An Assessment of Long-term Anticoagulant Administration after Cardiac Infarction

Second Report of the Working Party on Anticoagulant Therapy in Coronary Thrombosis* to the Medical Research Council

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Between November 1955 and May 1960 a controlled trial was carried out to compare the clinical progress of patients who had recovered from the acute stage of cardiac infarction when given high dosages of phenindione with the experience of a similar series of patients given low dosages. The patients on the high-dosage regime were given sufficient phenindione approximately to double the one-stage prothrombin time, while those on the low-dosage regime were given tablets containing only 1 mg. of phenindione. New patients were admitted to this trial between November 1955 and March 1958. The design of the trial and the progress of these patients up to the end of 1958 have already been given (Report to M.R.C., 1959). The present report describes the subsequent progress of the patients up to May 1960, when the trial in its original design was discontinued. A later phase of this trial extending up to December 1962 is also described.

Summary of Results at May 1960

On reviewing the full hospital case-notes of the patients in this trial, a few errors in transcription—for example, of age or date of birth (and in one instance of sex)—were discovered in the summary sheets used in the preparation of the preliminary report. These have been rectified in this report. A problem in the conduct of long-term clinical trials is the maintenance of contact with patients and follow-up of those who have either defaulted or been withdrawn, for one reason or another, from the trial. Thanks to the patients' family physicians and to the Ministry of Pensions and National Insurance, it has proved possible to obtain some information on 67 out of 78 (86%) of those lost from the original series.

Follow-up on Withdrawals

Table I shows the reasons for withdrawal and the subsequent fate of those withdrawn from the trial. Of the 188 patients in the low-dosage group 45 were withdrawn. Thirteen of them suffered recurrent myocardial infarction of such severity that their attendant physicians removed them from the trial in order that they might be treated without the resrictions imposed by it. Among the remainder, the medical reasons for withdrawal were: pulmonary embolism (1 patient), cardiac failure (8 patients), cerebrovascular accident (1 patient), signs and symptoms of peptic ulcer (3 patients), pulmonary tuberculosis (1 patient), phenindione-sensitivity skin rashes (2 patients), carcinoma of bronchus (1 patient), brain abscess (1 patient), atrial fibrillation and cerebral incident (1 patient). One patient was removed from the trial after publication of the initial report.

Of the 195 patients in the high-dosage group 33 were withdrawn from the trial. Among these patients the causes for withdrawal were: cerebrovascular accidents (3 patients), cardiac failure (3 patients), signs and symptoms of peptic ulcer (9 patients), traumatic episodes with bleeding (3 patients), other disorders associated with bleeding (3 patients), congestive

TABLE I.—*Cause and Fate of Withdrawals*

	No. of Patients	No. Followed Up	No. C.V. Deaths	No. Deaths all Causes
Low Dosage				
Severe cardiac infarcts	13	11	4	4
Pulmonary embolism	1	1	1	1
Cardiac failure	8	8	2	4*
Cerebrovascular accidents	1	1	1	1†
Peptic ulcer or dyspepsia	3	2	0	0
Pulmonary tuberculosis	1	1	0	0
Sensitivity to phenindione	2	2	1	1
Carcinoma of bronchus	1	1	0	1
Brain abscess	1	1	0	0
Atrial fibrillation and cerebral spasm or embolism	1	0	0	0
Failures in co-operation	11	9	1	1
Transfer (after initial report)	1	0	0	0
No further treatment and supervision justified	1	1	0	0
Total	45	38	10	13
High Dosage				
Cerebrovascular accidents	3	3	0	0
Cardiac failure	3	3	2	2
Peptic ulcer	9	8	2	3*
Traumatic episodes (with bleeding)	3	3	0	1‡
Other disorders (associated with bleeding)	3	3	3	3
Decreased dosage (C.C.F. and haematuria)	1	1	1	1
Treatment altered—therapeutic myxoedema	1	1	0	1
Failures in co-operation	10	7	3	3
Total	33	29	11	14

* One cause of death not known.
† Died two months after withdrawal from cardiac failure and pneumonia in post-operative period following prostatectomy.
‡ Patient with fractured skull died shortly after withdrawal.

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The centres taking part in the trial were: Radcliffe Infirmary, Oxford (Dr J. R. A. Mitchell); Newcastle General Hospital, Newcastle upon Tyne (Dr. W. G. A. Swan, Dr. C. B. Henderson); the General Infirmary, Leeds (Dr. W. Whitaker, Dr. C. P. Newcombe, Dr. S. C. Jordan); National Heart Hospital, London (Dr. L. G. Davies, Dr. L. Resnekov); St. Mary's Hospital, London (Dr. G. Rose, Dr. W. B. Thomson); Royal Infirmary, Edinburgh (Dr. D. Leak, Dr. D. Julian, Dr. R. Wilson); Royal Infirmary, Manchester (Dr. A. Morgan Jones, Dr. G. Wade, Dr. G. Howitt); Royal Infirmary, Glasgow (Dr. R. Fife, Dr. M. Dunnigan, Dr. J. A. Kennedy, Dr. M. MacDonald); Western Infirmary, Glasgow (Dr. R. L. Richards, Dr. W. M. McCrae); Royal Infirmary, Cardiff (Professor H. Scarborough, Dr. G. S. Kilpatrick); Royal Infirmary, Bristol (Professor C. Bruce Perry, Dr. D. W. Barritt); Queen Elizabeth Hospital, Birmingham (Dr. A. G. W. Whitfield, Dr. J. N. Marshall Chalmers); Maryfield Hospital, Dundee (Dr. W. Walker, Dr. M. F. Grayson); Royal Infirmary, Aberdeen (Dr. G. A. McDonald, Dr. A. A. Dawson).

cardiac failure and haematuria (1 patient), myxoedema (1 patient).

There was a high incidence of withdrawal (13 patients) in the low-dosage group because of severe cardiac infarcts, as compared with none in the high-dosage group. None of the three cerebrovascular accidents causing withdrawal in the high-dosage group was fatal. Sensitivity to phenindione manifesting as skin rashes was observed in the low-dosage group.

The frequency of failure to co-operate was similar in the two groups (11 patients in the low-dosage group and 10 in the high-dosage group).

The fate after withdrawal was established in more than three-quarters of the patients in each group, and this is shown in Table I. There is no significant difference between the groups either in the number of deaths from cardiovascular diseases or from other causes after withdrawal and during the period of follow-up.

Measures of Effects of High-dosage Regime

The obvious measure of the success or failure of long-term therapy is its effect on the mortality from reinfarction and other cardiovascular causes, but in a trial of this design the effect on mortality may be judged to be more important. Table II shows that there was still in May 1960 a difference

TABLE II.—*Deaths, Fatality Rates, and Subsequent Infarcts During the Trial*

Age	Males					Females				
	No. Patients	Deaths		Infarcts.		No. Patients	Deaths		Infarcts.	
		No.	%	No.	%		No.	%	No.	%
Low Dosage										
<55	69	18	26	43	62	5	—	—	1	20
≥55	91	17	19	30	33	23	5	22	7	30
Total	160	35	22	73	46	28	5	18	8	29
High Dosage										
<55	74	10*	14	11	15	5	—	—	—	—
≥55	92	15†	16	16	17	24	4	17	7	29
Total	166	25	15	27	16	29	4	14	7	24

* Includes one patient dying from coal-gas poisoning.
† Includes one patient dying from cancer of lung.

in mortality between the two groups, particularly in men under the age of 55. Among men in this age-group the difference between 18 and 9 deaths from non-violent causes failed to reach the conventional 5% level of statistical significance, although a difference of this order in either direction is likely to have arisen by chance only once in any 16 such trials. At 55 and over there was very little difference between the male groups, and among the women practically no difference between the two series. The overall survival rate in males is shown in Fig. 1.

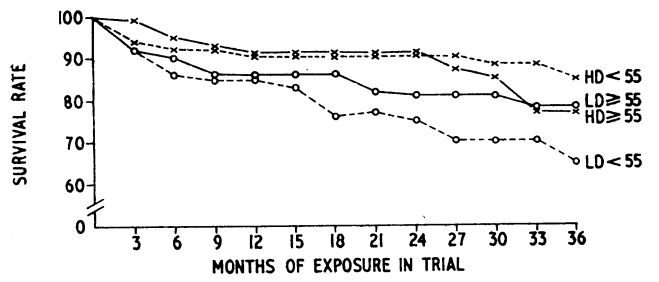

FIG. 1.—Overall survival rate in males in the high- and low-dosage groups for those under 55 and those aged 55 and over. This illustrates the number of patients out of an initial 100 who would still be alive at the intervals as shown after the start of treatment. ×--×, High dosage under 55 years of age. O--O, Low dosage under 55 years of age. ×——×, High dosage aged 55 and over. O——O, Low dosage aged 55 and over.

Comparison of Reinfarction Rates

The second major measure of therapeutic or prophylactic success is the rate of reinfarction. Table II shows that there were differences in the frequency of reinfarction in males, which were technically significant, in both age-groups. Below the age of 55 years the reinfarction rate in the high-dosage group was down to a quarter of that in the low-dosage group. In the patients aged 55 and over the reinfarction rate was down to a half, and in both instances the differences were technically significant ($P<0.001$ and $P<0.05$ respectively). In females there was almost no difference between the two groups.

A criticism of this trial was that when assessing the clinical and electrocardiographic (E.C.G.) evidence for reinfarction the physicians knew the treatment being received. The diagnosis of reinfarction at the centres rested on a combination of history, physical examination, and laboratory data as well as on E.C.G. changes. These two sources of evidence have now been independently assessed. Copies were made of all the tracings obtained at the centres in patients with reported reinfarction admitted long enough before death for records to be available. There were 70 such incidents ; in 63 of these the centres had decided that there was clinical and E.C.G. evidence of reinfarction, and in seven clinical but not E.C.G. evidence of reinfarction. These 70 sets of E.C.G. records were arranged in random order and presented without identification or clinical histories to a panel of three experienced cardiologists. These observers were asked to note the changes seen—for example, Q-wave changes, fresh S-T deviations, etc.—and to give an overall assessment on the likelihood of reinfarction on the basis of these E.C.G. tracings alone.

Table III sets out the frequency of agreement between two or more of the three observers on the presence of E.C.G. evidence of reinfarction in younger and older patients in the two series ; included in this Table are incidents when the centres had considered E.C.G. evidence of reinfarction to be present and others when the E.C.G. evidence was thought to be negative. On the seven tracings where the centres reported no clear E.C.G. changes, only one was accepted by two of the independent judges as showing evidence of recurrent infarction. The centres reported E.C.G. evidence of reinfarction in 16 sets of tracings from patients on high dosage ; and in 4 out of these 16 at least two of the assessors agreed on this interpretation. On the 47 E.C.G.s from patients on low dosage, the assessors agreed with the centre's interpretation in 24 out of 47. Table III also shows, however, that agreement is generally higher among the younger patients. The fact that more of the E.C.G.s sent in from the low-dosage groups came from such patients explains at least some of the overall disparity between the series in the frequency of agreement on the "certainty" of the E.C.G. evidence.

TABLE III.—*Independent Assessment of E.C.G. Evidence by Three Cardiologists*

	Low Dosage			High Dosage			Total		
	<55	≥55	Total	<55	≥55	Total	<55	≥55	Total
Reinfarctions	26	21	47	4	12	16	30	33	63
2 or more certain of reinfarction — No.	17	7	24	2	2	4	19	9	28
2 or more certain of reinfarction — %	65	33	51	50	17	25	63	27	44
"Negative" E.C.G.s	2	3	5	–	2	2	2	5	7
2 or more certain of reinfarction — No.	1	–	1	–	–	–	1	–	1
2 or more certain of reinfarction — %	50	0	20	–	0	0	50	0	14

The frequency of disagreement among three experienced cardiologists regarding the significance of E.C.G. changes may seem remarkable, but is similar to that reported by Davies (1958). From the standpoint of this trial the important issue is the finding that the independent review of the evidence fails to reveal bias in favour of reinfarction in the low-dosage group.

In considering the results given in Table III it should be remembered that the independent assessors of the E.C.G. evidence made their decision on the basis of tracings alone, whereas the centres made their decision on all the available information—clinical assessment as well as laboratory and E.C.G. evidence.

The case records (excluding the E.C.G.s) were therefore reviewed by an independent observer who was unaware of the treatment group to which the patients belonged. Unfortunately, complete clinical and laboratory details could be obtained in only a proportion of the total number of reinfarctions ; some were sudden deaths outside of hospital and some patients were not investigated in hospital at the time. Of these, in the high-dosage group the independent assessor considered infarction either " definite " or " probable " in 4 (out of 8) compared with 27 (out of 34) reports on infarcts in patients on low dosage. It would appear that in their original reports the centres had no less grounds for confidence in their diagnosis in the low-dosage series as compared with the high-dosage series, and that the excess rates of reinfarction reported in such patients is unlikely to result from observer bias in favour of the anticoagulant regime.

Timing of Deaths, Withdrawals, and Reinfarctions

Table IV brings up to date the information on the timing and frequency of deaths, withdrawals, and reinfarction among male patients during successive periods up to four years after admission to the trial. Table V contains the data separately for men under 55 and for those 55 and over, giving the results in terms of ratio per 100 man-months of exposure.

It is clear that, although the mortality was less in the high-dosage group in the first two years of follow-up, a series of deaths during the third year among men on high dosage reduced this difference. Table V also shows that these later deaths occurred mainly among older men. Reinfarction rates changed with time in the same direction, if not to the same extent, as the death rates ; and, again, this trend was most pronounced among men of 55 and over. The numbers involved are too small for a clear pattern to emerge.

The results can also be expressed in life-table form (Fig. 1). The death rate in successive periods prevailing in each of the dosage groups and age-groups can be used to estimate the number of patients out of an initial 100 who would still be alive at stated intervals after the beginning of treatment. There appears to be an initial advantage to those on high dosage in both age-groups, but the gap in overall survival rate in those aged 55 and over disappears in the third year of follow-up. The results in relation to infarction can also be expressed in life-table terms as the proportion of an initial 100 who would have survived to the time indicated without having suffered reinfarction (Fig. 2). There is a clear indication that, particularly at the earlier stages of follow-up, the groups on high dosage fare better in respect of the length of their period of freedom from recurrence.

TABLE IV.—*Timing and Frequency of Deaths, Withdrawals, and Fresh Infarcts Among Male Patients*

Months Since Admission	Low Dosage			High Dosage		
	Deaths	Withdrawals	Infarcts	Deaths	Withdrawals	Infarcts
3	12*	3	18	5	6	7
3—	6†	3	10	5	1	5
6—	4 } 22	4 } 13	8 } 41	2 } 15	4 } 16	3 } 19
9—	—	3	5	3‡	5	4
12—	9	12	24	0	8	2
24—	4	10	6	8§	4	6
36— } 48— }	0	0	2	2¶	0	0
Total	35	35	73	25	28	27

* One death from pulmonary oedema.
† One death from cerebral embolism.
‡ One death from cerebral haemorrhage.
§ One death from coal-gas poisoning.
¶ One death from cancer of lung.

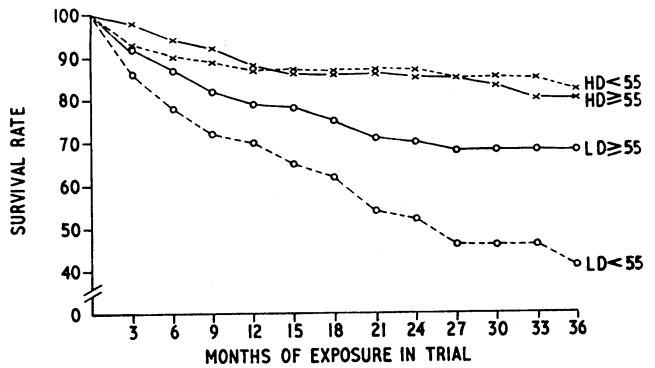

FIG. 2.—Survival rates in males at first reinfarction in the high- and low-dosage groups, below 55 and 55 and over. Number of patients out of an initial 100 who would have survived at the time intervals shown without having suffered reinfarction. ×--×, High dosage under 55 years of age. O--O, Low dosage under 55 years of age. ×——×, High dosage aged 55 and over. O——O, Low dosage aged 55 and over.

Condition of Survivors

The third criterion used in the preliminary report was the current occupational and physical status of the survivors. Table VI shows the position at March 1960. Of the men who had been on high dosage, 80% were back at work compared with 64% of those on low dosage. The frequency of angina reported among those on high dosage (39%) was appreciably

TABLE V.—*Timing and Frequency of Deaths and Fresh Infarcts among Male Patients*

Years Since Admission	Low Dosage					High Dosage				
	M.M.E.	Deaths		Infarcts		M.M.E.	Deaths		Infarcts	
		No.	Rate/100 M.M.E.	No.	Rate/100 M.M.E.		No.	Rate/100 M.M.E.	No.	Rate/100 M.M.E.
Males 40–54										
<1	689·5	10	1·5	22	3·2	795·5	7	0·9	9	1·1
1–	525·5	5	1·0	16	3·0	666·5	—	—	—	—
2–	250·0	3	1·2	5	2·0	451·5	2	0·4	2	0·4
3–	63·0	—	—	—	—	125·0	1	0·8	—	—
4+	1·5	—	—	—	—	3·0	—	—	—	—
Total	1,529·5	18	1·2	43	2·8	2,041·5	10	0·5	11	0·5
Males 55–69										
<1	953·5	12	1·3	19	2·0	983·0	8	0·8	10	1·0
1–	794·5	4	0·5	8	1·0	802·0	—	—	2	0·2
2–	472·0	1	0·2	1	0·2	439·0	6	1·4	4	0·9
3–	94·5	—	—	2	2·1	110·5	1	0·9	—	—
4+	—	—	—	—	—	3·0	—	—	—	—
Total	2,314·5	17	0·7	30	1·3	2,337·5	15	0·6	16	0·7

M.M.E. = Man-months of exposure.

lower than the level of 57% for those surviving on low dosage. In both instances these differences are statistically significant at the 5% level. On the other hand, there was, as before, no difference in the reported frequency of dyspnoea. It is also noteworthy that in female patients the levels of employment in both treatment groups are similar and that in this as well as other respects the results are dissimilar from those in males. These results for women are, of course, based on small numbers.

TABLE VI.—*Occupational and Physical Status of Survivors*

	Low Dosage				High Dosage			
	Males		Females		Males		Females	
	No.	%	No.	%	No.	%	No.	%
Employed:								
Yes	58	64	9	69	90	80	13	65
No	18	20	3	23	11	10	7	35
Retired	14	16	—	—	12	10	—	—
Not stated.. ..	—	—	1	8	—	—	—	—
Total	90	100	13	100	113	100	20	100
Angina absent ..	39	43	7	54	69	61	9	45
Dyspnoea absent ..	55	61	7	54	69	61	7	35

Death and Infarction in Relation to Prothrombin-time Levels

If anticoagulant therapy influences the risk of death or recurrent infarction, these events might be expected to occur when the prothrombin-time level is below the desired level of two to two and a half times the control value. Table VII gives

TABLE VII.—*Prothrombin Times in High-dosage Series (Optimum Range =2 to 2½ Times Control Level)*

	Below		Within		Above		Total	
	No.	%	No.	%	No.	%	No.	%
Deaths :								
Last available reading	13	50	11	42	2	8	26	100
Average reading	54	48	45	40	14	12	113	100
Survivors of reinfarction :								
Last available reading	3	33	4	45	2	22	9	100
Average reading	21	31	29	43	18	26	68	100
Other survivors :								
Average reading	385	33	540	46	254	21	1179	100

data on the distribution of ratios noted at the last visit to the follow-up clinic before either death or reinfarction, compared with the distribution during the whole of the trial ; figures are given for (*a*) deaths from reinfarction or other cardiovascular disorder, (*b*) patients surviving reinfarction, and (*c*) other survivors. Both during the trial and before death about half the readings in those who died from reinfarction or other cardiovascular cause were below the desired levels, compared with a third in both groups of survivors. The difference, however, is not technically significant. It should also be pointed out that the average dosage of phenindione given at the various participating centres varied widely but that this variation was not reflected in any corresponding variation in death or infarction rates at these centres. In the high-dosage group the average dose of phenindione was, at 108 mg./day, identical in those who survived and those who died.

Necropsy Evidence

Post-mortem examinations were carried out on 12 patients who had been on low dosage and eight who had been on high dosage. The results are summarized in Table VIII. There are certainly more thromboembolic phenomena and infarcts in the low-dosage group, but in relation to the numbers involved in each group the difference is small. On the other hand, there is no suggestion that cardiac aneurysm or rupture or haemopericardium is a frequent complication specific to anticoagulant therapy.

Risks of High-dosage Anticoagulants

During the extended follow-up 80 haemorrhagic incidents were reported among patients given high doses over a total period of 5,101 person-months, a rate of 1.6 per 100 man-months. Of these incidents 16 were potentially serious—a rate of one major event for every 27 person-years of treatment. Haematuria, which occurred in 12 patients, was described as "massive" in two of them, while bleeding from the alimentary canal was severe enough to cause withdrawal from the trial because of haematemesis in two patients and bleeding from haemorrhoids in two patients. Among the patients on the low-dosage regime, only 10 had minor haemorrhages—that is, a rate of 0.2 per 100 man-months. As already noted, three patients were withdrawn from the high-dosage group because of the onset of cerebrovascular accidents, compared with one on the other side. One patient on high dosage died from cerebral haemorrhage.

Frequency of Thromboembolic and Other Manifestations

In the low-dosage series eight patients suffered thromboembolic incidents of various kinds (excluding thrombi in the coronary vessels) compared with two on high dosage. Intermittent claudication was reported in 17 patients (16 males and 1 female) in the low-dosage group and 20 patients (18 males and 2 females) in the high-dosage group. Acute coronary insufficiency appeared in 14 males on low dosage and in 10 on high dosage ; there were three such reports in females in each group.

The criteria for the diagnosis of acute coronary insufficiency were left to the judgment of the individual clinician.

Final Stage of Trial

On reviewing these results the Working Party concluded that by the end of the third year any early advantage in mortality to the older males had largely disappeared, while in the younger males the disparity in survival rates between the two dosage groups was still present but was not apparently increasing. In the light of these findings it was questionable whether the difficulties and potential dangers of continuous anticoagulant therapy were justified by the results obtaining among the rather selected group of survivors in this trial. Furthermore, the removal of patients with serious infarcts from the low-dosage regime may have affected the initial equality between the two series, making the interpretation of comparative results progressively more difficult in a long-term trial. For these reasons

TABLE VIII.—*Summary of Post-mortem Findings*

	Low Dosage (12 cases)			High Dosage (8 cases)		
	Pos. Entry	Neg. Entry	Not Recorded	Pos. Entry	Neg. Entry	Not Recorded
Fresh infarct	6	6	—	5	3	—
Infarct haemorrhagic	2	4	—	1	4	—
Cardiac rupture	—	12	—	—	8	—
Ventricular aneurysm	3	9	—	1	7	—
Mural thrombus	4	5	3	—	8	—
Haemopericardium	—	12	—	—	8	—
Coronary arteries :						
Atheroma	11	—	1	8	—	—
Thrombosis	6	5	1	6	2	—
Subintimal haemorrhage	3*	6	3	—	8	—
Brain :						
Cerebral haemorrhage	—	8	4	—	8	—
Cerebral thrombosis or embolism..	2	6	4	1	7	—
Limbs :						
Phlebothrombosis	2	8	2	—	5	3
Arterial thrombosis	1	9	2	—	5	3
Arterial embolism	2	8	2	—	5	3
Lungs :						
Pulmonary embolism	—	11	1	1	6	1
Pulmonary infarction	1	10	1	1	6	1
Haemothorax	1	10	1	—	7	1
Spleen :						
Infarcts	1	9	2	—	7	1

* One ? positive included.

the Working Party decided to end the trial in its original form and to try to assess the risks, if any, involved in removing patients from a high-dosage regime to which they had been subject for periods of two years or more.

After May 1960 the patients who had been on the low-dosage regime were no longer followed in the trial and any restrictions on treatment were withdrawn. Those still on high dosage (126 patients) were then sorted according to sex, age, and hospital, and arranged in a series of pairs (63 pairs), each consisting of two patients of the same sex, age, and with the same hospital supervision. One of each of these pairs was then allocated at random to a subgroup who were to have their dosage reduced to the low level. The remaining member of each pair was maintained as before on a high dosage. The Working Party decided to taper off the dosage at weekly intervals until the end of the third week. So that any major change in the risk of reinfarction and death associated with this process could be detected as soon as possible, a sequential scheme was set up (see Armitage, 1960, Chapter 7).

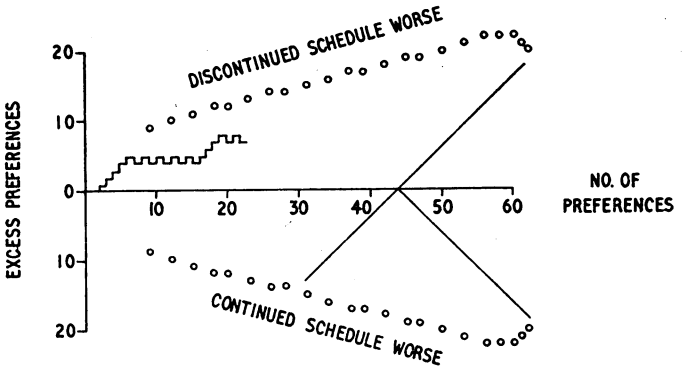

FIG. 3.—Sequential diagram on which were plotted the reinfarctions (fatal and non-fatal) and deaths from any cause occurring in the paired patients in the final stage of the trial.

Fig. 3 shows the diagram on which were plotted the reinfarctions, whether fatal or not, and deaths from any cause, occurring in the paired patients. If the first in a pair to be affected had been transferred to the low-dosage schedule the line moved up towards the upper limit; if the first in the pair to be affected was still on the high-dosage schedule the line moved towards the lower limit. These limits were fixed so that there would be a 95% chance of detecting a threefold excess in risk and they were rather arbitrarily chosen as an indication of a worthwhile gain which would outweigh the hazards of continued anticoagulant therapy and which would be detected with the number of patients available. Indeed, the restricted number of patients means that even a difference of this size would be detected only by a follow-up of perhaps two years at the low rate of reinfarction and death prevailing at this stage of the disease. Fig. 3 shows that after an initial disquieting rise the trend of results stabilized and failed to reach a significant level by the end of the period of follow-up. As shown in Table IX, when considering the occurrence of either infarction or death in the first of a pair, there were 12 probable reinfarctions and eight deaths from these and other causes in patients removed from high dosage compared with five reinfarctions and six deaths from these and other causes in those continuing on high dosage. When considering both of each pair, there were more reinfarctions in the new low-dosage group (14 compared with 8), but the numbers of deaths from all causes were practically the same (9 and 10). The deaths from reinfarction were also alike (6 and 6).

TABLE IX

	First of Pair		Both of Pair	
	Low Dosage	High Dosage	Low Dosage	High Dosage
Reinfarction:				
Non-fatal	7	2	8	2
Fatal	5 } 12	3 } 5	6 } 14	6 } 8
Other deaths	3*	3†	3*	4†
No. of patients involved	15	8	17	12

* Including two sudden deaths and one of unknown cause.
† Includes one sudden death.

Discussion

Since the publication of our interim report there have appeared further controlled studies of the use of anticoagulants in the care of patients after the acute phase of cardiac infarction (Borchgrevink, 1960; MacMillan *et al.*, 1960; Clausen *et al.*, 1961; Harvald *et al.*, 1961, 1962; Aspenström, 1962). Borchgrevink's study and its sequel (Borchgrevink, 1962) were concerned mainly with patients suffering from angina, without evidence of previous infarction, but also included a small number of patients who had clearly suffered infarction. Other studies dealt, like ours, only with the latter group. Table X sets out the major results in the same way, so far as the reported data in the various reports allow. Clearly there is quite close agreement between an earlier Norwegian study (Bjerkelund, 1957) and our own, while Borchgrevink's results are similar in direction but with levels of death and reinfarction rates which reflect the different outlook in the clinical groups included in his trial. Clausen *et al.* (1961), whose data are not presented in a form compatible with these summary tables, reported a significant reduction in reinfarction rates and some lowering in mortality in patients under the age of 55; but this effect was apparent only in the first year of follow-up. There were also fewer thromboembolic complications in the group given anticoagulants. Harvald *et al.* (1962), reported that, after an initial period of lowered mortality in the anticoagulant-treated patients during the first year of observation, the survival rates at the second and subsequent years were identical.

The results in the trial of Aspenström (1962) and of Lovell *et al.* (1962), are based on smaller numbers, but the relative superiority in survival rate among males on high dosage is similar to that found in our trial. Among the women in the Swedish trial, on the other hand, there is a lower death rate associated with high dosage which is not found to the same extent in any other comparable trial. The report by MacMillan and his colleagues is at variance with all the other results. The numbers involved in this Canadian study are small, but the run of eight deaths in patients put on high dosage presumably raised serious ethical problems. Of these eight deaths, however, three were in females and three were in men over the age of 55. In both Bjerkelund's study and our own, these patients belonged to age and sex groups in whom little if any benefit in terms of mortality could be observed. If attention is confined to men under the age of 55 years the two deaths in the high-dosage

TABLE X.—*Overall Results in Controlled Trials of Anticoagulants*

	No. Man-Months Exposure and No. of Patients		Deaths				Infarcts			
			Low Dosage*		High Dosage		Low Dosage*		High Dosage	
	Low Dosage*	High Dosage	No.	Rate†	No.	Rate†	No.	Rate†	No.	Rate†
Bjerkelund	3,844 (118)	4,879 (119)	38	1·0	23	0·5	47	1·2	26	0·5
M.R.C.	4,475 (188)	5,101 (195)	37	0·8	26	0·5	81	1·8	34	0·7
Borchgrevink	1,476 (100)	1,704 (103)	8	0·5	1	0·1	13	0·9	2	0·1
MacMillan *et al.*	622 (34)	670 (37)	3	0·5	9	1·3	7	1·1	7	1·0
Harvald *et al.*	5,415 (170)	4,350 (145)	45	0·8	34	0·8	67	1·2	52	1·2
Aspenström	2,441 (91)	2,412 (88)	34	1·4	20	0·8	30	1·2	12	0·5

* Or no anticoagulants.
† Rate/100 man-months exposure.

TABLE XI.—*Age Differences in Outcome (Male and Female)*

	No. of Patients		Deaths				Infarcts			
	Dosage		Low Dosage*		High Dosage		Low Dosage*		High Dosage	
	Low*	High	No.	Rate†	No.	Rate†	No.	Rate†	No.	Rate†
<60 Bjerkelund ..	63	61	18	28·6	8	13·1	21	33·3	8	13·1
<55 M.R.C. ..	74	79	17	23·0	9	11·4	44	59·5	11	13·9
<55 Borchgrevink ..	46	36	5	10·9	—	—	7	15·2	—	—
<55 Lovell *et al.* ..	28	46	4	14·3	3	6·5				
<60 Harvald *et al.* ..	86	69	17	19·8	13	18·8	32	37·2	23	33·3
<60 Aspenström ..	30	32	7	23·3	5	15·6	13	43·3	5	15·6
≥60 Bjerkelund ..	55	58	20	36·4	15	25·9	26	47·3	18	31·0
≥55 M.R.C. ..	114	116	20	17·5	17	14·7	37	32·5	23	19·8
≥55 Borchgrevink ..	54	67	3	5·6	1	1·5	6	11·1	2	3·0
≥55 Lovell *et al.* ..	52	34	7	13·5	4	11·8				
≥60 Harvald *et al.* ..	84	76	28	33·3	21	27·6	35	41·7	29	38·2
≥60 Aspenström ..	61	56	27	44·3	15	26·8	17	27·9	7	12·5

* Or no anticoagulants. † Rate/100 patients.

group in the Canadian series could have happened by chance without the evidence in the other larger series being contradicted.

The importance of this age effect is clear in Table XI, where the British, Scandinavian, and Australian trial results are summarized. These results, which represent all the controlled trials known to us, would be consistent with the view that long-term anticoagulant therapy in the conditions of these trials slightly reduces the probability of death, and to a greater extent the risk of reinfarction mainly in the younger males; Table XII suggests that it is practically without value in women. Table II shows that this is not because most women patients are aged 55 and over, for they do not share even the modest reduction of the reinfarction rate achieved in their male contemporaries.

The apparent improvement in the high-dosage group in anginal symptoms and disability may result from bias in assessment, but it is consistent with both Bjerkelund's and Borchgrevink's observations on these features in the survivors in their trials. In Borchgrevink's trial, which had the administrative advantage of being conducted at one centre, this assessment was made by independent observers.

One of the most striking features of Bjerkelund's trial is the limitation of the period of apparent reduction in mortality to about the first three months after the end of the acute phase. In our experience the differential in the risk of both death and reinfarction continued, although gradually diminishing, until about the end of the second year. Beyond that point the limited information available did not suggest any continuing important benefit, and the sequential stage of the trial did not reveal any major risk in the gradual cessation of high dosage. Bjerkelund (1961) and Harvald *et al.* (1962), came to similar conclusions. Bjerkelund discontinued treatment after three to four years and Harvald *et al.* after two to four years of treatment.

TABLE XII.—*Sex Differences in Outcome*

	No. of Patients		Deaths				Infarcts			
	Dosage		Low Dosage*		High Dosage		Low Dosage*		High Dosage	
	Low*	High	No.	Rate†	No.	Rate†	No.	Rate†	No.	Rate†
Males										
Bjerkelund ..	93	88	32	34·4	15	17·0	35	37·6	17	19·3
M.R.C. ..	160	166	33	20·6	22	13·3	73	45·6	27	16·3
Borchgrevink ..	82	82	7	8·5	1	1·2	12	14·6	2	2·4
MacMillan *et al.*	31	26	3	9·7	6	23·1				
Lovell *et al.* ..	69	72	10	14·5	5	6·9				
Aspenström ..	60	60	21	35·0	14	23·3	16	26·7	5	8·3
Females										
Bjerkelund ..	25	31	6	24·0	8	25·8	12	48·0	9	29·0
M.R.C. ..	28	29	4	14·3	4	13·8	8	28·6	7	24·1
Borchgrevink ..	18	21	1	5·6	—	—	1	5·6	—	—
MacMillan *et al.*	3	11	—	—	3	27·3				
Lovell *et al.* ..	11	8	1	9·1	2	25·0				
Aspenström ..	31	28	13	41·9	6	21·4	14	45·2	7	25·0

* Or no anticoagulants.
† Rate/100 patients.

As explained in our original report it was at first insisted that all patients should have had short-term anticoagulant therapy before entry to the trial, but this was relaxed later. However, nearly all the patients did, in fact, have anticoagulant therapy before entry in the trial. Only 3 out of 365 patients on whom information was available had no preceding short-term therapy. Table XIII shows that after a sudden stop, as in the first stage of the trial, there is no immediate effect such as might be expected from a "rebound" phenomenon. Moreover, the fact that this excess in mortality and reinfarction rates in the low-dosage group continues for some months at least makes such an explanation of the early advantage to the others rather unlikely.

Against these limited benefits must be balanced the difficulties and potential dangers of treatment affecting the blood-clotting mechanism. Haemorrhagic incidents ranging from bruising to severe haematuria were much commoner in the high-dosage group than in the low-dosage group, and among those withdrawn there were three cerebrovascular accidents in the high-dosage group compared with one in the low-dosage group. There was only one death from cerebral haemorrhage in the high-dosage group.

In our interim report we said that "phenindione administered continuously in the conditions of this trial can make a useful, if limited, contribution in the aftercare of patients who have recovered from the acute phase of myocardial infarction." This conclusion was inevitably restricted to the range of experience then available. It is now clear that anticoagulant therapy reduces the risk of reinfarction and, perhaps, of death, mainly in men and particularly in those under the age of 55, and that this effect largely disappears by the third year. At that stage this form of treatment can be gradually withdrawn without serious hazard.

The experience gained in this trial may be presented as a balance-sheet to guide the clinician's decision for or against long-term anticoagulant therapy. The estimates made on this limited basis inevitably lack precision but they are consistent with the results in at least one other large well-controlled study. They apply only to men between the ages of 40 and 69, selected as in this trial, who have survived one month after cardiac infarction. If 100 such patients were treated for two years,

TABLE XIII.—*Reinfarctions and Deaths in First Month and First Six Months in the Trial*

Week	Low Dosage (M + F)	High Dosage (M + F)	Month	Low Dosage (M + F)	High Dosage (M + F)
<1 ..	2*	–	0– ..	12	5
1– ..	1	2	1– ..	4	2
2– ..	3	1	2– ..	7†	1
3+ ..	6	2	3– ..	1	1
			4– ..	3‡	4
			5– ..	7	2
Total ..	12	5	Total ..	34	15

* Includes one death from pulmonary oedema.
† Includes one death from pulmonary embolism.
‡ Includes one death from embolism in mid-cerebral artery.

about 90 might still be alive at the end of that period, compared with perhaps 78 among 100 patients not so treated. Among the same 100 men, on the average 86 would have escaped reinfarction compared with approximately 62 in those not given anticoagulants. On the other hand, perhaps 1 of the 100 treated men would have suffered a fatal cerebrovascular accident and eight a potentially serious haemorrhage. These rough indications of possible benefit and risk will vary according to age and clinical conditions, but they may serve to put in perspective the possible benefits and risks of the continued administration of anticoagulant drugs.

Summary and Conclusions

An interim report has already been made (Report to M.R.C., 1959) on the results of a controlled trial of long-term anticoagulant therapy in 383 patients who had suffered one or more previous myocardial infarctions. This described the clinical progress of those patients from November 1955 to the end of 1958. New patients were admitted to the trial between November 1955 and March 1958. The subsequent progress of the patients up to May 1960 is described in the present report.

In this controlled trial a comparison was made between the clinical progress of patients given sufficient phenindione to prolong the one-stage "prothrombin" time to two to two and a half times the control value (high-dosage group) with the experience of a similar series of patients given tablets containing 1 mg. of phenindione (low-dosage group).

In May 1960 there was practically no difference in the frequency of death in male patients aged 55 and over and in females. Among men below 55 there was still a difference in mortality from non-violent causes—18 deaths among 69 men on the low dosage as compared with 9 out of 74 men on high dosage. This difference failed to reach conventional levels of statistical significance.

When fatal and non-fatal reinfarctions were considered together there were technically significant reductions in males in both age-groups. Below 55 years the rate was down to a quarter of the control level and in the older men to a half of the control level. The number of female patients was too small to permit firm conclusions, but the figures do not show any difference in reinfarction rate. The electrocardiographic evidence of reinfarction was submitted to physicians who did not know the treatment group. There was no evidence that reinfarction was being more readily diagnosed in the low-dosage group.

In May 1960 (after two to five years of treatment) the trial was discontinued in the low-dosage patients and they were treated as wished by their attendant physicians. Since the early advantage in mortality in favour of high-dosage therapy had become progressively less, it was thought justifiable at this stage to assess the risks, if any, of transfer of patients from high-dosage to low-dosage regimes. Though there were more non-fatal reinfarctions on the follow-up of this new low-dosage group as compared with the new high-dosage group, these did not reach significant levels. The deaths from all causes and the deaths from reinfarction were practically the same in the two groups.

The implications of these results are discussed in relation to the findings in other similarly controlled trials.

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Eight Years' Experience with Oral Contraception and an Analysis of Use of Low-dosage Norethisterone*

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In 1956 the Los Angeles Planned Parenthood Center initiated the first United States study of oral contraception and embarked on comprehensive and detailed investigations of this form of birth control, very shortly after Pincus began his pioneering work in Puerto Rico. The results of these studies of the effects of progestin-oestrogen combinations have been reported by my associates and me periodically (Tyler and Olson, 1959 ; Tyler *et al.*, 1961, 1964 ; Proceedings, 1963 ; Tyler, 1964). It was obvious quite early, and is now definitely established, that potent synthetic progestational compounds with sufficient oestrogen can be satisfactorily employed for contraceptive purposes on a 20-day schedule starting on the fifth day of each cycle and are as close to 100% effective as anything in medicine can be.

After a few years' use of relatively high doses of these combinations we began using a variety of lower-dosage forms (as well as new agents) in an attempt to modify some of the side-effects and also provide less medication and more inexpensive products. The current report relates to certain of our experience with various preparations, as well as some of the vicissitudes of oral contraception in the United States.

Our initial experiences with oral contraception involved the use of a tablet containing 10 mg. of norethisterone with a variable amount of mestranol (ethinyl-oestradiol, 3-methyl ether) not exceeding 0.06 mg. (The variation in oestrogen con-

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