Papers and Originals

Long-term Anticoagulant Therapy after Myocardial Infarction in Women*

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Summary: A multicentre trial from five medical departments in Oslo has been carried out to determine the value in women patients of one year's long-term anticoagulant therapy. Follow-up long-term laboratory control and anticoagulant dosage were performed at one centre (the Rikshospitalet). One hundred and fifty-nine patients were assigned randomly into two similar well-matched groups (control and treatment). Dosage was controlled by Thrombotest, aiming at 10–20% levels, and 50% of the tests were less than 14%. Compared with the control group, the treatment group showed a significant reduction in mortality and in reinfarction rate. No serious bleeding complications occurred. It is concluded that women benefit as much as men from long-term anticoagulant therapy.

Introduction

In 1960 the situation regarding long-term anticoagulant therapy in coronary heart disease seemed to be that some effect on both mortality and morbidity had been demonstrated in male patients, though there was apparently little effect, if any, in females (Bjerkelund, 1957; M.R.C., 1959). Nevertheless, most published studies included relatively few women, and the authors had been reluctant to draw conclusions about any sex difference. Thus the value of long-term anticoagulant therapy in women was far from settled.

With this background a co-operative study involving five medical departments in Oslo was launched in 1960. By giving anticoagulant therapy for one year after the first myocardial infarction to a fairly large number of female patients, and by comparing their mortality and reinfarction rate with that of an adequate control group, we hoped to answer the question whether long-term anticoagulant therapy after myocardial infarction in females was in fact beneficial or not.

Material and Methods

Women under 70 years of age who had been discharged from hospital (Departments VII, VIII, and IX, Ullevål Hospital; Medical Department A, Aker Hospital; and Krohgstötten Hospital) after surviving a first episode of myocardial infarction were included in the study. The diagnosis of myocardial infarction was based either on (*a*) definite electrocardiographic criteria or (*b*) changes in the electrocardiogram compatible with but not proving the diagnosis, and typical attacks of retrosternal pain of at least 30 minutes' duration, with *either* a rise in serum aspartate aminotransferase (S.AsT.) to 50 units or more *or* at least two of the following criteria: leucocytosis, increase in E.S.R., fever, precordial friction rub.

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The following reasons for exclusion of a patient were adopted: (1) hospital stay for more than eight weeks during the acute infarction; (2) infarction more than one month old on admission; (3) anticoagulant therapy already started before the attack; (4) general bleeding tendency; (5) a history of recurrent gastrointestinal bleeding or of a bleeding ulcer within the last six months; (6) hypertensive fundal changes of grade III or IV; (7) relative heart volume 550 or more millilitres per square metre of body surface, or aortic valvular disease; (8) obvious congestive heart failure on discharge from hospital; (9) cirrhosis of the liver, chronic renal insufficiency (serum creatinine more than 1.5 mg./100 ml.), pregnancy; (10) any serious disease likely to lead to death within one year, or any reason which would make it unlikely that the patient would be able to carry out the treatment.

During the stay in hospital for the acute infarction all patients received routine treatment, including anticoagulants. Allocation of the patients to the treatment or the control group was done by means of a table of random numbers, with the restriction (unknown to the participating doctors) that the number in the two groups should be equal after every second allocation. Separate lists were used for patients under 60 years and for those aged 60 and over. One group received oral anticoagulant therapy (dicoumarol, warfarin, or phenindione) with the aim of reducing clotting activity to between 10 and 20%, measured with the Thrombotest method. The other group received the same oral anticoagulant but in token doses only, resulting in insignificant reduction of the clotting activity. Both groups had regular control tests on clotting activity, at least every four weeks, at the Institute for Thrombosis Research at the Rikshospitalet. All patients had a clinical examination and E.C.G. investigation, 1, 4, 8, and 12 months after the start of the observation period, in the same medical department to which they had been admitted for their myocardial infarction.

The patients were asked to appear at the Institute for Thrombosis Research one week after discharge from hospital. The observation period began one week later in order to obtain the planned anticoagulant level in both groups at the *start* of the observation period, which lasted exactly one year for each patient.

If a patient in the control group sustained a reinfarction she was readmitted to hospital and was given intensive anticoagulant therapy, but she returned to her previous treatment when discharged from hospital. Except for the anticoagulant therapy, treatment, including diet, was left to the hospital doctor in clinical charge of the patient.

Clinical and Laboratory Data

Table I gives details of the two groups of patients before they sustained myocardial infarction. So far as can be judged, they were well matched. About half of them had had angina

pectoris before the infarction, and half of these had had it for less than one year. The same number in each group smoked cigarettes (55%), most of them between 10 and 15 cigarettes a day. About half the smokers had started smoking before the age of 30.

TABLE I.—*Details of the Two Groups Before Myocardial Infarction*

	No. of Patients	
	Treated	Control
No. of patients	80	79
Age < 60 years	33	32
Age 60+ years	47	47
Married	70	68
Childless	24	16
Miscarriage	22	13
Periods stopped Before 45 years	11	16
Periods stopped After 45 years	48	41
Still menstruating	6	4
Angina pectoris before infarction	40	34
Duration of angina pectoris < 1 year	21	16
Hypertension	18	21
Claudication	1	0
Stroke	1	4
Diabetes	7	3
Ulcer	9	9
Overweight	26	27
Cigarette smokers	44	44

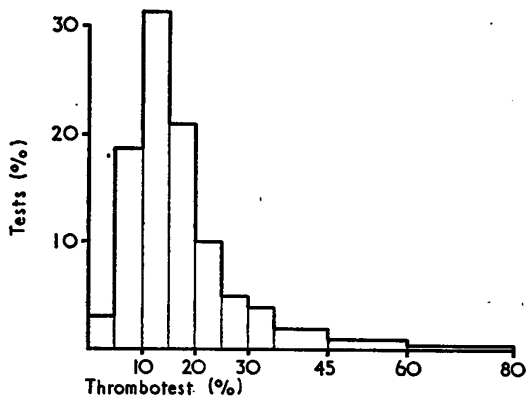
Table II gives relevant details of the acute infarction and of the patients when they were discharged from hospital. Of the 159 patients 128 had E.C.G. changes proving the diagnosis of myocardial infarction. There are small differences between the two groups, no greater than could easily have arisen by chance. On the whole there is no reason to believe that the prognosis in the two groups was different at the start of the observation period.

TABLE II.—*Data on Acute Myocardial Infarction and on Patients at Time of Discharge from Hospital*

	Treated	Control
Mean of peak values during stay:		
E.S.R. mm./hour	56	53
S.AsT.	139	157
Leucocytes	10,800	10,500
Mean serum cholesterol during stay (mg./100 ml.)	303	313
Mean heart volume at discharge (ml./sq.m.)	423	438
No. of patients with:		
Shock on admission	3	5
Shock during stay in hospital	5	6
Acute left-heart failure	4	6
Friction rub	8	8
Systolic blood pressure more than 165 mm. on discharge	6	10
Diastolic blood pressure more than 95 mm. on discharge	5	5
Pain on discharge	12	9
Dyspnoea on discharge	15	14

Anticoagulant Therapy

The Chart shows the result of the 1,599 Thrombotest values in the treated group. The grand mean value of the mean Thrombotest in each patient was 15.9% (S.D. 3.3%). Fifty per cent. of the tests were between 5 and 14%, and 85% less than 25%. The mean patient dose of the anticoagulant was phenindione (40 patients) 108 mg., dicoumarol (27 patients) 58 mg., warfarin (13 patients) 6.9 mg. In the control group 36% of all the tests were about 100%, the remainder being evenly distributed between 40 and 100%. It should be remembered that Thrombotest is rather insensitive in the normal or near normal range. It is arguable whether the treated group was sufficiently intensively treated, but there can be no doubt that the two groups were well separated in anticoagulant activity.



Thrombotest values of the 1,599 tests in the treated groups.

Results

One patient in the control group was given intensive treatment after one month, and one treated patient was advised to discontinue the anticoagulant therapy after three months, both by their family doctor. In the final analysis both patients were regarded as belonging to their original group; both survived without sign of reinfarction. Four patients, two in each group, did not appear at the 12 months' follow-up examination. They were all examined at a later date, and no evidence of reinfarction was found.

Follow-up examination at the end of the one-year observation period (Table III) showed that there were significantly more patients in the control group without angina pectoris ($P=0.012$) and more patients in the control group on diuretics. The same percentage in the two groups returned to work either at home or away from home. On the whole, however, there was little difference clinically between the survivors in the two groups.

TABLE III.—*Clinical Picture of Survivors at End of Observation Period in the Two Groups*

	Percentage of Patients	
	Treated	Control
No angina pectoris	41	63
Moderate angina pectoris	41	23
Pronounced angina pectoris	18	14
No dyspnoea	53	57
Moderate dyspnoea	32	26
Pronounced dyspnoea	15	17
On digitalis	21	27
On diuretics	12	21
On hypotensives	10	9
On mild sedation	16	17
On cholesterol-lowering diet	36	28
On low-salt diet	22	22
Full-time work at home	65	64
Part-time work at home	32	34
No work at home	3	2
Full-time work outside home	18	19
Part-time work outside home	9	8
No work outside home	73	73

The relative heart volume increased by more than 50 ml./sq. m. in 33.8% in the treated group (on average by 93 ml./sq. m.) and in 29% in the control group (on average by 112 ml./sq. m.).

Roughly 25% reduced their weight, 25% gained weight, and 50% did not significantly change their weight (less than ±2 kg.). There was no difference between the groups in this respect.

Mortality

Table IV shows the mortality in the two groups in patients aged below 60 and those aged 60 and over. Two patients in the control group (not included in Table IV) died before the

TABLE IV.—*Number and Causes of Death in Treated and Control Groups*

Cause of Death	No. of Deaths			
	Below 60 Years		60+ Years	
	Treated	Control	Treated	Control
Myocardial infarction	1	0	1	5
Sudden death	0	1	0	2
Pulmonary oedema	0	0	0	1

start of the observation period—that is, during the 14 days after discharge from hospital while the anticoagulant therapy they had had during the acute infarction was being tapered off. The difference in mortality in patients between 60 and 70 years, eight against one, is statistically significant ($P<0.05$).

One of the two deaths in the treated group occurred in the first month and the other in the fifth month. In the control group three patients died in the first month, three later in the first quarter, two in the second quarter, and one in the fourth quarter.

Necropsy in three patients (all in the control group), two of whom had died suddenly, showed widespread coronary atherosclerosis. In two patients an old infarction was found, but no fresh infarction or fresh coronary thrombus. In the third patient a fresh thrombus and infarction were found, as well as the old infarction.

Two patients in the treated group died at home after an acute attack of retrosternal pain, death being presumably due to recurrent infarction. Of the control patients in whom post-mortem examination was not carried out, one died suddenly, four had recurrent infarction clinically, and one died in an attack of acute pulmonary oedema without retrosternal pain. Thus all deaths were presumably cardiac.

Reinfarction

Table V gives the number of patients who sustained recurrent infarction, and includes cases classified as "definite" as well as "probable" infarctions by the different medical wards. The three patients who died suddenly are not included in this table. The difference in reinfarction (one and nine) between the two groups in patients aged 60 and over is statistically significant ($0.02>P>0.01$). If both age groups are combined the difference between treated and controls (4 and 16) is statistically significant at the 1% level.

TABLE V.—*Number of Patients With Definite and Probable Infarctions Both Fatal and Non-fatal. Figures in Parentheses Denote the Number of Recurrences*

	No. of Patients	
	Treated	Control
Below 60 years	3	7 (8)
60+ years	1	9 (12)

Table VI shows the time interval between discharge from hospital and the first cardiac episode (reinfarction or death). The effect of the treatment seems to be most pronounced in the first three months.

TABLE VI.—*Time Interval Between Discharge from Hospital and First Cardiac Episode (Myocardial Infarction, Sudden Death, Pulmonary Oedema Leading to Death). Figures in Parentheses Denote the Number of Deaths*

	No. of Patients	
	Treated	Control
Before observation period	1	2 (2)
1 month	2 (1)	7 (3)
1–3 months	0	7 (3)
4–6 „	1 (1)	2 (2)
7–9 „	1	1
10–12 „	0	3 (1)

Tables VII and VIII express the correlation between the effect of therapy and the existence and duration of angina pectoris previous to the myocardial infarction. The results suggest that the effect of anticoagulant therapy is better in patients with previous angina pectoris. The number of patients who had had angina pectoris for more or less than one year is too small to allow definite conclusions to be drawn. But our data do not support the hypothesis that the effect of anticoagulant therapy is better in patients with a short than with a long history of angina pectoris before their first infarction. Further analysis did not show that benefit from the treatment was correlated with any other factor, such as the nature of the infarction or the clinical situation at discharge from hospital.

TABLE VII.—*Cardiac Death + Non-fatal Reinfarction in Patients With or Without Angina Pectoris Prior to Their First Infarction*

	Treated		Control	
	No. of Patients	No. with Cardiac Episodes	No. of Patients	No. with Cardiac Episodes
Previous angina	40	1	34	11
No previous angina	32	2	33	7
Uncertain	8	1	12	2

TABLE VIII.—*Cardiac Death and Non-fatal Reinfarction in Patients with a History of Angina Pectoris of More or Less Than One Year Before Their First Infarction*

	Treated		Control	
	No. of Patients	No. with Cardiac Episodes	No. of Patients	No. with Cardiac Episodes
Angina pectoris < 1 year	21	0	16	3
Angina pectoris > 1 year	19	1	18	8

Bleeding Complications

In the treated group 17% of patients reported bleeding episodes, but no serious episode occurred. None of these patients had to be admitted to hospital, and in no patient was the treatment stopped. In the control group 3% reported minor bleeding episodes.

Discussion

Previous experience with long-term anticoagulant therapy in men showed clearly that this had better effect in patients under the age of 55 to 60 than in older ones (Bjerkelund, 1957; M.R.C., 1959). Hence we classified our patients by age in order to secure the same number of treated and control patients in women aged less than 60 and those aged 60 and over. A multicentre trial, such as the one reported here, always involves certain problems. We tried to avoid some of these by having the registration and randomization of all patients from the five medical departments involved in the study done centrally, and by letting the Institute for Thrombosis Research perform all the Thrombotests, and control and secure a stable standard of treatment.

This study, though dealing with only 159 patients, is the largest single study so far published on long-term anticoagulant therapy in women. The results have shown that this treatment has a significant effect both on the reinfarction rate and on the death rate in women aged 60 to 70. In patients under 60 treatment had no significant effect, but because of the method of selecting these patients the prognosis in control patients under 60 is so good that a much larger series would have been necessary to show a possible beneficial effect in this age group. Hence the apparent difference in effect in patients under 60 and those aged 60 and over may be artificial. Since the two groups were well matched prognostically at the start of the observation, it is reasonable to conclude that the anticoagulant therapy is responsible for the observed difference in morbidity (5% as against 20.8%) and mortality (2.5% as against 11.7%). So far as we can judge all deaths were cardiac.

Two patients in the control group died before the observation period started and are not included in the statistical analyses. Nevertheless, since they died in a period when anticoagulants for their acute infarction episode were being tapered off we cannot rule out the possibility that continuous anticoagulant therapy would have changed the prognosis. If we had included

these two patients the difference between the treated and the control group would have been correspondingly greater.

The clinical condition of the *survivors* was fairly similar in the two groups; significantly more control patients had no angina pectoris, but more control patients needed digitalis and diuretics. The same proportion of the survivors returned to work. It should be remembered, however, that 11 patients in the control group and two treated patients died before the end of the observation period.

The mean Thrombotest value achieved was 15.9%, which compares favourably with previous studies from Scandinavia (Bjerkelund, 1957; Borchgrevink, 1960, 1962; Harvald *et al.*, 1962; Aspenström and Bengtsen, 1964; Sørensen *et al.*, 1968), but which is higher than that recently reported from Holland (Loeliger *et al.*, 1967). Half the tests were between 5 and 14% Thrombotest, which is satisfactory. The bleeding complications were all trivial, and no patient had to be admitted to hospital or to stop treatment because of them.

Our results are in agreement with those of Claussen *et al.* (1961), Aspenström and Bengtsen (1964) and Sørensen *et al.* (1968), but differ from those obtained by Bjerkelund (1957) and the M.R.C. (1959), who did not find any beneficial effect of long-term anticoagulant therapy in female patients. It is possible that differences in selection of patients may explain the difference in the results. Other statistically satisfactory studies on long-term anticoagulant therapy have included only men (Veterans Administration, 1965; Lovell *et al.*, 1967) or have not given the morbidity or mortality separately for the two sexes (Harvald *et al.*, 1962; Seaman *et al.*, 1964), and hence cannot be compared with the present study.

An editorial in the *British Medical Journal* (1964), while advocating long-term anticoagulant therapy in younger men, concluded: "... there seems to be little justification for giving women long-term anticoagulant therapy." Nevertheless, there is no valid theoretical or practical reason for believing that the effect of long-term anticoagulant therapy is materially different in the two sexes. However, while in men the effect seems to be more pronounced below the ages of 55 to 60 years, in women our study shows that there is an effect on both the mortality and the reinfarction rate between the ages of 60 and 70. Our study does not answer the question whether younger women would also benefit from long-term anticoagulant therapy, though there is a suggestion of an effect on the reinfarction rate.

The present study cannot answer how long the therapy should last. The effect seems to be maximal during the first three months after discharge from hospital, but our results do not rule out that the effect lasts longer. From our study and from recently published accounts we think it is logical to adopt the same policy on instituting and maintaining long-term anticoagulant therapy in women as in men. By carefully cross-analysing all the data we had hoped to be able to correlate the positive effect of the treatment with certain features in the patient's history. We were, however, unable to find any subgroup of patients in whom the therapy was effective and other subgroups in whom it was ineffective. It may be argued, however, that with our method of selection we were already dealing with a subgroup of female patients with myocardial infarction.

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Effects of Asbestos in Dockyard Workers

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[WITH SPECIAL PLATE FACING PAGE 574]

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Summary: The prevalence of pleural and pulmonary abnormalities attributed to asbestos among 15,000 workers in a naval dockyard has been studied by means of a one-in-ten sample. Ninety-four per cent. of the men in the sample were examined. Of these, 3% had experienced continuous occupational exposure to asbestos and half of the remainder (representing approximately 6,800 men) had been exposed intermittently. The prevalence of pleural fibrosis ranged from 28% in continuously exposed workers to 1.9% in those with least exposure.

Most cases of pulmonary fibrosis occurred in laggers and sprayers who had been continuously exposed for between 15 and 20 years. Pulmonary fibrosis was also seen in a variety of intermittently exposed trades, and had been preceded by extensive pleural thickening in some cases. Ten cases of pleural mesothelioma have occurred in the last three years and a large number of men appear to be potentially at risk.

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Introduction

From 1958 onwards cases of pleural and pulmonary fibrosis have been discovered in men working at the Royal Dockyard at Devonport, partly in the course of routine examinations in the dockyard and partly among patients with symptoms referred to the local chest clinic. Further investigation has confirmed an association between these conditions and exposure to asbestos, and by 1964, when the first case of pleural mesothelioma was identified, it was evident that a serious increase in the hazards arising from the use of this material had developed.

In 1966 it became practicable to carry out a large-scale survey with a radiographic technique of adequate quality, and the opportunity was taken to incorporate a one-in-ten sample of workers. This paper is concerned mainly with the results of the survey, and in particular with the prevalence of abnormalities attributed to asbestos and their relation to exposure.

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