

METHODS

The Coronary Drug Project was a randomized, double-blind, placebo-controlled, multicenter clinical trial.[7,8] Its primary objective was to evaluate the efficacy and safety of several lipid-influencing drugs in the long-term therapy (secondary prevention) of coronary heart disease. The drugs given were mixed conjugated equine estrogens at two doses (2.5 and 5.0 mg per day), clofibrate (1.8 g per day), dextrothyroxine (6.0 mg per day), and nicotinic acid (3.0 g per day). Each of these drugs and a lactose placebo were dispensed in capsules that appeared identical.

From March 1966 to October 1969, 53 cooperating clinical centers entered 8341 patients into the study; approximately 1100 were randomized to each of the five drug groups, and 2789 were randomly assigned to the placebo group. To qualify, a prospective participant had to be a man 30 to 64 years of age with electrocardiographic evidence of a myocardial infarction that had occurred not less than three months previously. Patients were followed through clinic visits and examinations conducted every four months, for a minimum of five and a maximum of 8.5 years. The patient follow-up was concluded as scheduled, during the summer of 1974.

Each patient was given an initial prescription of one capsule of his assigned study drug or placebo, to be taken three times a day. Provided that this initial dose was well tolerated, the prescription was increased after one month to two capsules three times a day, and again after another month to the full dose of three capsules three times a day. At each of the four-month follow-up visits any changes in prescription were recorded, as well as the clinic physician's assessment of adherence to the drug regimen since the last scheduled follow-up visit. The physician made this latter assess-

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ment by counting or estimating the number of capsules returned by the patient at that visit and by talking with the patient about possible side effects or problems with the medication, difficulties in remembering to take the capsules, and similar topics. Thus, for each four-month follow-up period for each patient an estimate was obtained of the mean number of capsules actually taken per day. The percentage representing adherence to the protocol was computed as a ratio — the estimated number of capsules taken per day divided by the number of capsules dictated by the protocol dosage (nine per day) for each four-month period for each patient — multiplied by 100. The cumulative percentage of adherence was then computed for each patient for the first five years of follow-up or until death, if death occurred before the fifth anniversary of entry.

The risk factor chosen for intervention in the Coronary Drug Project was total serum cholesterol. This variable was measured at base line on three occasions at one-month intervals before the assigned study medication was started. Serum cholesterol was also measured at each of the four-month follow-up visits.[7] For the analyses involving cholesterol change that are reported in this paper, the change from base line (mean of the three values) to the fifth-anniversary value was recorded for patients surviving the first five years, and the change from base line to the last follow-up visit before death was recorded for those who died within five years of entry. Patients who died or left the study before any follow-up determination of serum cholesterol or adherence were excluded from the analyses.

The mortality results are presented as percentages ±1 S.E. of the percentage. The z values are defined in the usual way, i.e., drug-placebo difference in proportions divided by the standard error of the difference; z values of ±1.96 correspond to a conventional P value of 0.05. The method of multiple linear regression[9,10] was used to obtain drug-placebo differences in mortality adjusted for various base-line characteristics.

Results

Adherence and Mortality

As reported previously,[8] the five-year total mortality for the 1103 patients treated with clofibrate was only slightly lower, and not significantly lower, than that for the 2789 patients given placebo (20.0 vs. 20.9 per cent; $z = -0.60$, $P = 0.55$). Good adherers to clofibrate, i.e., patients who took 80 per cent or more of the protocol prescription during the five-year period, had a substantially lower five-year mortality than did poor adherers to clofibrate (15.0 vs. 24.6 per cent) (Table 1). The z value for this difference is −3.86, with a P value of 0.00011. But before accepting these values as evidence that clofibrate is beneficial, one must compare similar findings in the placebo group. The five-year mortality in good adherers to placebo was 15.1 per cent as compared with a 28.2 per cent mortality in poor adherers. The z value for this difference is −8.12, with a P value of 4.7×10^{-16} (Table 1). Since this difference cannot be due to a pharmacologic effect of the placebo, one must surmise that it is due to differences in patient characteristics in the two adherence subgroups. Therefore it may be inferred that even if some of the difference in mortality between good and poor adherers to clofibrate could be due to a beneficial effect, this effect would be entirely confounded by major differences in patient characteristics and prognosis in the two adherence subgroups.

In theory, it should be possible to account for the observed difference in mortality between good and poor adherers to placebo through use of multivariate statistical methods to adjust for differences at base line in the two patient groups. The 20 base-line characteristics most strongly associated with five-year mortality in the placebo group are given in Table 2 in the order of their selection by stepwise multiple regression analysis. This table shows that poor adherers did indeed tend to have a somewhat higher prevalence of base-line risk factors as compared with good adherers. A multiple linear regression analysis of five-year mortality and adherence was carried out on a total of 40 base-line characteristics (including the 20 in Table 2) as adjusting variables (the complete list of variables has been published elsewhere[9]). This analysis yielded adjusted five-year mortality figures of 16.4 per cent for good adherers and 25.8 per cent for poor

Table 1. Five-Year Mortality in Patients Given Clofibrate or Placebo, According to Cumulative Adherence to Protocol Prescription.

Adherence *	Treatment Group			
	Clofibrate		Placebo	
	no. of patients	*% mortality* †	*no. of patients*	*% mortality* †
<80%	357	24.6±2.3 (22.5)	882	28.2±1.5 (25.8)
≥80%	708	15.0±1.3 (15.7)	1813	15.1±0.8 (16.4)
Total study group	1065	18.2±1.2 (18.0)	2695	19.4±0.8 (19.5)

*A patient's cumulative adherence was computed as the estimated number of capsules actually taken as a percentage of the number that should have been taken according to the protocol during the first five years of follow-up or until death (if death occurred during the first five years).

†The figures in parentheses are adjusted for 40 base-line characteristics. The figures given as percentages ±1 S.E. are unadjusted figures whose S.E.'s are correct to within 0.1 unit for the adjusted figures.

Table 2. Prevalence of Base-Line Characteristics in Patients Given Placebo, According to Cumulative Adherence to Protocol Prescription.

Base-Line Characteristic	Per Cent Prevalence	
	<80% adherence	≥80% adherence
Depression of ST-segment	31.4	21.6
Use of diuretics	20.0	14.7
New York Heart Association Class 2	58.7	50.5
Ventricular conduction defect	3.1	4.5
Heart rate ≥70 on electrocardiogram	48.2	42.8
Cardiomegaly (definite or suspected)	20.9	16.3
≥2 previous myocardial infarctions	22.9	18.2
Intermittent claudication (definite or suspected)	10.5	7.4
Serum cholesterol ≥250 mg/dl (≥6.47 mmol/liter)	48.4	47.4
White-cell count ≥7500	49.3	42.2
Light physical activity	72.6	68.2
Ventricular premature beats	2.9	2.5
Serum total bilirubin ≥0.50 mg/dl (≥8.55 μmol/liter)	52.0	51.1
Q/QS patterns	64.8	60.4
Use of oral hypoglycemic agents	6.1	5.7
Serum triglycerides ≥5.0 meq/liter (≥1.67 mmol/liter)	54.8	52.1
Use of antiarrhythmic agents	4.2	4.3
Serum uric acid ≥7.0 mg/dl (≥0.42 mmol/liter)	43.1	44.1
Fasting plasma glucose ≥100 mg/dl (5.55 mmol/liter)	42.5	41.9
Use of antihypertensive agents	10.8	8.3

adherers, among subjects receiving placebo (Table 1). The adjusted z value is -5.78, with a P value of 7.3×10^{-9}. Therefore adjustment for the excess prevalence of base-line risk factors in the group of poor adherers accounts for only a small portion of the observed difference in mortality between good and poor adherers. Obviously, there must be characteristics differentiating between good and poor adherers (e.g., alcohol use and abuse, behavioral characteristics, or socioeconomic status) not accounted for by the variables assessed in the Coronary Drug Project.

Other analyses indicate additional difficulties in interpreting data on adherence and mortality. The five-year mortality was 24.6 per cent for poor adherers in the clofibrate group, as compared with 19.4 per cent for all patients, regardless of adherence, in the placebo group. On the other hand, mortality in good adherers in the clofibrate group was substantially lower than mortality in the placebo group (15.0 vs. 19.4 per cent) (Table 1). However, it may be argued that combining the two adherence subgroups of the placebo group in such an analysis is almost certainly inappropriate, since the two subgroups have such dissimilar mortality results. If the adherence subgroups for clofibrate are compared with the corresponding subgroups for placebo, the five-year mortality in poor adherers to clofibrate is lower than that in poor adherers to placebo (24.6 vs. 28.2 per cent), whereas there is no difference in mortality between good adherers in the clofibrate group and good adherers in the placebo group (15.0 vs. 15.1 per cent) (Table 1). Therefore, one can justify almost any conclusion, depending on the analysis chosen. It is doubtful that any valid conclusions can be drawn from such analyses, because there is no way of ascertaining precisely how or why the patients in the clofibrate and placebo groups have selected themselves or have become selected into the subgroups of good and poor adherers.

Cholesterol Response and Mortality

Table 3 shows some of the problems of interpreting the data on cholesterol response and mortality; it gives the five-year mortality according to base-line cholesterol level and change in cholesterol from base-line level to the last follow-up visit. The mortality results are adjusted by multiple regression for the 40 base-line characteristics. The first two entries in the table suggest that clofibrate is somewhat more efficacious than placebo in patients with base-line cholesterol levels of 250 mg per deciliter (6.47 mmol per liter) or higher, but that it has the same efficacy as placebo in patients with lower cholesterol levels. It might be supposed that the reason that clofibrate-treated patients with higher base-line cholesterol levels had better results is that they had a greater potential for lowering cholesterol. The next two entries in Table 3 strengthen this supposition since they indicate that patients given clofibrate had a lower mortality than patients given placebo among the patients whose cholesterol level fell, and that patients given clofibrate had a higher mortality than patients given placebo among the patients whose cholesterol rose above base line. The greatest reduction in mortality in response to clofibrate might therefore be expected in the group of patients with high initial cholesterol levels that fell during the follow-up period. However, the data in the last four lines of Table 3 do not bear out this expectation. In clofibrate-treated patients with lower base-line levels, a fall in cholesterol was associated with a much lower mortality than was a rise in cholesterol. But among patients with the higher base-line levels, those whose cholesterol rose actually did somewhat better than those whose cholesterol fell. It appears that the greatest reduction in mortality in response to clofibrate is found in patients with low initial levels of cholesterol that decreased even further and in those with high initial levels that increased even further. The group with high base-line levels and a later fall is only in third place, although well within random variation of the results for the two groups with the lowest mortality rates.

Table 3. Five-Year Mortality According to Base-Line Cholesterol Level and Change from Base-Line Level, Adjusted for 40 Base-Line Characteristics.

Base-Line Cholesterol mg/dl	Cholesterol Change *	Treatment Group			
		Clofibrate		Placebo	
		no. of patients	*% mortality* †	*no. of patients*	*% mortality* †
<250	All men	507	20.0±1.8	1319	19.9±1.1
⩾250	All men	490	17.5±1.7	1216	20.6±1.2
All men	Fall	680	17.2±1.4	1376	20.7±1.1
All men	Rise	317	22.2±2.3	1159	19.7±1.2
<250	Fall	295	16.0±2.1	614	21.2±1.6
<250	Rise	212	25.5±3.0	705	18.7±1.5
⩾250	Fall	385	18.1±2.0	762	20.2±1.5
⩾250	Rise	105	15.5±3.5	454	21.3±1.9

*The direction of change in patient's cholesterol level was determined by comparison of the fifth-anniversary value or last value before death (if death occurred during the first five years) with the base-line value.

†±1 S.E.

If there were no random error in the results given in Table 3, could such data represent true effects of clofibrate on mortality? Probably not, for the same reasons that the data on adherence and mortality cannot be taken at face value, i.e., not enough is known about the ways in which different patients are selected or select themselves into a group that has a response (lowered cholesterol) and a group that does not.

Discussion

Although treatment with clofibrate did not lessen mortality or cardiovascular morbidity in the Coronary Drug Project, the question has been raised, both within and outside[11] the group of study investigators, of whether mortality and morbidity were reduced in patients who adhered well to the clofibrate treatment regimen and in those in this study group who had a fall in serum cholesterol. But after looking at this

problem in several ways and carrying out many analyses on subgroups defined according to level of cholesterol change and level of adherence to the protocol dosage of nine capsules per day, the Coronary Drug Project Research Group concluded that no valid conclusions could be drawn from these data.

When the total group of patients or the subgroups defined by characteristics determined before initiation of treatment are being considered, the placebo group can be used as a valid comparison group against which to evaluate the results in the drug group. This comparison is made possible by the process of randomization, which tends to provide a balance of prognostic factors between the drug and placebo groups, whether or not these variables are known to the investigators. But for subgroups of patients defined after randomization by characteristics measured during the follow-up period (and influenced by the study protocol), it is difficult if not impossible to define subgroups of patients given a placebo that can serve as valid comparison groups for corresponding subgroups of patients given a drug. Consider the following arguments.

(1) The reasons for lowered cholesterol in the clofibrate group were quite different from those in the placebo group, e.g., a reduction in cholesterol in a patient treated with clofibrate was probably due, at least in part, to a biochemical response to the treatment, whereas a reduction in cholesterol in a patient given placebo may have been a result of regression to the mean, dietary changes, chance variation, or other factors. The reasons for good adherence were also different in the two groups.

(2) The factors predicting which patients will adhere well or poorly to a treatment protocol, or respond or not respond to it are not yet well identified, and those that are known are quite different in the two groups.

(3) Therefore, there is no assurance that the multitude of prognostic factors for mortality are even approximately balanced between the two treatment groups within each of the adherence subgroups or cholesterol-response subgroups. Although adjustments can be made in the analyses for factors that are known and measured, there are still many unknown prognostic factors affecting mortality, and the distribution of these factors in the two treatment groups, within adherence or cholesterol-response subgroups, cannot be determined.

For these reasons the many advantages provided by randomization when subgroups are defined by baseline characteristics are lost when follow-up responses are used to define patient subgroups.

In conclusion, analyses of data from the Coronary Drug Project have demonstrated the great difficulty, if not impossibility, of drawing any valid conclusions from findings about mortality or morbidity in subgroups defined by patient responses — such as adherence or biochemical response — to a treatment.

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