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LONG-TERM ANTICOAGULANT* THERAPY AFTER MYOCARDIAL INFARCTION*

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APPROXIMATELY 15% of patients who survive the acute phase of myocardial infarction die during the next 12 months.[1] After this first year the mortality rate is appreciably lower and a 10-year survival as great as 50% has been reported by some authors.[2] Many investigators have reported that the long-term administration of anticoagulant drugs has improved the prognosis after myocardial infarction.[3-5] This is a preliminary report of our experience with continued dicoumarol therapy in a small, carefully controlled group of patients.

SELECTION OF PATIENTS

The participants in this study were selected from patients who were still in hospital convalescing from recent myocardial infarction. They had all received anticoagulant therapy with dicoumarol during the period in hospital. The diagnosis of infarction was based on the clinical description of the attack, and supported by electrocardiographic changes and, in many instances, by the serum transaminase level as well. In all patients without significant Q waves in the electrocardiogram, serial T wave changes in keeping with recent myocardial infarction were required.

Patients were excluded from the study if they had any contraindication to out-patient anticoagulant therapy, e.g. previous hæmorrhage from peptic ulcer; evidence of a recently active peptic ulcer, or a diastolic blood pressure repeatedly in excess of 120 mm. Hg. Patients who were considered suitable were invited to participate in the research study.

METHOD OF INVESTIGATION

To provide satisfactory conditions for evaluations, the method used by the Medical Research Council of Great Britain was adopted. One group of patients received tablets containing 50 mg. of dicoumarol (this was called the high-dosage group). The dose was regulated to maintain the one-stage prothrombin time between 20 and 30 seconds (with a normal value of 15 to 17 seconds).

The other patients (the low-dosage group) were supplied with tablets identical in appearance but containing only 1 mg. of dicoumarol. In this group, the dose prescribed (which never exceeded 1½ tablets per day) was not sufficient to alter the normal prothrombin time. The prothrombin times were estimated on capillary blood by a method which provided values closely parallelling those obtained by the one-stage method of Quick. The details of this method have been published elsewhere.[6] Briefly, 0.1 ml. of blood obtained by finger-prick is mixed with 0.1 ml. of thromboplastin, and the clotting time of this mixture in a water bath at 37°C. is the capillary prothrombin time. The normal range by this technique is 15 to 17 seconds. This method has the advantage that the result may be obtained in one or two minutes and the patient can be instructed regarding the dosage and return appointment without delay.

At the outset it was hoped to give a low fat diet to half the patients. This plan was soon discontinued because of the difficulties in supervising the diets of out-patients.

Each new patient was assigned to either the high-dosage group or the low-dosage group by random selection. Aside from the difference in dosage levels, both groups were followed up in the same manner, returning to the clinic every two to four weeks. At each visit, the clinical progress was recorded, the prothrombin time was determined and the dose of tablets adjusted. This uniformity of follow-up controlled any psychological effect or other possible benefit that might come from regular attendance at the clinic.

If a patient on the low-dosage regimen suffered a recurrent myocardial infarction, he was admitted to hospital and treated with the usual anticoagulant doses of dicoumarol for four weeks. After discharge, treatment with the low-dosage schedule was resumed.

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Observations

A. *Data on Patients*

Between January 1, 1958, and January 1, 1960, 58 patients were accepted for the study. For various reasons eight of these patients failed to return for follow-up examination. Four of these were in the low-dosage group and four on the high-dosage schedule. These eight patients have not been included in the results of treatment.

TABLE I.—Composition of Each Treatment Group

Date	*Low dosage*	*High dosage*
No. of patients	23	27
Average age	58 years	58 years
Sex—No. of females	3	9
Previous hypertension	6 patients	5 patients
Previous angina pectoris	5 patients	12 patients
More than one previous myocardial infarction	9 patients	4 patients
E.C.G. in most recent infarct		
"Q" waves present	16	14
"T" wave changes only	7	13
Anterior infarction	12	16
Posterior infarction	11	11

By chance, 27 patients were assigned to the high-dosage group and 23 to the low-dosage group. The data on the patients in each of these groups are shown in Table I. The average age in both groups was 58. A few differences may be noted. For example, in the high-dosage group there were more females and more patients with a history of angina pectoris preceding the myocardial infarction. On the other hand, the number of patients with more than one previous myocardial infarction was larger in the low-dosage group. In other aspects which might influence the prognosis, the two groups are similar as shown.

B. *Hæmorrhagic Complications*

The incidence of hæmorrhagic episodes is given in Table II. There were no deaths attributable to bleeding, and none of the patients required admission to hospital on account of hæmorrhage. The one hæmorrhagic episode in the low-dosage group resulted from trauma. One patient on the high-dosage regimen was withdrawn from the study after severe hæmaturia. Several of these eight bleeding episodes were severe enough to provide a few anxious days for both patient and physician.

TABLE II.—Hæmorrhagic Episodes in Patients on Long-Term Dicoumarol Therapy

	Low-dosage group	*High-dosage group*
No. of patients	23	27
Patient—months of treatment	302	334
No. of bleeding episodes	1*	8
Sites of bleeding	*Fractured skull with subdural hæmatoma	Hæmaturia-4 Skin bruises-4

C. *Late Withdrawals*

In addition to those who died, eight patients left the study after they had been followed up for some time. As Table III indicates, four were in each treatment group. A variety of reasons for withdrawal are listed. In the three patients labelled

TABLE III.—Late Withdrawals from the Series

Group	*Patient*	*Duration of treatment*	*Reason for withdrawal*
LOW DOSAGE	Y. B.	3 months	Fractured skull, subdural hæmatoma
	E. H.	3 months	Gangrene of foot
	A. K.	15 months	Uncooperative
	E. W.	3 months	Withdrawn by physician after recurrent infarction
HIGH DOSAGE	J. B.	12 months	Agitated depression
	A. C.	8 months	Uncooperative
	E. E.	2 months	Hæmaturia
	V. P.	5 months	Uncooperative

"uncooperative" their enthusiasm for treatment dwindled as time went on, and eventually they failed to return. Since the average duration of follow-up on these eight patients was six months, they are included in the analysis of results.

D. *Incidence of Recurrent Myocardial Infarction and the Mortality Rate in the Two Treatment Groups.*

The preliminary results of the investigation are summarized in Table IV. The average duration of treatment of the patients was similar for the two groups. There was no significant difference in the incidence of recurrent myocardial infarction between the two series of patients.

TABLE IV.—Preliminary Experience with Long-Term Dicoumarol Therapy after Myocardial Infarction

	Low-dosage group	*High-dosage group*
No. of patients	23	27
Average duration of observation per patient	13.1 months	12.4 months
Recurrent myocardial infarctions	4	6
Deaths	0	8

Eight deaths occurred in patients on the high-dosage schedule. During the same period there were no deaths in patients in the low-dosage group.

Table V is a brief analysis of the eight deaths. There were three women and five men. The average age of those who died was the same as the average in the series as a whole. In five patients, death occurred suddenly and in three it followed attacks that were clinically diagnosed as myo-

TABLE V.—ANALYSIS OF THE EIGHT DEATHS

Patient	Age	Sex	Duration of treatment (months)	Manner of death
A. C.	62	M	3	Sudden death
J. D.	47	M	1.5	Sudden death
L. H.	62	F	3	Sudden death
A. H.	42	M	8	Severe chest pain 6 hours before death
N. H.	72	M	2	Sudden death
J. M.	57	M	1	Chest pain, sudden death
E. S.	61	F	15	In hospital 3 weeks with coronary insufficiency; sudden death
P. R.	57	F	20.5	Severe chest pain for 1 hour and death
Average	58		4.5	5 sudden deaths 3 myocardial infarctions

cardial infarction. There was only one autopsy (patient A.H.). This patient died six hours after admission to hospital with severe chest pain and shock. At post-mortem examination there was severe narrowing of the coronary arteries but no recent thrombus was demonstrated.

DISCUSSION

A. *Recurrent Myocardial Infarction*

The small size of the present study does not justify definite conclusions, but to date the continued administration of therapeutic doses of dicoumarol has failed to protect patients from further myocardial infarcts. This differs from the results published in some larger series (Table VI).

TABLE VI.—EFFECT OF LONG-TERM ANTICOAGULANT THERAPY ON INCIDENCE OF RECURRENT MYOCARDIAL INFARCTION
(based on an analysis of authors' tables)

Medical Research Council
—In males under 55—only 1/5 as many recurrences.
—In males over 55—only 1/2 as many recurrences.
—In females—no reduction.

Bjerkelund
—Overall group—only 3/5 as many recurrences.
—Significant reduction only in first 12 months of treatment.
—Over age 60—no significant reduction.
—Reduction also observed in females.

Manchester
—Both sexes—all ages—only 1/3 as many recurrences.
—Benefit not limited to first year.

In the Medical Research Council Study[4] (383 patients), the rate of recurrent myocardial infarction in men under 55 years of age who were in the high-dosage group was only one-fifth the rate in those in the low-dosage group. For men 55 years of age and older, the recurrence rate was 50% lower. There were 58 women in their series, with approximately half in each treatment group. In these women there was no difference in the frequency of recurrent infarction in the two treatment groups.

The Norwegian study[5] included 237 patients, approximately half of whom served as controls. In the dicourmarol-therapy group the rate of the recurrent infarcts was three-fifths of that in the controls. Again the drug appeared more effective in younger patients. There were 56 women in Bjerkelund's study. In contrast to the M.R.C. group, he observed a lower incidence of recurrent infarction in the women who received the anticoagulant. Bjerkelund pointed out that the protection was present only during the first 12 months of treatment and, in fact, was of much greater significance in the first six months.

A U.S.A. series, published in 1957, was that of Manchester.[6] In this study, 204 patients were treated with anticoagulant and 200 controls were given tablets of ascorbic acid. The patients were followed up for one to 10 years. The incidence of subsequent myocardial infarction in patients treated with anticoagulants was one-third that of patients who received ascorbic acid. This difference persisted after the first year.

In general these reports suggest that continued anticoagulant therapy afforded some protection against recurrent myocardial infarction. However, certain disturbing inconsistencies are evident. The benefit of this treatment in women remained unsettled. There appeared to be doubt as to its usefulness in men over 60 years of age and there was a difference of opinion as to its value beyond the first few months of treatment.

In patients who have survived a previous myocardial infarction, the accurate diagnosis of subsequent attacks is often difficult and uncertain. The ultimate measure of this type of treatment is whether or not it lowers the mortaliy rate.

B. *Mortality Rate*

The increased mortality in patients in our high-dosage group conflicts with the experience of others (Table VII).

In Bjerkelund's study, prolonged anticoagulant therapy appeared to reduce mortality by one-half. This reduction was evident only in men under 60 and only during the first year of treatment. In the 56 women in his series (31 treated and 25 controls), the mortality rate was not affected by treatment.

TABLE VII.—EFFECT OF LONG-TERM ANTICOAGULANT THERAPY ON MORTALITY
(based on an analysis of authors' tables)

Bjerkelund
Males —Mortality reduced by 1/2.
—Greatest reduction under age 60.
—No significant difference after the first year.
Females —No significant reduction.

Manchester
Both sexes, all ages—mortality reduced to 1/8.
Benefit not confined to 1 year.

Medical Research Council
Males —Mortality slightly less in high-dosage group (not statistically significant).
—Trend more marked in males under 55 in first 3 months of treatment.
Females —Mortality not reduced in high-dosage group.

In Manchester's report the mortality was lowered to one-eighth (Table VI). This reduction was observed over the 10 years of the study. There was no analysis according to age or sex.

The Medical Research Council observed a slightly lower mortality in men under 55 years who were on the high-dosage routine. Because their results were inconclusive, the Council was criticized for ending the study too soon.[8] In defence of their action a reply was published in August 1959,[5] in which some interesting additional findings were revealed.

TABLE VIII.—Distribution of Deaths During Trial

	Low-dosage group		*High-dosage group*	
Patients admitted	*No. of patients*	*Deaths*	*No. of patients*	*Deaths*
Nov. 1955—Oct. 1957	149	21*	152	5*
Oct. 1957—Mar. 1958	39	4	43	9
Final analysis Nov. 1955—Mar. 1958	188	31†	195	22†

*Reduction statistically significant.
†Reduction not statistically significant.

Midway through the third year of the investigation, the experience of the first two years was reviewed (Table VIII). It seemed well established that the high dosage of the anticoagulant saved lives in the first few months of treatment. With these figures at hand, the Council did not feel justified in admitting more new patients to the series. However, an additional 82 patients had already been admitted during the first six months of the third year. It was agreed to maintain all patients including these 82 on the treatments as begun, until the study had been in progress for three years. In these 82 patients there were twice as many deaths in the high-dosage group. This reversal of the earlier experience is difficult to understand, and in the final analysis the difference in mortality rate was no longer considered significant. It was unfortunate that the study was terminated.

Turning to our own mortality figures again, we are unable to explain why there were no deaths in the low-dosage group, just as we are unable to account for the eight deaths in the anticoagulant group.

If these treatments were neither beneficial nor harmful, four deaths would have been anticipated in each group. This is based on the expected mortality in untreated patients of 15% in the first year. It may be, as the series is enlarged, that the difference in mortality between our two dosage levels will be decreased.

As there were no deaths in the low-dosage group, it would have been impossible for any treatment to yield a better result. It is evident, in our study to date, that dicoumarol has not protected the patients from fatal myocardial infarction or sudden death. If a treatment is uniformly effective, its value can soon be recognized. Small degrees of improvement are difficult to establish by statistical analysis even with random selection. Human bias, both conscious and unconscious, on the part of the investigators must be avoided. With the exception of the third year of the M.R.C. study, it is difficult to reconcile our findings with the work of others. Our results lead us to question the value of prolonged anticoagulant therapy after myocardial infarction. Similar doubt was recently expressed by Professor R. McMichael.[8] It is obvious that further prolonged studies are required.

Summary

The preliminary results of a controlled study to determine the value of prolonged anticoagulant therapy in patients after myocardial infarction have been presented.

To date this treatment has failed to prevent further episodes of myocardial infarction or to save life.

These results are at variance with the more favourable experience reported in larger controlled studies. Certain inconsistencies in these series have been discussed.

Hæmorrhage is a serious and not infrequent complication of this treatment. Any benefit of treatment must be balanced against the danger of bleeding.

In our opinion the benefits of prolonged anticoagulant therapy after myocardial infarction have not been established.

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