The Coronary Drug Project

Initial Findings Leading to Modifications of Its Research Protocol

The Coronary Drug Project Research Group

Physicians face a difficult dilemma concerning pharmacologic therapy for hyperlipidemia in patients with a history of clinical coronary heart disease (CHD). They know that susceptibility to first episodes of premature CHD is directly related to serum levels of cholesterol, and low-density and very-low-density lipoproteins.[1] They are also aware that elevated serum lipids-lipoproteins frequently can be reduced long-term by available drugs. However, they lack the answers to key questions about these pharmaceutical agents: Do they prevent recurrent episodes of CHD and prolong life? What is their mechanism of action? Are they reasonably safe, in long-term usage?

The paucity of scientific data on these critical questions is especially troublesome in view of other problems: Treatment of coronary disease by control hyperlipidemia makes sense only as years-long therapy—and questions about drug toxicity are especially gnawing under this circumstance. Furthermore, almost all the data proving the association between hyperlipidemia and risk of CHD relate to *first* episodes of the disease.[1] It is not yet clear whether hyperlipidemia also influences risk of *recurrent* nonfatal and fatal CHD events in survivors of a first attack; only limited data are available on this important question.[2-6] Thus, no solid body of information exists to assure practitioners of the rationale for treating hyperlipidemia in patients with coronary disease. Finally, the physicians' dilemma—stemming from uncertainty as to rationale, safety, and efficacy—is compounded by awareness of the relatively recent unfortunate experience with triparanol. Therefore, the widespread uncertainty of many physicians with respect to long-term drug treatment of hyperlipidemia in patients with coronary disease is fully understandable.

Many pharmaceutical agents lower serum lipid levels, and several have been extensively investigated in man and animals. They include cholestyramine resin, clofibrate, estrogens, heparin, niacin (nicotinic acid), plant sterols, thyroid hormones and their dextro-analogues.[1] While a vast literature exists on these and other substances, definitive knowledge is not available concerning long-term safety and efficacy of any preparation. Until recently, few field trials had been undertaken to obtain the critically needed information. The earlier studies dealt exclusively with estrogens.[1,7-10] Carried out in the 1950s, they produced contradictory and inconclusive results, almost certainly because of the small size of the samples.

In recent years, more extensive studies have been launched. These include British trials assessing clofibrate (written communications, 1970, from H. A. Dewar and M. Oliver, respectively); a Veterans Administration cooperative study of dextrothyroxine, estrogens, and niacin (written communication, 1970, from H. Schnaper); and the Coronary Drug Project.[5,6,11] For the most part, these are still in progress, or at least their definitive findings have not yet been reported. One of these studies—the national cooperative Coronary Drug Project (CDP) in the United States—is the most extensive trial ever undertaken of secondary prevention of atherosclerotic coronary disease with pharmaceutical agents.[5,6,11]

The present report deals with early findings of the CDP, particularly the potentially adverse effects noted to date with certain of the drug regimens that have led to changes in the research protocol of this therapeutic trial.

Methods

After extensive planning for design, protocol, organization, implementation, and operations, initial field work in the Coronary Drug Project was begun in March 1965. Thereafter, the study was progressively expanded to 53 investigative centers. The CDP is proceeding under the operational scientific leadership of a Steering Committee, and under the supervision of a Policy Board. It is financed by the National Heart and Lung Institute as a collaborative study, with the NHLI as active participant through assignees from its professional staff. A Coordinating Center is located at the Institute of International Medicine, University of Maryland School of Medicine. This study is also served

For a complete list of the key bodies of the Coronary Drug Project and senior staff members see page 1312.

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by an ECG Center at the Laboratory of Physiological Hygiene, University of Minnesota; by a Central Laboratory for biochemical determinations at the National Center for Disease Control of the Public Health Service in Atlanta; and by a Central Drug Procurement Distribution facility at the PHS Supply Service Center, Perry Point, Md. Effective liaison and coordination are accomplished through the Steering Committee, with representatives from all key groups of the project, including the group of principal investigators responsible for the 53 field research centers. All the latter—as well as leaders of other operational units of the study—are members of the Technical Group, meeting semiannually. Another key body is the Data and Safety Monitoring Committee, with responsibility for bimonthly review of confidential interim data on the end points of the study.

The primary objective of the CDP is to test efficacy and safety of several drugs in the long-term therapy of coronary heart disease in men aged 30 to 64 with proved previous myocardial infarction (MI). The pharmacologic agents under investigation (with their abbreviated designations) are as follows: conjugated estrogens, 2.5 mg/day (ESG1); conjugated estrogens, 5.0 mg/day (ESG2); clofibrate, 1.8 gm/day (CPIB); dextrothyroxine, 6.0 mg/day (DT4); niacin, 3.0 gm/day (NICA); and placebo (PLBO). The primary end point for assessment of therapeutic value is five-year total death rate. In addition, many other end points are being monitored in relation to drug efficacy and toxicity, eg, incidence and mortality of myocardial infarction, congestive heart failure, and stroke; incidence rates of intermediate coronary episodes called acute coronary insufficiency (ACI), angina pectoris (AP), and ECG changes; and biochemical data relating to possible toxicity of drugs.

Assessment of the efficacy of drugs in this controlled study is being made by comparison of each drug group with the group randomly assigned to placebo treatment. The inclusion of a placebo group also affords the opportunity to accrue new information on the natural history of coronary heart disease, which is an important secondary objective of the study. An initial report concerning this aspect of the study is currently in press.[5]

The large sample of patients required for a definitive assessment of drug efficacy could be recruited only through a national cooperative effort involving many research groups. Another basic aim of this investigation, therefore, is to acquire additional experience and knowledge concerning the overall methodology of large-scale, long-term collaborative clinical trials in chronic, noninfectious diseases.

Patients randomized into the CDP were men aged 30 to 64 with evidence of one or more myocardial infarctions, categorized as class 1 or 2 of the functional classification of the New York Heart Association,[12] and free from a specified list of excluding diseases and conditions. All patients were confirmed to be at least three months beyond their most recent MI, and free of evidence of recent worsening of their coronary disease or of other major illnesses. They were also classified as to risk. Risk 1 includes men with a single MI free of defined serious complications during the acute episode. Risk 2 includes men with two or more MIs, and men with a single MI who during the acute episode did have one or more defined complications (eg, pericarditis, congestive failure, shock, arrhythmia, extension of infarction).

Patients still eligible at the end of a two-month control period were randomly allocated to one of the six medication schedules. A separate random allocation schedule was utilized by the Coordinating Center for each of the two risk groups within each participating clinic. Each schedule was designed to assure approximately equal numbers of patients in the five drug groups, and approximately five patients in the placebo group for every two patients in any of the other groups.

The first major task of the CDP was recruiting the required number of eligible patients. In accordance with sample size estimates originally made by CDP statisticians, the investigators in the clinical centers had pledged to enroll 8,210 patients. Intake of new patients ceased on June 30, 1969. The final total of men patients randomly assigned to treatment groups was 8,341.

The study is conducted as double blind in the sense that neither the patient nor the clinic staff is informed of patient drug allocation, except as may be required in a verified medical emergency. Initial prescription of assigned medication was three capsules per day, supplying one third of ultimate full dosage (see above), with an increase at monthly intervals to six and then to the maximum of nine capsules per day, unless the managing physician altered the regimen for specified reasons.

Each patient is to be followed for a period of at least five years. He reports to the clinic every four months for a follow-up visit. Complete routine examination, including a resting electrocardiogram, is made annually. Complaints and findings suggestive of illness or toxicity are thoroughly evaluated by the research clinic. In all circumstances, the Protocol and Manual of Operations allow full leeway for optimal medical care for patients with myocardial infarction.

Data in a standard format are sent to the Coordinating Center from the clinics and are continuously monitored for "events," including death, recurrent MI, ACI, angina pectoris, ECG changes reported by the investigators, stroke, venous thromboembolism, etc, and other findings such as flushing, feminization, nausea,

jaundice, or deviations of serum enzyme levels from baseline values.

Regularly scheduled annual resting ECGs are particularly free of possible sources of bias in that they are routinely recorded in all patients and centrally classified by technicians completely blinded to the study variables. A modification of the Minnesota Code allows tabulation of individual and group findings for ECG items of interest (Q waves, ST segment, and T waves) according to three anatomical sites (anterior, lateral, and inferior) as well as by severity within sites, and by classes for rhythm and conduction defect, etc.[13,14] Serial changes between scheduled ECGs are also coded by unambiguous "criteria for a significant change" so that it is possible to make objective group comparisons of the time trends in the ECG.

One of the major challenges facing the Coronary Drug Project has been in the area of the techniques to be used for statistical evaluation of observed differences between an individual treatment group and the placebo group. The usual approach to tests of significance—eg, declaring a Student's t of 2 as significant with $P = 0.05$—has definite limitations in application for a study of this type. The difficulties in applying these tests stem from at least three specific design features of the CDP: its effort to evaluate five treatment groups, rather than merely one; its plan to review end point data at frequent intervals throughout the study, to detect any positive therapeutic effects as soon as possible and to assure maximum safety and minimize the impact of possible adverse effects; and its plan to evaluate multiple fatal and nonfatal end points as well as to examine subgroups of the population. In an attempt to cope at least partially with these problems, two approaches for evaluation of statistical significance were developed by CDP statisticians. One is a modification of fairly standard sequential statistical testing procedures, the other is a Bayesian approach.[15] Both methods are more stringent than usual significance tests in terms of differences in rates between an experimental and control group required to designate statistical "significance."

In the first approach, the observed drug-placebo differences in proportions of individuals with a given event are plotted over time, a new point being plotted every month. Sequential boundaries have been constructed in such a way that, if the null hypothesis of no treatment difference is true, there is only a 5% chance of the observed drug-placebo difference in event rate crossing the boundaries. A crossing of the upper boundary would indicate that the drug is worse than placebo, while a crossing of the lower boundary would signify a beneficial drug effect.

The Bayesian approach produces a numerical value designated as RBO, which stands for relative betting odds. An RBO value of 4 means the relative odds for the null hypothesis of no treatment difference are 4 to 1, ie, are in favor of the null hypothesis. Similarly a value of 0.25 means the relative odds for the null hypothesis are .25 to 1, ie, are 4 to 1 against the null hypothesis.

At scheduled meetings of the Data and Safety Monitoring Committee, Policy Board, Steering Committee, and Technical Group in May 1970, extensive interim reviews were accomplished of data relating to all end points under surveillance. Complete data were available as of Feb 1, 1970, representing an average follow-up of 18 months, and data on total mortality were current to May 12, 1970. As a result of this review, protocol changes—as described below—were made for two of the study regimens.

Results

The 5.0-Mg Estrogen Group (ESG2).—The data reviewed in May 1970 indicated that certain nonfatal adverse effects were occurring substantially more often in the ESG2 group than in the placebo group. With an average of 18 months of follow-up, the data analysis indicated an excess number of events of nonfatal myocardial infarction, pulmonary embolism, and thrombophlebitis for the ESG2 group, compared with the placebo group (Table 1). Only 3.2% of placebo patients had experienced a definite nonfatal myocardial infarction as of Feb 1, 1970, as opposed to 6.2% of men in the 5.0-mg estrogen group. The difference was significant at the 0.05 level by the modified sequential testing procedure. The statistical evaluation by the Bayesian method yielded an RBO of 0.02, ie, relative odds of 50 to 1 against the null hypothesis of no treatment difference.

The overall percentages for new events of definite coronary disease, ie, the combination of nonfatal myocardial infarction and coronary death, were 7.5 for the placebo and 11.0 for the ESG2 group (Table 1). The RBO for this comparison is 0.13, indicating odds of almost 8 to 1 against the null hypothesis. (Results are not available using the sequential boundaries method.)

Death rates evaluated—ie, coronary death, sudden death, and total mortality—were all slightly although insignificantly higher for the ESG2 group, compared to placebo. The RBOs were 0.46 for sudden death, 2.48 for coronary death, and 3.20 for total mortality. The differences in total mortality between the ESG2 and placebo groups at no point reached the sequential boundaries (Table 1).

Further evaluation of these findings included life table analyses for each of the foregoing end points, with the placebo and 5.0-mg estrogen groups stratified by entry risk classification and age. The graphic representation in the Figure deals with differences in cumulative event rates between ESG2 and placebo

groups at specified intervals after entry into the study. Any curve above the 0.0 line indicates a higher rate for the estrogen than for the placebo group. As of the Feb 1, 1970, data analysis, about two thirds of the patients had completed one year in the study, and almost one quarter had completed two years.

The Figure illustrates the trend of higher incidence rates of nonfatal MI developing in three of the four subgroups during the 24-month period of observation. The difference increased progressively during the first year of follow-up, and then remained at a more-or-less fixed level thereafter. The one seemingly exceptional ESG2 subgroup—men aged 55 and older, risk 2—experienced higher CHD death rates than the placebo group. Therefore, its lower rate for nonfatal MI may be due to greater susceptibility to fatal MI, rather than resistance to nonfatal MI (Figure).

The Figure also shows that when the data on nonfatal and fatal coronary events were combined to yield a life table graph, each of the four ESG2 subgroups registered a trend for the rates to be higher than rates of the placebo group, although in no case was the difference statistically significant.

Only one subgroup of ESG2 patients—the aforementioned men aged 55 or older, risk 2—showed a clear-cut trend to higher mortality from all causes. No such trend was present for the other three subgroups (Figure), or for all four subgroups combined (Table 1).

Data on reported percentages of pulmonary embolism and thrombophlebitis for the ESG2 and placebo groups are presented in Table 1. Although the percentages were generally low, they were significantly higher in the 5.0-mg estrogen than in the placebo group. No fatal venous thromboembolic events occurred in the estrogen group; one pulmonary embolism was fatal in the placebo group.

Table 1.—Nonfatal and Fatal Events in 5.0-Mg Estrogen (ESG2) and Placebo Groups*

Event	ESG2 (total 1,119) No.	ESG2 (total 1,119) %	Placebo (total 2,788) No.	Placebo (total 2,788) %	RBO†
Definite nonfatal MI‡	63	6.2	82	3.2	0.015
MI incidence (definite nonfatal MI + coronary death)	123	11.0	209	7.5	0.13
Definite pulmonary embolism	17	1.5	10	0.4	0.045
Suspect and definite pulmonary embolism or thrombophlebitis	39	3.5	37	1.3	0.004
Coronary death	67	6.0	133	4.8	2.48
Sudden death	48	4.3	76	2.7	0.46
Total mortality	91	8.1	193	6.9	3.20
Total mortality§	108	9.7	230	8.2	3.38

*All data in this and subsequent tables are as of Feb. 1, 1970, except for data in bottom row (second listing of "total mortality") in this table.
†RBO signifies relative betting odds (Bayesian approach[15]).
‡MI signifies myocardial infarction. Denominators for nonfatal MI are 1,022 and 2,580 for ESG2 and placebo groups, respectively.
§As of May 12, 1970.

Table 2.—Clinic Distribution of ESG2-Placebo Differences in Percentages of Various Events*

Event	Number of Clinics: ESG2 >Placebo	ESG2 <Placebo	ESG2 = Placebo
Definite nonfatal MI	33	13	7
MI incidence	36	16	1
Coronary death	24	22	7
Total mortality	30	22	1

*ESG2 signifies 5.0 mg conjugated estrogen per day; MI, myocardial infarction.

Differences in percentages of nonfatal adverse events between ESG2 and placebo groups were also compared clinic by clinic, and the number of clinics exhibiting a higher percentage for each of the specified end points for the ESG2 compared with the placebo group was determined (Table 2). This additional comparison shows that the higher percentages for patients receiving estrogen compared with placebo patients for definite nonfatal MI did not arise from a mere handful of clinics.

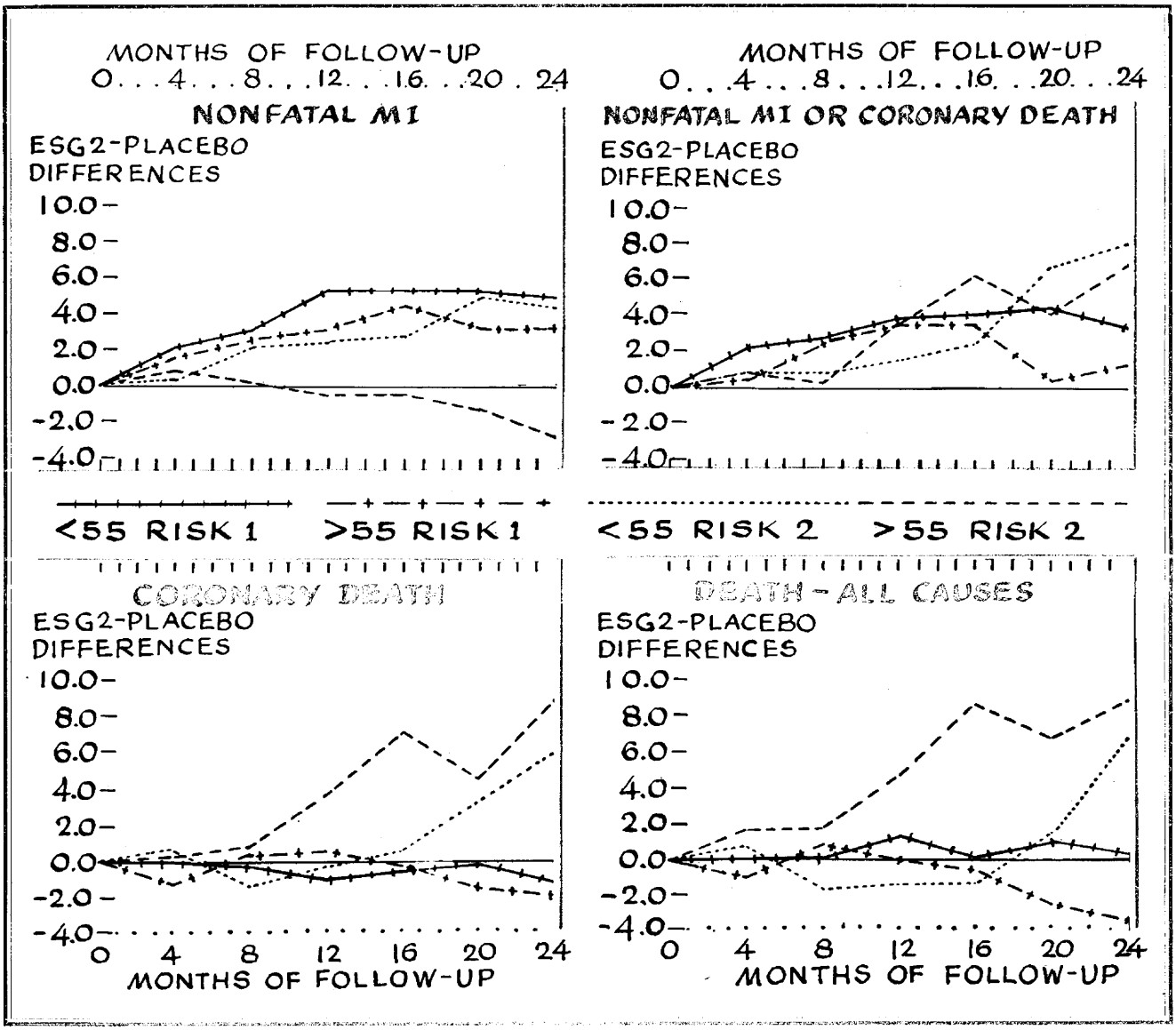
Obviously, for the valid evaluation of these findings, it is essential to assess whether the process of randomization resulted in similarity of the ESG2 and placebo groups in regard to characteristics known or suspected to influence long-term prognosis of middle aged men with previous MI. To evaluate this matter of comparability, detailed tabulations for the two treatment groups were made for multiple baseline findings, considered singly and in various combinations (Table 3). These data, as well as many other comparisons, show that randomization had resulted in marked similarity of the two treatment groups with respect to baseline demographic, medical, biochemical, and electrocardiographic findings. Therefore, any significant differences in findings with respect to nonfatal adverse effects apparently cannot be attributed to baseline differences between the two groups in susceptibility to these events.

An analysis of covariance was also done to assess whether the observed differences in nonfatal MI rates were attributable to differences in risk of the two groups at entry. This involved 22 variables known or presumed to be related to long-term prognosis for patients recovered

Table 3.—Percentage of Men With Various Findings at Entry: 5.0-Mg Estrogen (ESG2) and Placebo Groups

Risk Factors*	Percentage Distribution	
	ESG2 (1,119 Men)	Placebo (2,788 Men)
Age at entry < 55	52.0	55.0
Age at entry ≧ 55	48.0	45.0
Risk group 1	66.0	65.7
Risk group 2	34.0	34.3
White race	93.6	93.3
Nonwhite race	6.4	6.7
One MI only—good risk	66.0	65.6
One MI only—poor risk	16.3	14.5
Two MIs only	15.4	16.4
Three or more MIs	2.3	3.5
NYHA class 1	46.1	46.5
NYHA class 2	53.9	53.5
History of CHF—no	82.6	84.0
History of CHF—yes	17.4	16.0
History of AP—no	42.3	42.2
History of AP—yes	57.7	57.8
History of ACI—no	82.7	83.6
History of ACI—yes	17.3	16.4
History of IC—no	91.1	91.2
History of IC—yes	8.9	8.8
Heart rate < 80/min	67.4	67.1
Heart rate ≧ 80/min	32.6	32.9
Qualifying ECG—ST-T criteria only	18.4	16.6
Qualifying ECG—class 2 Q Waves	32.6	34.2
Qualifying ECG—class 1 Q Waves	49.1	49.2
Baseline ECG—no Q/QS abnormality	41.5	37.8
Baseline ECG—minor Q/QS abnormality	14.9	16.1
Baseline ECG—moderate Q/QS abnormality	20.2	22.2
Baseline ECG—major Q/QS abnormality	23.4	23.9
Age ≧, 55, risk 2, AP, NYHA 2, CHF		
None of five	13.7	13.7
One only of five	20.3	22.0
Two only of five	28.3	27.0
Three only of five	20.7	22.4
Four only of five	12.9	11.1
All five	4.1	3.8
Cholesterol < 250 mg/dl	51.9	53.5
Cholesterol ≧ 250 mg/dl	48.1	46.5
Triglyceride < 5.0 mEq/liter	50.3	49.8
Triglyceride ≧ 5.0 mEq/liter	49.7	50.2
Uric acid < 8.0 mg/dl	78	80.4
Uric acid ≧ 8.0 mg/dl	21.3	19.6
Fasting plasma glucose < 100 mg/dl	57.4	57.9
Fasting plasma glucose ≧ 100 mg/dl	42.6	42.1
1 Hr plasma glucose < 205 mg/dl	77.2	77.0
1 Hr plasma glucose ≧ 205mg/dl	22.8	23.3
Noncigarette smokers	63.5	62.1
Cigarette smokers	36.5	37.9
Systolic BP < 140 mm Hg	68.0	69.3
Systolic BP ≧ 140 mm Hg	32.0	30.7
Diastolic BP < 90 mm Hg	73.9	71.9
Diastolic BP ≧ 90 mm Hg	26.1	28.1
Relative body weight < 1.25	80.5	77.6
Relative body weight ≧ 1.25	19.5	22.4
Cholesterol ≧ 250, 1-hr glucose ≧ 205		
Uric acid ≧8.0, DBP ≧ 90		
Cigarette smoker, relative wt ≧ 1.25		
None of six	22.0	21.5
One only of six	40.6	41.0
Two only of six	27.7	28.2
Three only of six	8.8	8.0
Four or more of six	1.0	1.3

*MI signifies myocardial infarction; CHF, congestive heart failure; NYHA, New York Heart Association; AP, angina pectoris; ACI, acute coronary insufficiency; IC, intermittent claudication; DBP, diastolic blood pressure.



Differences between ESG2 and placebo groups in morbidity and mortality rates—life table analyses. Any curve above 0.0 line indicates higher rate for ESG2 than placebo group; any curve below line indicates a lower rate. Data are as of Feb 1, 1970.

from myocardial infarction. As expected from the comparability data of Table 3, this analysis showed that the differences between estrogen and placebo groups in rates of nonfatal MI could not be attributed to differences in susceptibility at entry, based on these variables.

It was further recognized that occurrence of such side effects as breast tenderness, breast enlargement, and suppressed libido in most ESG2 patients led to effective "unblinding" of the double-blind design to a considerable degree, for both clinicians and patients. Therefore, the possibility presented itself of bias against the estrogen group in the presentation and evaluation of complaints and consequently in diagnoses of nonfatal events. In an attempt to assess this problem as objectively as possible for the project overall, five types of analyses were accomplished.

One approach involved a detailed analysis of all hospitalizations for nonfatal adverse cardiovascular events in the two groups, estrogen and placebo. It was hypothesized that any observer bias in the direction of overdiagnosis of events for the ESG2 group would be associat-

Table 4.—Patients Hospitalized Since Entry: 5.0-Mg Estrogen (ESG2) and Placebo Groups

Duration of Hospitalization	Cause of Hospitalization	ESG2 (total 1,022)		Placebo (total 2,579)	
		No.	%	No.	%
> 28 Days	All causes	41	4.0	62	2.4
	Circulatory causes	32	3.1	41	1.6
	Cardiac causes	27	2.6	28	1.1
> 14 Days	All causes	120	11.7	191	7.4
	Circulatory causes	89	8.7	129	5.0
	Cardiac causes	69	6.8	103	4.0
All	All causes	280	27.4	564	21.9
	Circulatory causes	171	16.7	301	11.7
	Cardiac causes	139	13.6	257	10.0

Table 5.—Subsequent Cardiovascular Deaths of Patients With Definite Nonfatal MI After Entry: 5.0-Mg Estrogen (ESG2) and Placebo Groups

ESG2 (63 Men)		Placebo (82 Men)	
No.	%	No.	%
8	12.7	7	8.5

Table 6.—Patients With Various Cardiovascular Events*: 5.0-Mg Estrogen (ESG2) and Placebo Groups

Event†	ESG2			Placebo		
	Men at Risk, No.	Men With Event‡		Men at Risk, No.	Men With Event‡	
		No.	%		No.	%
(A) Cardiovascular death	1,119	75	6.7	2,788	151	5.4
(B) Definite MI—not event A	1,044	55	5.3	2,637	75	2.8
(C) Suspect MI—not A or B	989	13	1.3	2,562	29	1.1
(D) Definite ACI—not A-C	976	28	2.9	2,533	73	2.9
(E) Suspect ACI—not A-D	948	46	4.9	2,460	115	4.6
(F) Definite AP—not A-E	902	48	5.3	2,346	134	5.7
(G) Suspect AP—not A-F	854	41	4.8	2,212	88	4.0
(H) Definite or suspect CHF—not A-G	813	68	8.4	2,124	117	5.5

*Conditional on absence of other events.
†MI signifies myocardial infarction; ACI, acute coronary insufficiency; AP, angina pectoris; CHF, congestive heart failure.
‡Each man appears in no more than one numerator.

Table 7.—Patients With Significant Worsening of ECG: 5.0-Mg Estrogen (ESG2) and Placebo Groups*

Type of ECG Worsening	ESG2 (622 Men)		Placebo (1,672 Men)	
	No.	%	No.	%
(A) Q/QS patterns	56	9.0	143	8.6
(B) Q/QS and T	18	2.9	44	2.6
(C) T-Wave items	61	9.8	153	9.2
(D) ST depression	53	8.5	104	6.2
(E) ST elevation	11	1.8	43	2.6
(F) A-V conduction	8	1.3	26	1.6
(G) Ventricular conduction	17	2.7	34	2.0
(H) Frequent ventricular ectopic beats	20	3.2	56	3.3
(I) Arrhythmia†	0	0.0	9	0.5
(J) A or B	72	11.6	179	10.7
(K) A, B, or C	119	19.1	293	17.5
(L) C, D, or E	93	15.0	233	13.9
(M) A-E	144	23.2	361	21.6
(N) Any of above	174	28.0	447	26.7

*Worsening of ECG as compared to baseline; all follow-up visits combined.
†Includes ventricular tachycardia, supraventricular tachycardia, atrial fibrillation, idioventricular rhythm and A-V nodal rhythm, but not supraventricular premature beats, sinus tachycardia or sinus bradycardia.

ed with shorter durations of hospitalization for these patients, since they would tend to be admitted more frequently for suspect events, only to be discharged relatively early. Data to test this hypothesis are presented in Table 4. The findings do not support the hypothesis, since they indicate at least an equal frequency—in fact a somewhat higher frequency—of prolonged hospital stays for the 5.0-mg estrogen group, compared with placebo.

It was further hypothesized that overdiagnosis of nonfatal cardiovascular events, particularly definite MI, due to any bias among clinicians would find its reflection in a lower subsequent death rate in such patients, compared with their counterparts from the placebo group. Although only a limited time experience has thus far been accumulated to test this hypothesis, the data do not sustain it (Table 5). In the ESG2 group, of 63 men with a diagnosis of definite nonfatal MI, eight (12.7%) had died subsequently by Feb 1, 1970. For 82 corresponding men of the placebo group, seven (8.5%) had died subsequently. Mortality was higher—rather than lower—for men with a previous diagnosis of definite nonfatal MI in the 5.0-mg estrogen group than for men in the placebo group. This evidence, therefore, can be regarded as inconsistent with the hypothesis of biased overdiagnosis of nonfatal definite MI in ESG2 patients.

A third analysis in this area dealt with all nonfatal events in a ranked order, and yielded rates for the occurrence of each in the absence of a diagnosis of an event of the higher rank. The data generated in this analysis are presented in Table 6, presenting the ranking utilized. If it be hypothesized that observer bias might lead to overdiagnosis of a

more severe type of nonfatal cardiac event, in preference to a less severe type—eg, diagnosis of definite MI rather than suspect MI or ACI—then it follows that the higher rates for the more severe event, definite MI, in the ESG2 group would be associated with correspondingly lower rates for the less-severe events. Again, the data do not support this hypothesis. For all but one of the cardiac diagnoses, the rate for the ESG2 group was at least as high as the rate for the placebo group. (The only apparent exception was definite angina pectoris, with rates of 5.3% and 5.7%, for the ESG2 and placebo groups, respectively.) These data, then, do not support the hypothesis of spurious overdiagnosis of nonfatal major cardiac events in the 5.0-mg estrogen group, compared with the placebo.

Another evaluation of possible bias utilized all available routine ECGs, taken at annual physical examinations on anniversary of entry into the study. These were evaluated on a blind basis by the ECG Center (Table 7). This analysis revealed that rates for "significant worsening" of the ECG—in the form of Q/QS, plus Q/QS and T pattern—were higher for both the 5.0-mg estrogen and placebo groups than incidence rates of reported clinical nonfatal MI (cf Table 1). In fact, the combined rates for these two types of ECG developments—11.6% and 10.7% for ESG2 and placebo groups respectively—were more than double the reported rates for clinical nonfatal MI. Moreover, in contrast to the higher rate of clinical MI reported for the ESG2 group compared with placebo, the analysis of annual ECGs revealed only a small and insignificant difference in rate of worsening between the two groups. This inconsistency appears to favor the hypothesis that the difference in rate between the estrogen and placebo group is spurious, possibly a by-product of diagnostic bias. However, a routine annual ECG—because of the well-known reversibility of some ECG infarct manifestations, and other inherent limitations in the ECG diagnosis of infarction—may not be a highly accurate measure of interim infarction. No guidelines are available in the medical literature to aid in definitively assessing the significance of the relatively high rates recorded by the CDP for significant worsening of the ECG in both ESG2 and placebo groups, particularly in the absence of clinically diagnosed MI, as was often the case. Only long-term prospective observation of these patients can clarify the prognostic significance of such previously unreported ECG trends. The Coronary Drug Project anticipates that it will be able to clarify this matter appreciably over the next years.

Table 8.—Significant Worsening on Event ECG in Patients With Clinical Diagnosis of Definite Nonfatal MI: ESG2 and Placebo Groups*

Type of ECG Worsening	ESG2 (63 Men)		Placebo (82 Men)	
	No.	%	No.	%
Q/QS	23	36.5	26	31.7
Q/QS and/or T	42	66.7	45	54.9
Q/QS, T, ST depression and/or ST elevation	46	73.0	52	63.4
Any significant worsening†	47	74.6	56	68.3
No significant worsening	8	12.7	19	23.2
No ECG data available	5	7.9	5	6.1
ECG pending	3	4.8	2	2.4

*Worsening on event ECG as compared to previous annual ECG.
†Includes foregoing items, also arrhythmias and conduction defects.

Finally, central reading was done of ECGs submitted in connection with coronary events reported by the clinics. The CDP Protocol and Manual of Operations provide that ECGs must be submitted to the Coordinating Center in connection with diagnosis of all such events, definite and suspect, in addition to routine ECGs done as part of annual-visit examinations. Electrocardiograms submitted with reports of coronary events are transmitted by the Coordinating Center to the ECG Center for "blind" reading according to the special Minnesota code developed for this purpose (see *Methods*). It is reasonable to hypothesize that biased overdiagnosis of nonfatal MI in ESG2 patients by clinicians would be associated with a lower proportion of ECGs with definite evidence of acute myocardial infarction for ESG2 compared with placebo patients. As is evident from Table 8, the data do not support this hypothesis. Rather they support the conclusion that similar substantial ECG confirmation was present in a high proportion of both ESG2 and placebo patients with diagnosis locally of recurrent nonfatal MI.

Based on these several central evaluations of objective data, it seems reasonable to conclude that the evidence largely supports the inference that the higher rate of nonfatal MI in the 5.0-mg estrogen group is a valid phenomenon, and not a spurious result of biased overdiagnosis associated with "unblinding" of hormone treatment due to side effects.

The Dextrothyroxine (DT4) Subgroup With Frequent Ectopic Ventricular Beats (FEVBs) at Entry: Altogether, 1,109 men were randomized to the DT4 group. As with all six groups in the study, a small proportion of the DT4 patients—2.3% (26 men)—exhibited FEVBs (10% or more of all beats) on the baseline

ECG. This small subgroup experienced a higher death rate than the corresponding subgroup of 78 placebo patients, ie, 38.5% vs 11.5%. All deaths in the DT4 subgroup were attributed to cardiovascular causes, and all but two were known to be sudden deaths.

In the subgroup with FEVBs receiving DT4, the ten deaths occurred particularly among the older men requiring digitalis or diuretics or both. Of the 26 patients in this subgroup, nine were receiving digitalis (with or without concomitant diuretic); of these nine patients, seven died. Six of these deaths were known to be sudden (with no information available on the seventh), and were attributed to coronary disease. They occurred 41, 72, 130, 138, 148, 250, and 648 days, respectively, after entry. Deaths also tended to occur among men with FEVBs in runs, multifocal FEVBs, FEVBs of left ventricular origin, and early FEVBs (ie, FEVBs near the vulnerable period).[16]

The few DT4 treated patients who developed FEVBs after entry into the study, ie, with CDP medication, have not experienced any excess mortality. Similarly, for the more than 1,000 other patients in the DT4 group, no statistically significant excess has been recorded in rates of adverse events, nonfatal and fatal.

Comment

With an average of 18 months of follow-up, the Coronary Drug Project has registered an excess number of events of nonfatal myocardial infarction, pulmonary embolism, and thrombophlebitis in the ESG2 group, receiving 5.0 mg daily of conjugated estrogens, compared with the placebo group. These findings were not associated with significantly higher fatality rates from any of these causes or from all causes in the ESG2 group, compared with placebo.

Detailed statistical evaluation indicates that the higher percentages of specified nonfatal events in the ESG2 group are probably not attributable to chance variation. Further, they are probably not due to greater proneness at entry of this group to these nonfatal cardiovascular complications, nor to biased overdiagnosis of these complications in this group by managing physicians in the study's 53 clinical research centers. Therefore, the excess number of nonfatal events appears to be attributable to the 5.0-mg estrogen regimen.

These findings and inferences led to the conclusion that the potential long-term value of this level of estrogen medication is probably limited in middle-aged men who have recovered from one or more MIs. This conclusion was reinforced by the absence in the 5.0-mg estrogen group of an overall trend toward a beneficial effect in reducing total mortality, to outweigh the apparent nonfatal adverse effects. Moreover, serious difficulties were encountered in maintaining long-term adherence of patients to this dosage of estrogens because of troublesome side effects, particularly decreased libido and breast enlargement and tenderness, present in a majority of patients in the ESG2 group. Thus, life tables for adherence showed that after one year, 11.6% of men in this group were recorded as taking no medication, in contrast to only 1.0% of placebo patients; 46.4% were recorded as receiving reduced medication, in contrast to only 5.8% of placebo patients. These findings were consistent with the conclusion that this level of estrogen medication probably has limited potential long-term value for middle-aged men with coronary heart disease.

The decision was therefore made and implemented to discontinue the 5.0-mg estrogen regimen for all patients randomized to this study group. This group of patients, numbering 1,118 men at entry, will continue to be followed up by Coronary Drug Project, with regular visits according to the study protocol described here.

Other reports published during the last decade are consistent with the CDP finding reported here of a possible excess risk of thromboembolic cardiovascular complications with sizeable dosages of estrogens for middle-aged and elderly men, particularly those with a history of previous atherosclerotic vascular disease.[1,7-9,17,18] Although none of these studies was closely similar to the CDP, their results lend support to the interpretation that the adverse findings reported here for the CDP ESG2 group are real and not due to some unidentified vagary of the study.

Obviously, under these circumstances the Coronary Drug Project has taken special pains to evaluate the data trends for its other group of patients receiving conjugated estrogens, that is at the lower dosage level of 2.5 mg/day (ESG1)—particularly since reports are available indicating that under certain circumstances even small dosages of estrogen may be associated with an excess number of recurrent MIs.[19-23] However, to date this group on the 2.5 mg/day dosage has not shown the apparent excess risk of nonfatal cardiovascular complications identified with the 5.0-mg estrogen dosage. Therefore the ESG1 group is being continued with its study medication.

These early findings of the Coronary Drug Project—considered in relation to the accumulated evidence in the literature[1,7-9,17-24]—may be of value in clarifying further the precautions appropriate with estrogen therapy for middle-aged and elderly men with a history of atherosclerotic disease, especially coronary heart disease. When in the physician's judgment a valid indication for estrogen therapy arises for middle-aged and elderly men (eg, for long-term treatment of prostatic carcinoma), it would appear wise

to institute therapy only when the patient is stable medically (ie, at least several weeks postoperative, and fully recovered from any acute cardiovascular event), to start with a small dose, increase dosage only gradually (if desired), and monitor carefully for cardiovascular complications.

The Coronary Drug Project has also recorded a higher death rate in a small subgroup of 26 dextrothyroxine-treated patients—those with FEVBs in the baseline resting ECG—compared with similar patients in the placebo group. Therefore, this medication has been discontinued in all patients with FEVBs at entry. Dextrothyroxine treatment was stopped for all these patients as a reasonable precautionary measure, although the excess deaths were clustered among older men receiving digitalis (with or without concomitant diuretic). The mechanism of this apparent adverse effect remains to be clarified.

Similar adverse effects have not been noted among other patients taking this medication, including those who developed FEVBs after entry into the study. Therefore, only the few identified patients in the susceptible group have been removed from this drug regimen. The remainder of the patients assigned to treatment with dextrothyroxine—numbering approximately 1,000 men—continue to receive the study drug.

The decisions of the Coronary Drug Project with respect to protocol changes for the ESG2 and DT4 groups indicate its continuing determination and concern—as provided from the beginning in its Protocol and Manual of Operations, and implemented through its Data and Safety Monitoring Committee—to minimize any possibility of subjecting study patients to potential harm. All data from the study continue to be reviewed frequently for possible adverse trends as well as beneficial effects.

Summary

1. The Coronary Drug Project (CDP) is a national collaborative study to evaluate long-term effects of five drug regimens: conjugated estrogens, 2.5 mg/day (ESG1); conjugated estrogens, 5.0 mg/day (ESG2); clofibrate, 1.8 gm/day (CPIB); dextrothyroxine, 6.0 mg/day (DT4); niacin, 3.0 gm/day (NICA)—compared with placebo, for men aged 30 to 64 who have recovered from myocardial infarction (MI).

2. From 1965 to 1969, the 53 CDP clinical centers recruited 8,341 patients, who were randomly assigned to the six groups.

3. By early 1970, with an average follow-up of 18 months, the accumulated data—systematically reviewed bimonthly by the CDP Data and Safety Monitoring Committee—indicated that, compared to placebo, an excess number of adverse events had occurred in the ESG2 group and a small subgroup of patients receiving DT4. These findings led to changes in the CDP protocol.

4. Specifically the group receiving 5.0 mg/day of estrogens (ESG2) experienced an excess number of events of nonfatal MI, pulmonary embolism, and thrombophlebitis, compared with the placebo group. No overall trend towards a beneficial effect in reducing mortality was evident to outweigh these apparent adverse effects. These findings lessen the potential long-term value of this 5.0-mg dosage level of estrogen in men with previous MI. This regimen has been discontinued for all patients originally randomized to this group. The group of patients receiving the 2.5-mg estrogen regimen does not show the apparent excess risk identified with 5.0-mg estrogen dosage, and is therefore continuing with the study medication.

5. A small subgroup of 26 dextrothyroxine-treated patients—those with frequent ectopic beats of ventricular origin on the resting ECG taken at baseline—have experienced a somewhat higher mortality than 78 similar patients receiving placebo. Therefore, medication has been discontinued for these patients. Similar adverse effects have not been noted among other patients with this medication. Consequently, the remainder of the patients assigned to dextrothyroxine treatment—numbering approximately 1,000 men—are continuing to receive the study drug.

6. These decisions are in conformity with the determination and concern of the Coronary Drug Project to minimize any possibility of subjecting study patients to potential harm.

7. All data from the study are continuing to be reviewed systematically at bimonthly intervals for both possible adverse trends as well as beneficial effects.

Nonproprietary and Trade Names of Drugs

Cholestyramine resin—*Cuemid, Questran.*
Dextrothyroxine sodium—*Choloxin.*

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