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LONG-TERM ANTICOAGULANT THERAPY FOR CORONARY THROMBOSIS

BY

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As a result of the early promising reports (Nichol and Fassett, 1947; Owren, 1954; Tulloch and Wright, 1954) on the value of long-term anticoagulant therapy for coronary heart disease, it was decided to treat all severe cases of coronary thrombosis with continuous anticoagulant therapy. The following gives the preliminary results of this trial.

Selection of Patients

From 1955, all patients (except those who could not operate) discharged from New End Hospital who had sustained a severe attack of thrombosis or who had had recurrent episodes of infarction were kept on continuous anticoagulant treatment. Patients who had had only a moderately severe attack of thrombosis, without complications such as heart failure, or who had had only a single episode of infarction, were not treated. To date 117 patients have been under treatment for at least six months and are the subject of this report.

For purposes of comparison all patients with coronary thrombosis discharged from New End Hospital between 1948 and 1955 were followed up (Table I). Non-cardiac deaths were excluded, as were all patients who died within one month after discharge from hospital.

TABLE I.—*New End Control Series, 1948–55*

	6 Months	12 Months	18 Months	24 Months
No. followed up ..	125	125	125	125
Mortality ..	18 (14.5%)	26 (20.8%)	32 (35.6%)	39 (31.2%)

As an unusually high proportion of patients with coronary thrombosis are admitted to New End Hospital, to obviate any possibility of bias all patients with proved coronary thrombosis discharged from other hospitals in the same

group between 1953 and 1955 were also followed up (Table II). The mortality rates for both groups are statistically similar, and the two groups can therefore be regarded as one. Table III gives the combined mortality rate for both groups. In every case a copy of the death certificate was obtained to verify the cause of death.

TABLE II.—*Whittington Control Series, 1953–5*

	6 Months	12 Months	18 Months	24 Months
No. followed up ..	202	202	200	163
Mortality ..	19 (9.4%)	34 (16.8%)	47 (23.5%)	54 (33.1%)

TABLE III.—*Combined New End and Whittington Control Series*

	6 Months	12 Months	18 Months	24 Months
No. followed up ..	327	327	325	288
Mortality ..	37 (11.3%)	60 (18.3%)	79 (24.3%)	93 (32.2%)

Results of Treatment

Table IV shows the results of long-term anticoagulant therapy for 117 patients treated for six months or longer. The mortality rate for the first six months was 1.7% com-

TABLE IV.—*Long-term Anticoagulant Treated Series*

	6 Months	12 Months	18 Months	24 Months
No. followed up ..	117	99	77	42
Mortality ..	2 (1.7%)	3 (3.0%)	9 (11.6%)	9

pared with 11.3% in the untreated control series (Table III). Ninety-nine patients have been treated for 12 months or over, and for these the mortality rate at 12 months was only 3.0%, compared with 18.3% for the control group. To date, 77 patients have been treated for 18 months or longer, with a mortality rate of 11.6%, compared with 24.3% for the control series. These results are statistically significant. The number of patients treated for two years or longer is too small for any statistical analysis.

As mentioned earlier, only the more severely ill patients were treated. The untreated group of patients discharged from New End from 1955 onwards therefore consisted only of those with less severe attacks of thrombosis without complications and those sustaining their first episodes of infarction. It was therefore to be expected that the mortality rate in this group would be lower than that in the unselected control group. This proved to be so, as can be seen from Table V, which shows the mortality rate of untreated patients discharged from New End Hospital from 1955 onwards (from which date nearly all patients with severe or recurrent episodes of thrombosis were selected for long-term anticoagulant treatment). The mortality rates at 6, 12, and 18 months were 3.6%, 10.3%, and 15.1%, compared with 11.3%, 18.3%, and 24.3% for the control group.

TABLE V.—*New End Untreated Series, 1955–7*

	6 Months	12 Months	18 Months	24 Months
No. followed up ..	109	87	66	45
Mortality ..	4 (3.6%)	9 (10.3%)	10 (15.1%)	11

TABLE VI.—*Combined Anticoagulant Treated Cases and Untreated Series, 1955–7*

	6 Months	12 Months	18 Months	24 Months
No. followed up ..	226	186	143	87
Mortality ..	6 (2.6%)	12 (6.4%)	19 (13.2%)	20

Table VI shows the combined mortality rate for the 226 patients (treated and non-treated) discharged from New End from the time that nearly all severe cases were treated with anticoagulants. It can be seen that there is a significant reduction in the overall mortality rate. This mortality rate could almost certainly have been lower still if the deaths

among the patients who were considered sufficiently ill to warrant therapy, but who were not treated because they could not co-operate or lived too far away, were excluded.

It can be seen, therefore, that long-term anticoagulant therapy has reduced the mortality rate after 18 months from an expected rate of 24.3% in an unselected group of 325 patients to 11.6% in a selected group of 77 patients with severe disease. In this selected group of severe cases the percentage of patients with recurrent infarction was 66%, compared with only 19% in the unselected control series. The incidence of heart failure in the treated group was 44%, compared with 36% in the untreated control group. Had no anticoagulant therapy been given, one would certainly have expected the mortality rate in the treated group of selected severe cases to be much higher than that in the control series, to counterbalance the much lower mortality rate in the group of untreated patients who were not considered sufficiently ill to warrant therapy (Table V). The results of treatment with anticoagulant therapy are therefore better than appears from a straight comparison of the mortality rates for the treated patients (Table IV) and the control series (Table III).

Analysis of Deaths in Treated Series

A brief summary of the condition and progress of the patients who died whilst receiving long-term anticoagulant therapy may be informative.

1. Woman aged 74. Twice admitted to hospital for congestive cardiac failure and coronary thrombosis. After third admission to hospital for second attack of coronary thrombosis complicated by arterial embolism of the leg, long-term anticoagulants started, but patient died at home six weeks after discharge from hospital. Was not under adequate anticoagulant cover at time of death. No necropsy.

2. Man aged 75. Long-term anticoagulants started after second episode of coronary thrombosis. Patient in persistent severe congestive cardiac failure with grossly enlarged heart. Developed retention of urine from an enlarged prostate, for which suprapubic cystotomy needed whilst patient was on anticoagulants; was not fit to undergo prostatectomy, being practically bedridden throughout. Died after ten months' treatment; anticoagulants stopped one week before death. Necropsy showed whole of left ventricle replaced by shell-like aneurysm of muscle wall. Death due to heart failure with no evidence of recent infarction.

3. Woman aged 76. Attack of coronary thrombosis four years previously. Long-term anticoagulants continued after recurrence of infarction accompanied by severe congestive cardiac failure, which persisted throughout her illness. Grossly enlarged heart and auricular fibrillation present. Died after three months' treatment. Necropsy showed an old but no recent infarction, death being due to cardiac failure.

4. Man aged 81. Anticoagulants continued after severe attack of thrombosis accompanied by shock, hypotension, cardiac failure, and heart block. Heart greatly enlarged. Remained remarkably well and active, with few signs of cardiac failure for 12 months. He then developed severe cardiac failure and auricular fibrillation. Anticoagulant therapy, which had been under excellent control, became unstabilized, presumably because patient was not able to co-operate; he lived alone. Found dead at home; was presumed to have been dead for four days before being discovered. Coroner's post-mortem examination gave the cause of death as cardiac failure and coronary thrombosis.

5. Man aged 66. Long-term anticoagulants continued after his second coronary thrombosis. He had also been treated in hospital on four occasions for chronic bronchitis. Twice admitted to hospital for bronchitis and cardiac failure whilst on anticoagulant therapy. Developed recurrence of cardiac failure and died in hospital 13 months after starting anticoagulant therapy. Necropsy showed almost totally occluded coronary arteries from advanced atherosclerosis with greatly enlarged heart. No recent thrombus discovered in vessels, but section of myocardium reported as organizing infarct present in muscle with multiple old infarcts.

6. Man aged 64. Treated for hypertension for several years with blood pressure 230/140 and heart grossly enlarged with cardiac failure present. Long-term anticoagulants continued after first attack of coronary thrombosis and also treated with hypotensive drugs. Required admission to hospital on three occasions whilst on anticoagulant therapy for treatment of cardiac failure. Died quietly in his sleep at home 14 months after starting treat-

ment. Necropsy was not held. Anticoagulant therapy was not easy to control, and patient was thought to have had inadequate anticoagulant cover.

7. Man aged 63. In hospital on three occasions for two attacks of coronary thrombosis and basilar artery insufficiency. The blood pressure was 220/120, with a grossly enlarged heart. Patient developed cardiac failure with second attack of thrombosis. Collapsed at a football match and died shortly afterwards, 14 months after starting long-term anticoagulant therapy. Coroner's post-mortem examination reported cause of death as coronary thrombosis.

8. Man aged 61. Three-year history of intermittent claudication before development of first episode of coronary thrombosis, after which long-term anticoagulants continued till patient's death 15 months later. Died in his sleep at home. Coroner's post-mortem examination reported cause of death as severe coronary atherosclerosis and ruptured aortic aneurysm.

9. Man aged 51. Anticoagulant therapy continued after second episode of coronary thrombosis. Patient remained active and relatively fit for 15 months and then developed left ventricular failure. Admitted to another hospital for treatment; anticoagulant therapy continued. Died after running to his car several weeks after discharge from hospital. Coroner's post-mortem examination reported extensive fibrosis and dilatation of heart with coronary arteries narrowed to almost pinpoint diameter from advanced atherosclerosis. Thrombus present in one coronary artery. He had not been seen at our anticoagulant clinic for 10 weeks for control of his anticoagulant therapy and did not attend the New End Clinic after his discharge from hospital.

It can be seen from the above that in four of the nine patients adequate anticoagulant cover was not considered to have been given. In a fifth patient anticoagulants were stopped one week before death, but it was obvious from his critical state that death was inevitable.

Final evaluation of the results of long-term anticoagulant therapy and the decision whether or not it should be used in the treatment of all patients will depend on the results achieved when all patients have been treated for a much longer period. Nevertheless these preliminary results are promising enough to warrant wider adoption of the treatments. It should be noted, however, that several patients who have been on anticoagulant therapy for many years have died from progressive cardiac failure, so that while long-term anticoagulant therapy significantly prolongs life it is not a sufficient cure in itself.

Control of Long-term Anticoagulant Therapy

The control of long-term anticoagulant therapy demands considerable skill and individual attention for each patient. This is necessary not only to prevent haemorrhage but also—and just as important—to ensure adequate treatment. It is essential when dealing with large numbers of patients to provide special clinics. For laboratory control both Quick's and Owren's methods give reliable results, the essential factor with both methods being the provision of a reliable thromboplastin (Toohey, 1958a).

Choice of Anticoagulant Drug

Two anticoagulant drugs were used—the very long-acting "marcoumar" and the shorter-acting phenindione ("dindevan"). Once experience was gained in allowing for the very slow delayed effect and pronounced cumulative action the results with marcoumar were excellent. When the correct maintenance dose has been exactly ascertained there is much less fluctuation in the prothrombin times with long-acting drugs owing to their cumulative effect, and therefore much less danger of the patient's escaping from anticoagulant cover. This is particularly important if inadvertently the patient misses a dose.

From a brief experience with the anticoagulant warfarin sodium, which gives excellent results for short-term therapy (Toohey, 1958b), it seems that this anticoagulant will also prove valuable for long-term treatment and will give better results than phenindione.

Undoubtedly the greatest single factor in maintaining adequate long-term anticoagulant cover and also in avoiding

severe haemorrhage is experience in the regulation of the dose of the anticoagulant drug. The greater the care taken to determine the exact maintenance dose, the smaller the fluctuations in the prothrombin times and also the less frequent the need for blood tests. A very exact assessment of the maintenance dose was possible for most patients, with the result that out of a total of 117 patients under treatment 105 attend only at intervals of 6 to 12 weeks for blood tests and are nevertheless having adequate anticoagulant cover. A small number of patients are for some reason less stable, but even in this group the minimum period between blood tests is four weeks.

It is amazing how stable are the requirements of the majority of patients with regard to the dose of the anticoagulant drug, provided that there is not intercurrent illness or marked change in diet and that the patient is not taking certain drugs which may interfere with the treatment. In the absence of such circumstances, any marked fluctuation in the prothrombin times will usually be caused by too large a change in the dosage of the anticoagulant drug. It has been definitely found in this series that as much as a 5% variation in the dose will cause appreciable fluctuations in the prothrombin times over a period of a few weeks. In the vast majority of patients it is essential to assess the maintenance dose to within 2% to 3% if the prothrombin times are to remain steady over long periods and so allow the patient to attend at intervals of 8 to 12 weeks. Such widely spaced attendances are of course highly desirable.

Instructions for Patients

The patients must be given the fullest information about all aspects of their treatment, such as the dose, strength of tablet, possible side-effects, the danger of intercurrent illness, and the danger of taking certain drugs. As long-term anticoagulant therapy has to be continued indefinitely it is only by taking all possible precautions that successful therapy can be maintained. All instructions should be written. There must be the fullest co-operation with the patient's private doctor, who must in particular be made fully aware of the danger of prescribing drugs which may interfere with the treatment, such as aspirin, phenylbutazone, and oral antibiotics—especially broad-spectrum antibiotics. The possible need to reduce, but not stop, the maintenance dose of the anticoagulant drug and the necessity to take more frequent blood tests during intercurrent illness are particularly stressed.

Surgical Procedures

Many dental extractions have been performed without undue bleeding and without the need for any material alteration in the dose of the anticoagulant. Several major operations, including intestinal anastomosis and prostatectomy, have been carried out whilst the patient has continued to have adequate anticoagulant cover. It is considered most inadvisable to stop anticoagulant therapy completely in order to carry out surgical procedures; it is only necessary to ensure that the prothrombin times are at the lower therapeutic limit of approximately twice the normal control time when Quick's method is used, or 20% to 25% by Owren's technique.

Summary and Conclusions

From 1955 onwards all patients discharged from New End Hospital who had sustained a severe attack of coronary thrombosis, particularly when complicated by heart failure, or who had had more than one episode of infarction were treated with long-term anticoagulant therapy. In all, 117 patients were treated for six months or longer. In this selected group of treated patients the incidence of recurrent infarction was 66% compared with 19% for a control series of patients. The mortality rate for the treated severe cases was 1.7%, 3.0%, and 11.6% at 6, 12, and 18 months, compared with

11.3%, 18.3%, and 24.3% for the control series of 325 unselected patients discharged from New End and other hospitals in the same group between 1948 and 1955. It can be seen, therefore, that long-term anticoagulant therapy has reduced the expected mortality rate at 18 months by at least a half.

In all, 226 patients were discharged from New End Hospital following attacks of coronary thrombosis from 1955 onwards, from which date long-term anticoagulant therapy was given to all patients with severe or recurrent infarction who could co-operate or attend for treatment. The total mortality rate for all these patients—treated severe cases and untreated milder cases—was 2.6%, 6.4%, and 13.2% and 6, 12, and 18 months. There was therefore a significant lowering of the total mortality rate compared with that of the control series. In the untreated group of patients discharged from 1955 onwards several patients died whose condition would have justified treatment, but who did not receive anticoagulant therapy because they could not co-operate or attend for control of their treatment. If these patients were excluded the mortality rate would be still lower.

Several of the most severely ill patients who have been on continuous anticoagulant therapy for many years have died from progressive cardiac failure, so that while long-term anticoagulant therapy does significantly prolong life, something more is needed to halt the underlying atherosclerosis.

Long-term anticoagulant therapy is a feasible practical procedure, and the vast majority of patients can be adequately controlled with blood tests taken not more frequently than every 8 to 12 weeks. The minimum period required for attendance for routine blood tests in the small minority of patients who prove difficult to control is four to five weeks. To ensure that patients are co-operating fully over their treatment it is essential that they should attend for their blood tests whenever possible and a "postal service" is not advised as a routine.

Full written instructions about all aspects of the treatment must be given to the patient and his private doctor, particularly with regard to the risk of bleeding, the need for more frequent blood tests during intercurrent illness, and the possible necessity for a reduction in the maintenance dose of the anticoagulant drug during such illness. The anticoagulant drug must not, however, be stopped, as there is a definite danger of a recurrence of thrombosis, particularly in severe cases. The danger of taking certain drugs such as aspirin, phenylbutazone, and oral broad-spectrum antibiotics is especially stressed.

Major surgical procedures, such as intestinal operations and prostatectomy, have been performed whilst the patients continued to have adequate anticoagulant therapy, and it is inadvisable and unnecessary to stop treatment completely at such times.

When large numbers of patients are being treated with long-term anticoagulant therapy it is essential to have special clinics with personnel who are experienced in the use of anticoagulant drugs and who fully understand the necessary laboratory procedures.

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