PAPERS AND ORIGINALS

Trial of Clofibrate in the Treatment of Ischaemic Heart Disease

Five-year Study by a Group of Physicians of the Newcastle upon Tyne Region*

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Summary

In a double-blind clinical trial of clofibrate versus identical quantity of corn oil 497 patients with ischaemic heart disease were observed over a period of five years. The death rate and the rate of non-fatal infarcts were significantly less among the clofibrate group, and the difference was greatest in respect of sudden deaths and among patients who had previously suffered from angina rather than infarction.

The cholesterol- and triglyceride-reducing properties of clofibrate were maintained throughout the period of the trial and side effects were very few. But the protective action of the drug against new infarcts and death bore no apparent relation to these properties.

Introduction

It is well established that raised serum lipoprotein levels are associated with an increased risk of subsequent development of ischaemic heart disease. It is less clear how useful lipoprotein levels are as a guide to prognosis once the symptoms of ischaemic heart disease have developed. The purpose of the trial described here was to find out whether the drug clofibrate, which has been shown to return raised lipoprotein levels towards normal (Symposium on Atromid, 1963), had any effect on the morbidity and mortality of patients with established ischaemic heart disease. Secondary aims of the study were to discover whether the hypolipaemic effect of clofibrate was maintained over long periods of administration and whether long-term treatment with the drug led to any serious side effects.

*The physicians who took part in the trial were: Dr. J. B. Arthur (assisted by Dr. R. B. Raffle), Dr. D. W. R. Ashby, Dr. C. Bremer, Dr. D. M. Davies, Dr. H. A. Dewar (organizing secretary), Dr. A. W. B. Edmunds, Dr. T. A. Grimson, Dr. A. R. Horler, Dr. G. Ismay, Dr. F. S. Jackson (to whom Dr. F. Clark, Dr. C. B. Henderson, Dr. C. Strang, Dr. W. G. A. Swan, and Dr. P. Szekely referred cases), Dr. R. Mowbray, Dr. A. A. M. Nicol, Dr. F. Robertson, Dr. J. B. Ryder (who took over cases from the late Dr. G. J. Murray), Dr. I. O. B. Spencer, Dr. P. Stephenson, Dr. G. F. Turner, Dr. R. H. Vasey, and Dr. A. A. Williams.

Design of Trial and Selection of Patients

The trial was designed as a double-blind study, the patients being randomly allocated to treatment with clofibrate or a matching placebo containing corn oil. Twenty-two consultants in general medicine or cardiology in the Newcastle region agreed to work to a common protocol. They were asked to select for inclusion in the trial patients of either sex who, they were certain, suffered from and had symptoms of ischaemic heart disease—that is, they either had symptoms of angina or had had a myocardial infarct or both. A preliminary electrocardiogram was always taken, but abnormalities either at rest or on exercise were not insisted on. No limits were set on the duration of the angina or on the number of infarctions, but patients with a history of recent infarction were not admitted to the trial until at least six weeks had elapsed from the time of the last episode of infarction pain.

Patients were excluded from the trial for the following reasons: (1) aged 65 or over; (2) valvular heart disease, cardiovascular syphilis, myxoedema (treated or untreated), diabetics on insulin or oral hypoglycaemics, idiopathic or familial hypercholesterolaemia (serum cholesterol exceeding 400 mg/100 ml and/or xanthomatosis), chronic nephritis, significant hypertension (B.P. 200/100 mm Hg on more than one occasion or patients receiving therapy for hypertension), incipient or established heart failure; (3) patients with serious intercurrent diseases or with diseases requiring such other drug treatment as to make it unlikely that they would take the trial capsules regularly; (4) patients who had taken part in earlier trials of clofibrate or who had been treated with it at any time; and (5) patients whose co-operation seemed doubtful.

Anticoagulant treatment was discouraged, but if a physician was anxious to continue long-term anticoagulant treatment already started, he was asked to do so throughout the trial. Since clofibrate alters anticoagulant requirements arrangements were made for another clinician to supervise the anticoagulant therapy. If a physician wished to treat a fresh infarct with anticoagulants he was to do so for three to four weeks only.

The patients were allotted to one or other treatment group by means of a randomization scheme prepared by Professor D. J. Newell, of the Department of Industrial Health, University

of Newcastle, and supervised by the pharmacists of the hospitals taking part in the trial. One group received clofibrate in 250-mg capsules; the other group received matching capsules containing corn oil. The dosage was six capsules daily for patients weighing less than 140 lb (63·5 kg) and eight capsules daily for patients weighing more than that.

Procedure

A comprehensive initial history sheet was used to record duration and severity of angina, the history of infarction or hypertension, previous anticoagulant therapy, past and current smoking habits, and maximum weight in the past. Also recorded were blood pressure, height, weight, E.C.G., and ability to exercise. Each patient was seen twice before being admitted to the trial. On both occasions blood was taken for estimation of serum total cholesterol by an automated method (Green *et al.*, 1963) and of total esterified fatty acids by the method of Connerty *et al.* (1961).

After admission to the trial patients were seen monthly for the first three months and thereafter every three months, except during the final year, when the interval sometimes increased to four months. At each attendance a standard 12-lead E.C.G. was taken and a visit report sheet was used to record weight, blood pressure, severity of angina, physical activity, change in E.C.G., and side effects of treatment. The sheets were also used to record the occurrence of a fresh infarct or death or reasons for withdrawing from the trial. At each follow-up attendance blood was taken for cholesterol and total esterified fatty acid estimations. In the later stages of the trial detailed lipoprotein analyses were also carried out by the method of Stone *et al.* (1970). Equations were derived by correlating the results of the two procedures, and these were used to calculate the lipoprotein concentrations of the samples taken earlier in the trial.

Each physician was asked to follow his usual practice in recommending dietary measures to his patients and to be sparing in his use of drugs other than nitroglycerin, and to record but not withhold any necessary treatment.

Admission to the trial began in February 1964 and most patients had entered by the end of 1965. The trial was terminated on 31 August 1969. In the last few months of the trial each physician was asked to review his patients and to record on a special form their smoking habits during the major (more than 50%) part of the trial, and any change in diet, work, or exercise. Any intercurrent illness was noted, together with any treatment prescribed for it. He compared the last three E.C.G.s of the trial with the first three and categorized them as being on average the same, better, or worse; the changes were specified, as were any new and persistent abnormalities of rhythm or conduction.

Recording and Classification of Events

DEATHS

When a patient died the fact was recorded on a visit record sheet with such detail as was available at the time. Whenever possible a necropsy was performed. In a number of cases the next of kin were interviewed, though this was sometimes not done until quite a long time after the event. The decision on whether death had been due to a fresh infarct or to a purely ischaemic dysrhythmia was often very difficult to make. To ensure uniformity therefore the organizing secretary, while still ignorant of group allocations, made the decision on the basis of all the information which could be obtained. If there was a clear history of preceding chest pain for a few minutes or more, or if there was E.C.G. or enzyme evidence of infarction, or if necropsy showed coronary thrombosis or myocardial infarction, or if the attendant doctor had certified death as being due to coronary thrombosis and no other information was obtainable, then the death was classified as due to fatal infarct.

Deaths due to non-cardiac causes were excluded, and those due to congestive heart failure classified separately. All others were classified as "sudden."

NON-FATAL INFARCTS

Patients who had an infarct were admitted to hospital under the care of their original physician, or admitted to another hospital, or cared for at home by the family doctor. Some patients sought no treatment for their symptoms but reported them, weeks later, at the next follow-up visit. Occasionally new infarcts were detected only by the routine E.C.G. Therefore the evidence on which the diagnosis of infarction was initially based varied considerably, and since many patients already had abnormal E.C.G.s from previous episodes, standard criteria of E.C.G. diagnosis could not be applied. In order to achieve uniformity of classification the organizing secretary visited every physician at the end of the trial and reviewed all the evidence available on each case of reported new infarction. This was done without knowledge of the patient's treatment group. The opportunity was also taken to make sure that no event had gone unreported.

New non-fatal infarctions were categorized by the following criteria:

Definite.—(*a*) Pain lasting at least one hour and accompanied by new and persistent abnormalities in the E.C.G., or by a documented rise in serum aspartate aminotransferase of 10 sigma Frankel units or more, or by a level above the upper limit of normal (provided cardiac failure could be excluded as the cause); or (*b*) pain lasting more than six hours; or (*c*) pain lasting less than six hours but followed by fever and/or a high E.S.R.; or (*d*) new abnormalities (Q waves or inverted T waves) seen in the E.C.G. and persisting for at least 24 hours.

Probable.—(*a*) Pain lasting less than six hours but accompanied by prolonged hypotension; or (*b*) if the attendant doctor was so impressed by the severity of the episode as to keep the patient in bed for at least a week, even though E.C.G. and enzyme tests were negative or inconclusive.

Possible.—Pain lasting at least one hour but not more than six hours with no other available evidence of infarction.

Results

COMPARABILITY OF GROUPS

A total of 497 patients were recruited into the trial. Of these, 244 (192 men and 52 women) were allocated to the clofibrate group and 253 (208 men and 45 women) to the placebo group. The main characteristics of the two groups are compared in Tables I and II, and also in Reserve Tables 1-7.*

There were no significant differences between the two groups in mean age, height/weight index, systolic or diastolic blood pressure, or serum cholesterol. They were comparable in history of infarction and angina, in smoking habit, in past treatment with anticoagulants, and in distribution of E.C.G. patterns. The mean weight of the men in both groups remained fairly constant throughout the trial. The mean weight of the women taking clofibrate rose by about 7 lb (3·2 kg). Blood pressure fluctuated slightly and comparably in both sexes and in both treatment groups. Most patients did not vary their diet during the course of the trial; the few who did generally reduced their consumption of both fat and carbohydrate.

ANTICOAGULANTS

In the event, for a variety of reasons, anticoagulants were administered not only, as envisaged, throughout (clofibrate (C.) 12, placebo (P.) 12) but also to some (C. 6, P. 13) for an initial period only, to three (C. 1, P. 2) for a middle post-infarction period exceeding four weeks, and to some others

*A number of Reserve Tables giving additional information and analyses have been prepared and are available on request.

TABLE I—*Status on Entry. All Patients*

	No. of Patients	Age	Weight/Height Index	Blood Pressure (mm Hg)		Blood Cholesterol (mg/100 ml - mean of 2)
				Systolic	Diastolic	
Clofibrate:						
Men	192	51·9 ± 8·5	3·6 ± 0·9	137 ± 23	84 ± 12	245 ± 49
Women	52	52·7 ± 9·2	3·6 ± 1·4	141 ± 17	84 ± 10	270 ± 77
Placebo:						
Men	208	52·5 ± 8·5	3·6 ± 0·9	138 ± 21	84 ± 12	247 ± 50
Women	45	55·2 ± 8·1	3·8 ± 1·3	148 ± 26	86 ± 12	259 ± 47

Previous History

	Angina	Infarct		Angina and Infarct		Not Recorded	Menopause		
		Single	Multiple	Single	Multiple		Pre-	Post-	Age at
Clofibrate:									
Men	65	41	5	61	15	5			
Women	29	8	1	12	1	1	19	33	45·7 ± 4·6
Placebo:									
Men	77	47	6	63	14	1			
Women	24	7	0	11	3	0	13	32	45·9 ± 5·6

TABLE II—*Status on Entry. All Patients*

	Total No. of Patients	Smoking												
		Past							Present					
		None	Pipe	Cigarettes/day			N.R.	Points per Patient	None	Pipe	Cigarettes/day			N.R.	Points per Patient
				1-10	11-20	>20					1-10	11-20	>20		
Clofibrate:															
Men	192	20	17	26	66	73	1	2·93	63	19	48	59	10	0	1·73
Women	52	15	0	19	11	7	0	1·9	21	0	24	4	2	1	1·33
Placebo:															
Men	208	13	20	30	70	80	3	2·98	58	15	60	56	19	3	1·85
Women	45	22	0	13	8	2	0	1·29	32	0	7	6	0	0	0·71

	Anticoagulants					Electrocardiograms					
	Begun	Discontinued	Continued	None	N.R.	Normal	Ischaemia or Old Infarct	Abnormal Rhythm	Conduction Defect	Other Abnormality	N.R.
Clofibrate:											
Men	1	31	15	139	6	43	142	2	8	2	4
Women	0	4	2	45	1	12	35	1	4	1	1
Placebo:											
Men	1	29	23	148	7	50	144	1	12	3	5
Women	0	6	1	34	4	12	29	2	2	1	0

Smoking: Points allocation—none = 0; pipe and cigars = 1; cigarettes 1-10 = 2, 11-20 = 3, >20 = 4. N.R. = not recorded.
Some patients smoked both pipe and cigarettes and appear under both headings.

(C. 6, P. 8) in the latter part of their trial only. Full details are given in Reserve Table 10, and in terms of man-months in Table III. Treated and controlled groups in this table do not differ significantly, and in the more important tables of results the analyses have been made both with and without this anticoagulant group. Its influence has always been small.

TABLE III—*Duration in Trial (Months)*

	Clofibrate			Placebo		
	Men	Women	Total	Men	Women	Total
All Patients						
Angina	2,658	1,189	3,847	2,906	1,007	3,913
Infarct	1,866	368	2,234	2,287	350	2,637
Both	3,651	631	4,282	3,400	715	4,115
All anginas	6,309	1,820	8,129	6,306	1,722	8,028
All infarcts	5,517	999	6,516	5,687	1,056	6,752
Not classified	112	65	177	123	—	123
Total	8,287	2,253	10,540	8,716	2,072	10,788
Excluding Anticoagulant Group						
Angina	2,613	1,189	3,802	2,512	941	3,453
Infarct	1,477	368	1,845	1,742	350	2,092
Both	3,041	602	3,643	2,826	665	3,491
All anginas	5,654	1,791	7,445	5,338	1,606	6,944
All infarcts	4,518	970	5,488	4,568	1,015	5,583
Not classified	67	65	132	77	—	77
Total	7,198	2,224	9,422	7,157	1,956	9,113

EVIDENCE OF PATIENTS' CO-OPERATION

Evidence that the patients actually took the capsules that they were given was obtained in two ways. In the later phases of the trial blood was taken on one or more occasions from 401 patients for estimation of serum levels of clofibrate. On only 10 occasions were anomalous results obtained. Three patients were not taking their capsules regularly, five had temporarily been the subject of a dispensing error, one had consistently been allocated to the wrong group, and there was no explanation for one, who had clofibrate when he should not have done. The last patient was the only one of the 10 to suffer an event. The relatives of 30 of the 78 patients who died were questioned. They all replied that the deceased patients (C. 16, P. 14) had been most careful about taking the capsules.

WITHDRAWALS

Forty-four patients were withdrawn from the clofibrate group and 29 from the placebo group (Table IV). The most frequent reason for withdrawal was that the patient failed to co-operate. A few patients were withdrawn by their family doctors. One of the participating physicians withdrew all his patients because he thought the trial had finished; his patients happened to include an excess of men in the clofibrate group. Patients withdrew from both groups because of side effects, and these

were rather more frequent among the treated. The category "other reasons" includes intercurrent diseases, some of which were serious—for example, cancer and strokes—and may have later led to the death of patients from non-cardiac causes.

The characteristics of the patients withdrawn from the trial are compared in Tables V and VI. There are no significant differences between the patients in the two treatment groups or between the patients withdrawn and those who remained in the trial.

Events

Two sorts of event were recorded—cardiac deaths and first non-fatal infarcts. Deaths have been subdivided into sudden deaths, fatal infarcts, and cardiac failure, while non-fatal infarcts have been subdivided into categories designated as certain, probable, and possible. The possible non-fatal infarcts are excluded from the analyses which follow, the number so excluded being virtually the same in each treatment group (C. 11, P. 12). Only the first non-fatal infarcts have been included in the tables. A number of patients, mostly in the placebo group, had repeated non-fatal infarcts. It was felt that these multiple events might weight the results disproportionately if they were all included. If a patient had an infarct and died later of a further infarct, both events have been included in the appropriate categories.

All the events have been subdivided according to the patient's history on admission to the trial into five categories—namely: angina only, infarct only, both, all anginas, and all infarctions.

TABLE IV—*Patients Withdrawn*

Reasons	Clofibrate			Placebo		
	Men	Women	Total	Men	Women	Total
Side effects:						
Gastrointestinal	4	0	4	3	1	4
Non-gastrointestinal	3	2	5*	1	0	1†
Defaulted	14	4	18	9	4	13
Other reasons‡	13	4	17	10	1	11
Total	34	10	44	23	6	29
Mean duration in months	25·7 ± 14·2	16·7 ± 9·9	23·6 ± 13·8	22·7 ± 19·6	15·8 ± 14·3	21·2 ± 18·6

*Includes alopecia (1), rash (2), non-specific pain (1).
†Due to depression.
‡Includes intercurrent disease, leaving district, etc.

TABLE V—*Status on Entry. Patients Withdrawn*

	No. of Patients	Age	Weight/Height Index	Blood Pressure (mm Hg)		Blood Cholesterol (mg/100 ml — mean of 2)
				Systolic	Diastolic	
Clofibrate:						
Men	34	50·3 ± 7·9	3·6 ± 0·5	138 ± 27	84 ± 1	245 ± 43
Women	10	50·3 ± 7·8	3·7 ± 0·56	143 ± 19	86 ± 9	255 ± 63
Placebo:						
Men	23	53·3 ± 7·8	3·6 ± 0·42	142 ± 25	85 ± 10	237 ± 68
Women	6	54·3 ± 8·1	3·6 ± 0·22	152 ± 31	84 ± 13	266 ± 48

Previous History

	Angina	Infarct		Angina and Infarct		Not Recorded	Menopause		
		Single	Multiple	Single	Multiple		Pre-	Post-	Age at
Clofibrate:									
Men	18	5	1	7	1	2			
Women	7	1	0	1	1	0	4	6	44·3 ± 4·6
Placebo:									
Men	11	6	0	5	1	0			
Women	5	1	0	0	0	0	2	4	49·7 ± 4·0

TABLE VI—*Status on Entry. Patients Withdrawn*

	Total No. of Patients	Smoking												
		Past							Present					
		None	Pipe	Cigarettes/day			N.R.	Points per Patient	None	Pipe	Cigarettes/day			N.R.	Points per Patient
				1-10	11-20	>20					1-10	11-20	>20		
Clofibrate:															
Men	34	3	1	4	14	12	0	2·94	10	1	9	13	1	0	1·85
Women	10	2	0	4	1	3	0	2·30	2	0	4	1	2	1	2·11
Placebo:															
Men	23	3	0	2	10	8	0	2·87	4	0	9	7	1	2	2·05
Women	6	2	0	0	3	0	1	1·80	3	0	1	2	0	0	1·33

	Anticoagulants					Electrocardiograms					
	Begun	Discontinued	Continued	None	N.R.	Normal	Ischaemia or Old Infarct	Abnormal Rhythm	Conduction Defect	Other Abnormality	N.R.
Clofibrate:											
Men	0	3	1	29	1	9	23	0	1	0	1
Women	0	1	2	7	0	3	5	0	2	0	1
Placebo:											
Men	0	1	2	15	5	7	13	0	0	1	2
Women	0	0	0	5	1	2	4	1	0	0	0

Smoking: Points allocation—none = 0; pipe and cigars = 1; cigarettes 1-10 = 2, 11-20 = 3, >20 = 4. N.R. = not recorded.
Some patients smoked both pipe and cigarettes and appear under both headings.

The fourth and fifth categories are the totals of the first and third and of the second and third categories respectively.

Table VII summarizes the events, which are displayed in more detail in Tables VIII-XII.

DEATHS

Fewer patients died in the clofibrate group than in the placebo group. Of the total of 75 deaths due to cardiac causes, 27 patients were taking clofibrate and 48 were taking the placebo. If these deaths are expressed as a rate per 1,200 patient-months, using the periods of duration in trial shown in Table III, the figure for the clofibrate group is 3·07 and that for the placebo group is 5·34. This difference is significant (P = 0·02) (Table VII).

A striking difference is seen in the number of sudden deaths between the two groups. Nine patients in the clofibrate group died suddenly, compared with 21 in the placebo group (P = 0·03). The difference, however, is not significant if the patients on anticoagulants are excluded.

In Tables VIII and IX deaths are related to both treatment and the history of the patient on entry. Once again the results are affected if the patients on anticoagulants are excluded, but it is nevertheless clear that patients taking clofibrate were protected if they had a history of angina or of both angina and myocardial infarction. They were particularly protected against sudden death. Patients with a history of myocardial infarction alone derived no benefit from clofibrate.

In Reserve Table 15 the death rates have been related to age groups. The numbers are too small for valid comparison to be possible, but the differences are not confined to one particular decade.

NON-FATAL INFARCTS

Fewer non-fatal infarcts occurred in the clofibrate group than in the placebo group (C. 30, P. 46) (Table VII). The rates per 1,200 patient-months are calculated on the basis of the patient-months accumulated to the time of the event (Reserve Table 14). The difference between the rates does not quite reach accepted levels of significance (C. 3·68, P. 5·76; P = 0·055). However, if the patients taking anticoagulants are excluded the difference is significant (C. 3·88, P. 6·52; P = 0·032).

In Tables X and XI non-fatal infarcts are related to treatment and the history of the patient on entry. As only a very small number of these patients received anticoagulant therapy, separate tables excluding this group have not been included. If the non-fatal certain and probable infarcts are considered for both sexes combined, and in relation to their previous history, then the angina only clofibrate group has a significantly lower rate than the corresponding placebo group (P <0·05). In

TABLE VII—*Deaths and Non-fatal First Infarcts in Trial*

	Deaths		Significance		Infarcts		Significance
	Clofibrate	Placebo			Clofibrate	Placebo	
All Patients							
Sudden deaths	9	21	P = 0·03	First infarcts surviving to end of trial	27	37	N.S.
Fatal infarcts	16	23	N.S.	First infarcts dying at subsequent event	3	9	N.S.
Congestive H.F.	2	4	N.S.				
Total deaths	27	48		Total non-fatal first infarcts	30	46	
% Mortality	11·1	19·0		% non-fatal first infarct rate	11·9	18·2	
Rate/1,200 patient-months	3·07	5·34	P = 0·02	Rate/1,200 patient-months	3·68	5·76	N.S. (P = 0·055)
Excluding Anticoagulant Group							
Sudden deaths	9	16	N.S.	First infarcts surviving to end of trial	25	34	N.S.
Fatal infarcts	11	20	N.S.	First infarcts dying at subsequent event	3	9	N.S.
Congestive H.F.	1	3	N.S.				
Total deaths	21	39		Total non-fatal first infarcts	28	43	
% Mortality	9·6	18·0		% non-fatal first infarct rate	12·7	19·8	
Rate/1,200 patient-months	2·67	5·14	P = 0·02	Rate/1,200 patient-months	3·88	6·52	P = 0·032

Rate of first non-fatal infarcts is calculated on the basis of the patient-months up to time of the infarct. N.S. = not significant.
The significance is calculated on rates/1,200 man-months.

TABLE VIII—*Deaths Related to Previous History*

	Clofibrate									Placebo								
	No. in Group on Entry		Sudden		Fatal Infarct		C.H.F.		Total	No. in Group on Entry		Sudden		Fatal Infarct		C.H.F.		Total
	M.	F.	M.	F.	M.	F.	M.	F.	M. + F.	M.	F.	M.	F.	M.	F.	M.	F.	M. + F.
All Patients																		
Angina	65	29	2	0	4	0	0	0	6	77	24	5	0	5	3	0	0	13
Infarct	46	9	2	1	4	1	0	0	8	53	7	4	0	4	0	0	0	8
Both	76	13	4	0	6	0	2	0	12	77	14	12	0	8	3	4	0	27
All anginas	141	42	6	0	10	0	2	0	18	154	38	17	0	13	6	4	0	40
All infarcts	122	22	6	1	10	1	2	0	20	130	21	16	0	12	3	4	0	35
N.R.	5	1			1	0			1	1	0							
Total	192	52	8	1	15	1	2	0	27	208	45	21	0	17	6	4	0	48
Excluding Anticoagulant Group																		
Angina	64	29	2	0	4	0	0	0	6	69	23	4	0	4	3	0	0	11
Infarct	38	9	2	1	2	1	0	0	6	43	7	3	0	4	0	0	0	7
Both	62	11	4	0	4	0	1	0	9	63	13	9	0	6	3	3	0	21
All anginas	126	40	6	0	8	0	1	0	15	132	36	13	0	10	6	3	0	32
All infarcts	100	20	6	1	6	1	1	0	15	106	20	12	0	10	3	3	0	28
N.R.	4	1								0	0							
Total	168	50	8	1	10	1	1	0	21	175	43	16	0	14	6	3	0	39

C.H.F. = Congestive heart failure. N.R. = Not recorded.

the case of men only, a trend in favour of the clofibrate group is seen in all history subcategories. If the probable infarcts are ignored and only the certain infarcts considered, then not only does the clofibrate group as a whole do significantly better than the placebo group, but so do the angina only and all angina subgroups. Patients with a history of infarction but not of angina seem to benefit from clofibrate, but this trend does not reach the conventional level of significance.

In Reserve Table 16 the numbers of first new non-fatal infarcts have been related to age, and if the numbers in the age groups entering the trial are taken into account the protection seems to diminish with age, being greatest (but not significantly so) in the 40-50 age group and imperceptible after the age of 60.

TOTAL INFARCTS (FIRST NON-FATAL AND FATAL)

The rates of these are set out in Table XII and related there to the history of the patients before entry. The women as a whole are shown to have fared much better on clofibrate, and both sexes combined also showed a significant trend in favour of the drug. This trend affected principally those patients who had entered the trial with a history of angina.

RISK OF DEATH FROM FIRST INFARCT

The total numbers of first new infarcts in the trial (fatal or non-fatal) in the clofibrate and placebo groups were 37 and 60 respectively, of which 9 (24%) and 17 (28%) proved fatal. It seems, therefore, that clofibrate does not reduce the risk of dying from an infarct if one occurs.

RELATION OF EVENTS TO SMOKING HABITS

The relationship between incidents and smoking habits is set out in Table XIII. There seems to be a tendency in the placebo group for heavy smokers to die suddenly and for clofibrate to nullify this trend, but the numbers are too small for firm conclusions to be reached.

TABLE IX—*Death Rate (per 1,200 Patient-months) Related to Previous History*

	Clofibrate					Placebo				
	Sudden		Fatal Infarct		Total§	Sudden		Fatal Infarct		Total§
	M.	F.	M.	F.	M. + F.	M.	F.	M.	F.	M. + F.
All Patients										
Angina	0·9	—	1·81	—	1·87	2·06	—	2·06	3·57	3·99
Infarct	1·29	3·26	2·57	3·26	4·30	2·10	—	2·10	—	3·64
Both	1·31*	—	1·97	—	3·36‡	4·24*	—	2·82	5·03	7·87‡
All anginas	1·14†	—	1·90	—	2·66‡	3·24†	—	2·47	4·18	5·98‡
All infarcts	1·31*	1·20	2·18	1·20	3·68	3·38*	—	2·53	3·41	6·22
Total	1·16‡	0·53	2·17	0·53	3·07†	2·89‡	—	2·34	3·47	5·34†
Excluding Anticoagulant Group										
Angina	0·9	—	1·81	—	1·87	1·91	—	1·91	3·57	3·82
Infarct	1·29	3·26	1·61	3·26	3·90	2·07	—	2·10	—	4·02
Both	1·31	—	1·58	—	2·96*	3·82	—	2·55	5·03	7·22*
All anginas	1·27	—	1·70	—	2·42‡	2·92	—	2·25	4·48	5·53‡
All infarcts	1·59	1·24	1·59	1·24	3·28*	3·15	—	2·63	3·55	6·02*
Total	1·16	0·53	1·67	0·53	2·67†	2·68	—	2·35	3·47	5·14†

A significant difference between corresponding numbers in the clofibrate and placebo groups is indicated by *P≤0·05, †P≤0·02, ‡P≤0·01.
§Total includes small group (see Table VIII) of deaths due to congestive heart failure.

TABLE X—*First Non-fatal Infarcts in Trial Related to Previous History. All Patients*

	Clofibrate								Placebo							
	No. of Patients		Certain		Probable		Certain and Probable		No. of Patients		Certain		Probable		Certain and Probable	
	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.
Angina	65	29	4	0	2	0	6	0	77	24	9	4	1	1	10	5
Infarction	46	9	5	0	1	1	6	1	53	7	9	0	1	0	10	0
Both	76	13	9	2	6	0	15	2	77	14	16	0	3	2	19	2
All anginas	141	42	13	2	8	0	21	2	154	38	25	4	4	3	29	7
All infarcts	122	22	14	2	7	1	21	3	130	21	25	0	4	2	29	2
N.R.	5	1							1	0						
Total	192	52	18	2	9	1	27	3	208	45	34	4	5	3	39	7

N.R. = not recorded.

TABLE XI—*First Non-fatal Infarcts in Trial Related to Previous History. Rates per 1,200 Patient-months. All Patients*

	Clofibrate						Placebo					
	Certain		Probable		Certain and Probable		Certain		Probable		Certain and Probable	
	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.
Angina	1·92	0T†	0·96	0	2·88	0T*	4·05	5·72T†	0·45	2·05	4·50	7·77T*
Infarction	3·49	0	0·70	3·40	4·19	3·40	5·59	0	0·62	0	6·21	0
Both	3·28	4·33	2·19	0	5·47	4·33	6·46	0	1·21	3·41	7·67	3·41
All anginas	2·70*	1·38T†	1·66	0	4·36	1·38	5·32*	3·11T†	0·85	2·33	6·17	5·44
All infarcts	3·35	2·65	1·68	1·32	5·03	3·97	6·12	0	0·98	2·28	7·10	2·28
Total	2·84*	1·11T‡	1·42	0·56	4·26	1·67	5·30*	2·54T‡	0·78	1·90	6·08	4·44

A significant difference between corresponding numbers in the clofibrate and placebo groups is indicated by *P≤0·05, †P≤0·02, ‡P≤0·01.
Addition of T indicates a significant difference when men and women are combined into a single group.

TABLE XII—*Fatal and First Non-fatal Infarcts Related to Previous History. Rates per 1,200 Patient-months. All Patients*

	Clofibrate			Placebo		
	Men	Women	Total	Men	Women	Total
Angina	4·51	—	3·12*	6·19	9·53	7·05*
Infarction	6·43	6·52	6·45	7·35	—	6·37
Both	6·9	3·8	6·45	9·53	8·39	9·33
All anginas	5·9	1·32	4·87†	7·99	9·06	8·22†
All infarcts	6·74	4·8	6·45	8·65	5·68	8·18
Total ..	6·08	2·13†	5·24*	7·71	7·53†	7·68*

A significant difference between corresponding numbers in the clofibrate and placebo groups is indicated by *P≤0·05, †P≤0·02.

TABLE XIII—*Events Related to Cigarette Smoking Habits*

	No. in Group on Entry	Sudden Deaths		Fatal Infarcts		First Non-fatal Infarcts		All Events*	
		No.	%	No.	%	No.	%	No.	%
In the Past (Maximal)									
Clofibrate:									
Non-smokers	35	0	—	3	8·6	4	11·4	8	22·9
Light smokers	45	0	—	2	4·4	5	11·1	7	15·6
Heavy smokers	157	9	5·7	9	5·7	20	12·7	39	24·8
Placebo:									
Non-smokers	35	0	—	4	11·4	4	11·4	8	22·9
Light smokers	43	4	9·3	2	4·7	7	16·3	13	30·2
Heavy smokers	160	15	9·4	15	9·4	31	19·4	65	40·6
On Entry (Average)									
Clofibrate:									
Non-smokers	84	3	3·6	6	7·1	10	11·9	21	25·0
Light smokers	72	3	4·2	4	5·6	8	11·1	15	20·8
Heavy smokers	75	3	4·0	5	6·7	10	13·3	18	24·0
Placebo:									
Non-smokers	90	3	3·3	10	11·1	14	15·6	27	30·0
Light smokers	67	5	7·5	5	7·5	13	19·4	25	37·3
Heavy smokers	81	12	14·8	6	7·4	14	17·3	34	42·0

*Includes deaths due to congestive heart failure.
Light smokers, 1-10 cigarettes daily. Heavy smokers, 11 or more cigarettes daily. Pipe smokers not included. Information on habits had not been recorded for a small number of patients.

RELATION OF EVENTS TO INITIAL CHOLESTEROL LEVEL

The changes in serum cholesterol level during the course of the trial are shown in Fig. 1. Clofibrate caused a fall in the mean cholesterol level in men (28 mg/100 ml) and women (41 mg/100 ml) after six months' treatment, which was maintained throughout the trial. The fall was greatest when the starting levels were high and greater in women than in men; the extent of the fall made the difference in cholesterol level seen between the sexes at the start of the trial subsequently disappear.

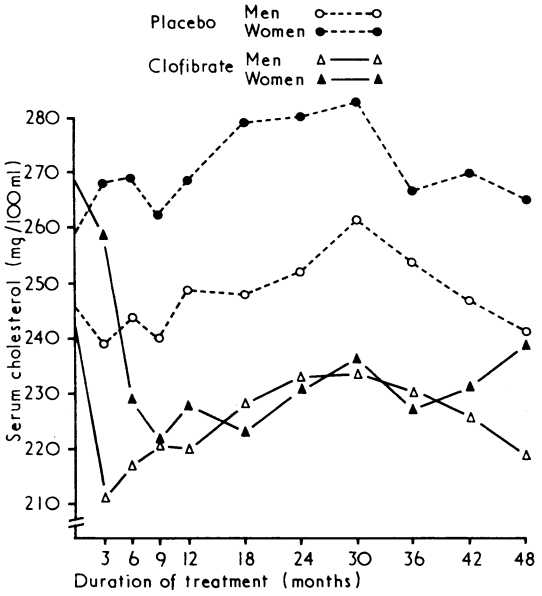

FIG. 1—Mean cholesterol levels in treated and control groups.

All subsequent analyses have been restricted to men only, as they form a homogeneous group; the women were few in number and had considerably higher levels of serum cholesterol on entry. The response of the cholesterol level was calculated in arbitrary units by using the formula: (pretreatment cholesterol level − mean of levels at all following visits) × 100 ÷ (pretreatment level − 150). Where the initial levels were so low that the denominator became very small, the quotient was arbitrarily fixed at a maximum of 100. Where only a single treatment level was available the patient was excluded from the analysis.

In Tables XIV and XV the incidence of events in men only is related to the initial blood cholesterol levels and to the extent of their response to treatment. The grouping into high cholesterols in Table XIV indicates a level exceeding 260 mg/100 ml; the remainder are classed as low. It will be seen that patients with an initially high cholesterol reading sustained more incidents (deaths and infarcts) than did those with a low one, and that those with a history of infarction did a little worse than those with a history of angina. These results accord with expectations. It is evident also that both those with high initial readings and those with low ones derived benefit from clofibrate, but that the former derived slightly more. Patients who died suddenly, however, did not have high initial cholesterol levels.

TABLE XIV—*Relationship Between Events During Trial and Cholesterol Classification on Entry in Men*

	All Infarcts				All Anginas			
	Clofibrate		Placebo		Clofibrate		Placebo	
Cholesterol group:	Low	High	Low	High	Low	High	Low	High
No. of patients ..	81	40	74	56	87	50	87	61
Mean cholesterol (mg/100 ml) ..	221	296	220	292	219	298	220	302
Rate/1,200 patient-months	6·57	10·02	8·59	13·82	5·30	9·14	8·52	11·81

TABLE XV—*Events During Trial Related to Initial Cholesterol Levels (mg/100 ml) and Their Response to Treatment in Men*

	Whole Group	Sudden Deaths	Fatal Infarcts	Non-fatal Infarcts	No Incidents
Clofibrate:					
No. of patients ..	181	8	13	23	137
Initial cholesterol	247·7	237·4	257·7	268·3	243·9
Response ..	16·6	46·9	14·8	25·1	13·6
Placebo:					
No. of patients ..	189	19	14	30	126
Initial cholesterol	252·9	243·0	281·7	255·5	250·2
Response ..	−2·7	−6·9	11·9	−8·5	−2·3

Response in units = (Pretreatment cholesterol level − mean of levels at all following visits) × 100 ÷ (Pretreatment level − 150).
Where only a single treatment level was available the patient was excluded from this analysis. The numbers of patients in the groups above are consequently smaller than the numbers shown in other tables.

When it comes, however, to relating the benefit from clofibrate to cholesterol "response" (expressed as an arbitrary and positive figure), the results are not as expected (Table XV). Those patients who had incidents had responded at least as well as, and in the case of the sudden deaths, considerably better than those who had none. The pronounced reduction in sudden deaths among the clofibrate group and the more modest reduction in non-fatal infarcts seems to be quite independent of the extent to which the drug lowered the amount of cholesterol in the blood.

RELATION OF EVENTS TO LIPOPROTEIN LEVELS

Figs. 2 and 3 show the number of men in the clofibrate and placebo groups on entry according to the lipoprotein classifications of Fredrickson *et al.* (1967) and Beaumont *et al.* (1970), and their mean lipoprotein levels during treatment. The initial lipoprotein levels were comparable for the two treatment

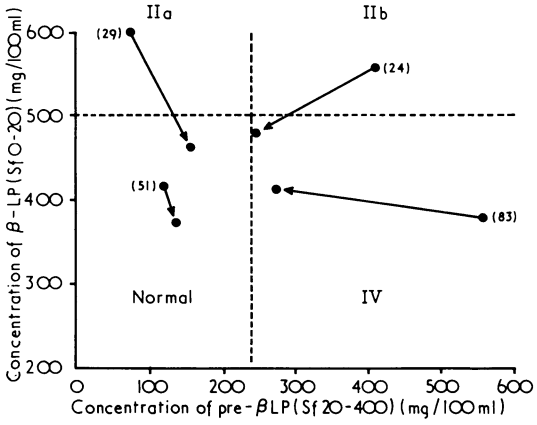

FIG. 2—Initial lipoprotein concentrations (number of patients shown in parentheses) and mean levels during treatment with clofibrate for men classified into four types.

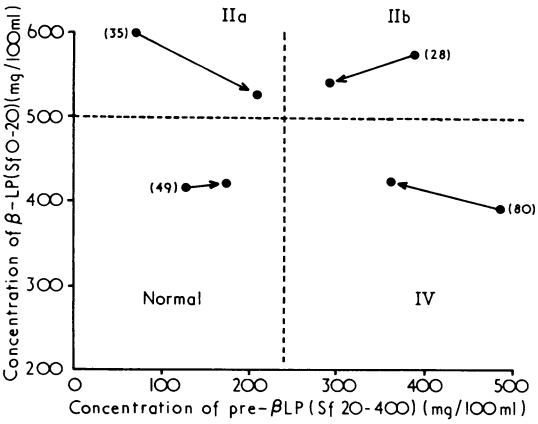

FIG. 3—Initial lipoprotein concentrations (number of patients shown in parentheses) and mean levels during treatment with placebo for men classified into four types.

groups in each of the lipoprotein types. The prevalence of the different types in the two treatment groups was similar. Overall, 26% were classified as normal, 43% as type IV, 17% as type IIa, and 14% as type IIb.

The same figures show that all the abnormal lipoprotein types in both treatment groups tend to return towards normal though the effect is much more pronounced in the clofibrate group. It can be seen also that in the case of types IIa and IV the response of the abnormal lipoprotein fraction to both treatments is accompanied by an increase in the other lipoprotein fraction. However, the latter remains within the normal range. This should be borne in mind in interpreting the changes in these fractions shown in Table XVI (see below).

Table XVI shows events during the trial related to initial triglyceride-rich (pre-beta, Sf 20-400) lipoprotein concentrations (mg/100 ml) and their response to treatment in men. Those

TABLE XVI—*Events During Trial Related to Initial Triglyceride-rich (Pre-beta, Sf 20-400) Lipoprotein Levels and Their Response to Treatment in Men*

	Whole Group	Sudden Deaths	Fatal Infarcts	Non-fatal Infarcts	No Incidents
Clofibrate:					
No. of patients ..	185	8	14	23	140
Initial lipoprotein levels (mg/100 ml)	337	272	444	326	331
Change on treatment	−122	−66	−188	−134	−116
Placebo:					
No. of patients ..	201	21	16	30	134
Initial lipoprotein levels (mg/100 ml)	317	357	430	256	311
Change on treatment	−36	−94	−61	−4	−31

who survived had lower mean initial levels (256 to 331) than those suffering fatal events (357 to 444), with the exception of the eight patients in the clofibrate group who died suddenly (272). Three patients in this last group had very low initial levels.

Survivors treated with clofibrate showed much greater mean responses (—134, —116) than the corresponding placebo groups (—4, —31). However, in the clofibrate group those patients who experienced any event had similar mean responses to those in whom no incident occurred. It can be concluded that the improvement in prognosis following clofibrate therapy is not solely dependent on a reduction of triglyceride-rich lipoproteins.

SIDE EFFECTS

As with most clinical trials, side effects were encountered in the placebo group as well as in the clofibrate group, and there was only a slight preponderance of patients in the latter (C. 46, P. 41). The incidence was low, and in only 14 patients did side effects lead to withdrawal from the trial (C. 9, P. 5). Mild gastrointestinal symptoms were the most frequent. There was one case of alopecia attributable to clofibrate; the patient recovered completely when the drug was discontinued.

Discussion of Results

Four features of the results were unexpected and are possibly connected. If confirmed in other trials they would have interesting implications. The first is the protection against deaths and new infarcts afforded by the drug to patients who gave a history of angina and failure of the drug to do so (and especially to protect against death) to those whose background was solely one of previous infarction. The second is the greater protection given against sudden death than against fatal infarct. The third is the lack of any correlation between these results and either the initially high blood cholesterol or triglyceride levels or their response to treatment. Patients with high initial blood cholesterol levels had, as might be expected, a worse prognosis than those with low ones, but clofibrate gave nearly equal protection to both. Yet those who did have events, including sudden deaths, were not "non-responders"—that is, drug-resistant. Finally, clofibrate seemed to give more protection to smokers than to non-smokers. But not one life-long non-smoker died suddenly.

In this trial the term "sudden death" implied death which was virtually instantaneous, without preceding pain. It has been known for many years that when patients with ischaemic heart disease die suddenly like this, necropsy often shows no evidence of infarction or of recent thrombosis of a coronary artery. It is also a matter of common experience that during an attack of angina disturbances of rhythm can occur and that these may include or lead on to asystole or ventricular fibrillation. In this trial the sudden deaths, most of which seemed likely to be of this dysrhythmic nature, occurred predominantly in patients who entered the trial with a history of angina (17 out of 21 in placebo and six out of nine in clofibrate groups—Table VIII). They did not, however, enter the trial with higher than average cholesterol or triglyceride levels, and when they were treated with clofibrate, these levels fell fully as well as the average. It would seem likely, therefore, that clofibrate has its most striking, though not its only, effect in ischaemic heart disease by protecting patients who suffer from angina from succumbing to dysrhythmic sudden deaths, and this effect is mediated through some other mechanism than its cholesterol- and triglyceride-reducing properties.

The protection given by the drug is greater for smokers than for non-smokers, probably because the former are more prone to these sudden dysrhythmic deaths. This deleterious effect of smoking diminishes but does not disappear immediately the habit is abandoned.

Requests for reprints and Reserve Tables should be made to Dr. H. A. Dewar, Royal Victoria Infirmary, Newcastle upon Tyne NE1 4LP.

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Ischaemic Heart Disease: A Secondary Prevention Trial Using Clofibrate

Report by a Research Committee of the Scottish Society of Physicians*

British Medical Journal, 1971, **4**, 775-784

Summary

A trial is reported of the effects of giving clofibrate to prevent progression of pre-existing ischaemic heart disease. There were two groups randomly distributed between clofibrate (350 patients) and placebo (367 patients) regimens. The trial lasted about six years and was conducted in 19 hospitals in Scotland. The criteria of acceptance into the trial were precise and were monitored by one observer. The standards of diagnosis of events were defined and all protocols and electrocardiograms were read blind by one observer.

Three categories of patients were admissible to the trial: (1) patients with one myocardial infarction (W.H.O. E.C.G. criteria) between 8 and 16 weeks before the start of the trial; (2) patients with angina of a duration of 3 to 24 months, provided their E.C.G. showed signs of myocardial ischaemia at rest or after exercise; and (3) patients with one recent myocardial infarction and pre-existing angina as defined above.

There were fewer deaths in patients with angina (categories 2 and 3 above) treated with clofibrate than in those on placebo. The mortality in the former group was reduced by 62%, and this is a statistically significant difference. Clofibrate did not have any statistically significant effect in reducing the rate of non-fatal infarction in patients with angina or in those with myocardial infarction and pre-existing angina, though a beneficial trend was evident when both subgroups were combined (a 44% reduction compared with the placebo group). There was a significant reduction in all events (fatal and non-fatal) in patients with angina ("all anginas") in the clofibrate-treated group; the rate was reduced by 53%.

Clofibrate did not alter the overall mortality or morbidity rates in patients admitted to the trial with recent myocardial infarction *without* preceding angina of more than three months' duration. In one subgroup there was a statistically significant adverse effect in the clofibrate-treated group. The lack of any overall effect in patients with myocardial infarction might be related to the unexpectedly low mortality rate (2·97%) in the placebo group; it is usually in the region of 4-9% per annum after first myocardial infarction.

In patients categorized as "all anginas" there was significant reduction in events whether the initial serum cholesterol level was high (greater than 260 mg/100 ml) or normal. Clofibrate seemed to have a small but not significant beneficial effect in patients with myocardial infarction with initially high serum cholesterol levels, but was of no value in those with initially normal serum cholesterol levels. There was no significant relationship between the response or lack of response of serum cholesterol to clofibrate and the incidence of events either in patients with angina or in those with infarction.

The main conclusion of this trial is that clofibrate had a beneficial effect in reducing mortality and, to a lesser extent, morbidity in patients who presented with angina ("all anginas"). This effect was independent of initial serum cholesterol levels or the extent to which serum cholesterol was lowered. The drug had no significant overall effect on prognosis in patients with myocardial infarction alone.

Co-ordinator: Dr. M. F. Oliver, Department of Cardiology, Royal Infirmary, Edinburgh.

Participants: Professor S. Alstead, Stobhill General Hospital, Glasgow; Dr. J. D. Aitchison, Royal Infirmary, Stirling; Dr. J. Barclay Barr, Royal Infirmary, Kilmarnock; Dr. T. B. Begg, Victoria Infirmary, Glasgow; Dr. P. N. Bennett, Royal Infirmary, Aberdeen; Dr. J. W. Buchanan, Victoria Hospital, Kirkcaldy; Dr. A. J. V. Cameron, Western Infirmary, Glasgow; Dr. W. D. H. Conacher, Bangour Hospital, Broxburn; Dr. Hugh Conway, Royal Alexandra Infirmary, Paisley; Dr. George M. Currie, Royal Infirmary, Kilmarnock; Dr. E. B. French, Western General Hospital, Edinburgh; the late Professor H. W. Fullerton, Royal Infirmary, Aberdeen; Dr. W. R. Gauld, Woodend General Hospital, Aberdeen; Dr. W. Gray, Bridge of Earn Hospital, Perthshire; Dr. M. Keith, Bruntsfield Hospital, Edinburgh; the late Dr. J. Laurie, Dumfries and Galloway Royal Infirmary, Dumfries; Dr. S. McAlpine, Royal Alexandra Infirmary, Paisley; Professor A. G. Macgregor, Royal Infirmary, Aberdeen; Dr. G. D. Malcolm, Bridge of Earn Hospital, Perthshire; Dr. W. G. Manderson, Royal Infirmary, Glasgow; Dr. M. B. Matthews, Western General Hospital, Edinburgh; Dr. J. S. Meredith, Bridge of Earn Hospital, Perthshire; Dr. K. Morris, Hairmyres Hospital, East Kilbride; Dr. M. F. Oliver, Royal Infirmary, Edinburgh; Dr. K. N. V. Palmer, Royal Infirmary, Aberdeen; Dr. A. A. F. Peel, Victoria Infirmary, Glasgow; Dr. A. S. Rogen, Stobhill General Hospital, Glasgow; Dr. G. B. Shaw, Southern General Hospital, Glasgow; Dr. A. W. M. Smith, Victoria Hospital, Kirkcaldy; Dr. J. M. Stowers, Royal Infirmary, Aberdeen; Professor J. A. Strong, Western General Hospital, Edinburgh; Dr. R. B. Wilson, Dumfries and Galloway Royal Infirmary, Dumfries; Dr. W. M. Wilson, Royal Infirmary, Perth.

Introduction

Much emphasis has been given to the association between hyperlipidaemia and ischaemic heart disease. The risk of apparently healthy individuals developing ischaemic heart