Survival Rates after Acute Myocardial Infarction with Long-Term Anticoagulant Therapy

By John W. Keyes, M.D., Ellet H. Drake, M.D., and F. Janney Smith, M.D.

Evidence is set forth to show the value of continuous long-term anticoagulant therapy by comparison with a control group of patients who have also had multiple coronary occlusions or single infarcts, followed by severe angina pectoris or episodes of coronary failure. Statistical life-estimate determinations are included. Bleeding complications are encountered less frequently with improved methods of management and are considered a justifiable risk, in view of the serious consequences of the natural progress of the disease. After a program of long-term anticoagulant treatment has been instituted, cessation of therapy may be hazardous.

The value of anticoagulants in the treatment of the acute phase of myocardial infarction has been established by favorable reports from many clinics, although some difference of opinion exists regarding the selection of patients. To date, however, there have been but few reports of well-controlled studies in the use of the so-called "long-term" anticoagulant therapy. Although continuous protection from thromboemboli is desirable for all cases of coronary artery disease, particularly those with recurrent episodes of infarction, worthwhile evaluation cannot be obtained from following a small number of patients over a short period of time without adequate controls. In the series we are reporting, enough patients have been followed closely for 6 months to 5 years to allow statistically valid conclusions.

The cases given long-term therapy have been divided into 2 classifications. In the first or "single infarct group" are included those patients who have had a single myocardial infarction with transmural muscle damage. All have had satisfactory recovery from the acute phase (initial 6 weeks), but suffered recurring bouts of coronary failure or angina that did not respond to the conventional modes of therapy. In this respect they present a more serious prognosis than corresponding control patients that were unselected cases with single infarcts without regard to the subsequent occurrence of coronary pain. In the second or "recurrent infarct group" the patients had survived the acute phase of 2 or more well-substantiated episodes of acute myocardial infarction before being placed on therapy. The control group was composed of consecutive unselected cases treated at this hospital, by the Cardiology Division, prior to the use of anticoagulants for acute myocardial infarction, (1940 to 1946). In other words, patients in the control group were not cases discarded from the anticoagulant group; they were not selected in any way. The controls were divided into "single infarct" and "recurrent infarct" groups to correspond to the anticoagulant-treated classification. The control cases received the same general medical supervision as the treated group. Both control and anticoagulant cases enjoyed the same degree of physical activity and did not differ in occupation, economic status, or any other important characteristics.

In most instances, Dicumarol was employed although a few cases received phenylindanidine, which we consider a less desirable drug for long-term therapy. Except for a few cases where the individual's reaction to anticoagulants had been determined in a previous course of therapy, the patients were placed in the hospital for induction of therapeutic hypoprothrombinemia. This procedure is considered highly desirable, since daily prothrombin determinations are necessary at the onset owing to the varying and unpredictable responses to
the drug. In a group of patients on the same anticoagulant, it is not unusual to find a 300 to 400 per cent variation in maintenance dosage. In general, an attempt was made to maintain cases in both groups at from 31 to 50 per cent of prothrombin activity (22 to 27 sec. prothrombin time with a normal of 14 sec.). The Quick method was used; it is considered a satisfactory clinical tool for regulation of dosage if its limitations in relation to other methods of determining prothrombin activity are recognized. The usually accepted criteria were employed for rejecting cases for anticoagulant therapy. They included the presence of some defect in the coagulation mechanism; certain lesions of the gastrointestinal tract, urinary tract, or central nervous system that were considered a potential bleeding point; or some functional inadequacy such as mental deficiency, emotional instability, or alcoholism. It was also necessary to exclude those patients who were unwilling to have regular tests of their prothrombin time. In each instance, care was taken by the physician to make certain that the patient and members of his family understood their responsibility and the risks involved.

After the initial induction period on the anticoagulant, blood samples were drawn from the patients in the clinic at intervals, depending upon the stability of the prothrombin time. In no case did we intentionally allow more than 2 weeks between prothrombin determinations. The patients were instructed to call the clinic later in the day of the test, or at least by the following day, for instructions as to future dosage. A team especially trained in anticoagulant therapy supervised the entire procedure.

GROUP WITH SINGLE INFARCT

This group consisted of 186 control cases and 71 treated cases. Figure 1 compares the death rate of the treated and control groups with mortality determinations made at 6-month intervals for the first 2 years, and then at yearly intervals up to 5 years. The mortality rate of the treated group is well below that of the control group except at 36 months, where it is higher by 1 case.

![Comparative mortality rates in group with single infarct.](image)

In any group some patients die and others are lost to follow-up during the period of the study. In order to be more than fair in our evaluation, patients in the control group who were lost to follow-up during a 6-month interval were considered to be living and well at the time the mean life estimates were calculated (table 1). The rate of death in this group was 3 times greater for patients without anticoagulants than with anticoagulants. It should be pointed out that a predicted survival time of 24 years is calculated on the basis of this single pathologic condition alone, and, therefore, should not be construed as indicating the patient's remaining years of life. If the upper extreme of the confidence interval for the control is compared to the lower extreme for the treated group, the rate of death is still 2 times greater without anticoagulants than with treatment.

GROUP WITH RECURRENT INFARCTS

This series involved 48 control cases and 50 treated cases. The marked difference in

| TABLE 1.—Group with Single Infarct Predicted Survival Time (Mean Life Estimate) |
| Rate of Death—3 Times Greater Without Anticoagulants |
| Average | Confidence Interval in Months |
| Control | 83 mos. (7 yrs.) | 72-97 |
| Anticoagulant | 292 mos. (24 yrs.) | 90% of cases would fall in range of 190 or above, 10% below |
mortality rates during the entire period of study is noteworthy (fig. 2). Table 2 shows the predicted survival time for the recurrent group, the rate of death is 5 times greater without anticoagulants than with treatment. Again, if the upper extreme of the confidence interval for the controls is compared with the lower extreme for the treated group, the rate of death is still almost 3 times greater without treatment than with anticoagulants. The difference is most obvious in the predicted survival times of 31/2 years without anticoagulants as compared with the time of 17 years with anticoagulant therapy.

Table 3 summarizes the total mortality rates in the 2 series at the end of each year. The most startling result is seen in the 4-year calculation for the recurrent infarct group, where 62.5 per cent of the controls are dead versus 12 per cent of the anticoagulant-treated group. It might be well to point out again that the treated
cases represent, on the whole, more severely ill patients than do the controls.

A total of 7 new myocardial infarctions occurred in the 121 patients undergoing treatment, an incidence of 5.7 per cent (table 4). The prothrombin time was considered “adequate” in 5, unsatisfactory in 1, and unknown in 1 of them. Actually, the term “adequate time” is somewhat misleading, since the last prothrombin determination may have been taken 10 to 14 days prior to the infarction, and does not give an accurate indication of the prothrombin level at the time infarction actually occurred.

Twelve deaths occurred in the 121 treated cases. They represented 9 per cent of the total as compared with 48 per cent in the control group of 234 cases (table 5). In 2 of the deaths, in the treated group, a recurrent myocardial infarction was demonstrated electrocardiographically. In 5 others, the death was described as “sudden” and probably represented either an infarct or arrhythmia. In these 7 cases of arrhythmia or infarction, the prothrombin times were thought to be “adequate” in 5 and “inadequate” in 2. Hemorrhage was a contributing cause of death in 3 cases, although in none was the terminal event directly due to blood loss alone. Two suffered new myocardial infarctions coincident with the correction of their hypoprothrombinemia. Another patient contracted infectious hepatitis while on anticoagulant therapy, and the accompanying liver disturbance resulted in marked elevation of the prothrombin time. In this case, death was considered directly due to the hepatitis itself.

The cause of death was examined in detail in the treated group to investigate a possible relation between an inadequate prothrombin time and a coronary accident. In table 5 is an analysis of the deaths in the control group. It will be noted that deaths from other than cardiovascular causes were negligible.

Follow-up studies are of interest in patients who stopped anticoagulants after having started a long-term program. A total of 28 patients fell into this classification. Almost half were stopped because of hemorrhage, and an equal number stopped of their own accord. In addition, 2 were stopped temporarily in order to permit surgery. In 1 case, the physician believed that need for anticoagulant therapy no longer existed; in the other the physician, considered the patient no longer mentally responsible and, therefore, not suitable for further anticoagulants. Of the total number, 5 were subsequently restarted. Of the 28 patients who stopped therapy, new infarcts occurred in 14, during a period of 3 days to 20 months following the cessation. Six of these 14 infarcts were fatal. In addition, 1 patient suffered a popliteal embolus after cessation of therapy. The remaining 13 are alive 4 to 54 months after the cessation of anticoagulant therapy.

Hemorrhage

Hemorrhage has been the main reason against acceptance and wider application of anticoagulants, particularly the oral ones. Bleeding does occur and has been reported by all who use these drugs. It is an accepted, undesirable effect that we believe is less of a hazard to the patient with coronary disease than the risk from the disease itself. It is sometimes desirable to give anticoagulants to patients who present added risks, like inactive peptic ulcer or impaired liver function.

In our experience of over 5 years of long-term anticoagulant therapy, bleeding has occurred 54 times in 51 patients (42.1 per cent). What might be termed “serious” or “major” bleeding occurred in 16 cases (13.2 per cent); in 35 cases (38 instances) it could be termed minor bleeding (29 per cent). In view of the time involved, the incidence is not excessive, since the hazard from hemorrhage is considerably less than from the progress of the disease. Many of the hemorrhagic complications occurred in the early period of long-term therapy and are much less frequently encountered now. It has been under 5 per cent in the past 2 years. Very minor hemorrhagic phenomena, such as ecchymoses, epistaxes, and bleeding gums, continue to occur frequently. It is not imprudent to state that they are to be expected if the patient remains on anticoagulant therapy for any length of time. They may occur at “safe” or “inadequate” levels of hypoprothrombinemia.
They have never by themselves been dangerous nor have they resulted in serious trouble. Table 6 lists the chief forms of hemorrhage that have occurred in over 5 years of long-term therapy.

As previously mentioned, 3 deaths have occurred that must be ascribed to the treatment. However, bleeding was not the chief cause of death. In each instance, a new infarction occurred during the period of normal prothrombin levels following the use of whole blood and vitamin K. Autopsy examination revealed infarctions in each instance; 2 were due to thrombotic occlusion and 1 was probably secondary to prolonged coronary artery insufficiency with an inadequate hemoglobin level and red blood cell count. Should major bleeding take place, blood must be given continuously to restore the blood count and hemoglobin to normal to prevent coronary artery insufficiency, arrhythmia, pulmonary edema, and death.

For a successful program, consistently reliable prothrombin determinations are the first requisite. Without them, the practitioner should not attempt to carry out this type of therapy. Regular weekly prothrombin determinations, or semi-monthly if the patient is easily stabilized, must be done.

The management of a large number of patients on this program requires considerable time and effort, and a well-trained team is essential. Experience is required, not only for advice on dosage regulation, but in management of severe hypoprothrombinemia, both with and without hemorrhage.

<table>
<thead>
<tr>
<th>Source of Hemorrhage</th>
<th>Minor—38 instances in 55 patients (99%)</th>
<th>Major—16 patients (13.2%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematuria</td>
<td>10</td>
<td>Renal</td>
</tr>
<tr>
<td>Ecchymosis</td>
<td>10</td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>5</td>
<td>Hematomas</td>
</tr>
<tr>
<td>Hematomas</td>
<td>6</td>
<td>Lacerations</td>
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<td>Hemothysis</td>
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<tr>
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<td>2</td>
<td>Generalized</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>1</td>
<td>Retroperitoneal</td>
</tr>
<tr>
<td>Gums</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Ear</td>
<td>1</td>
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</table>

Total patients—51 (42.1%)

DISCUSSION

We believe that the mortality figures presented here give unequivocal proof of the protective value of long-term anticoagulant therapy. Statistical analysis of our results was carried out by Dr. Benjamin Epstein, professor of Mathematics, Wayne University, who suggested the method of Predicted Survival Times to demonstrate the value of anticoagulants in these patients. In compiling the results, any factors that could be interpreted in more than one way were always presented against the case for anticoagulant therapy in order not to favor this form of treatment in our evaluation. An example has already been cited that, in general, the control cases included many patients with relatively mild disease, whereas our treated patients, almost without exception, were the severely ill ones. In addition, control cases lost to follow-up were considered to be living and well to the end of the period of calculation, while it is probable that many had died, either at home or in other hospitals.

Another factor should be pointed out that increases the value of long-term anticoagulant therapy in the single infarct group. The rate of death here is only 3 times greater without anticoagulants, and in the recurrent group it is 5 times greater. It must be remembered, however, that the immediate mortality (first 6 weeks) of the second myocardial infarction is in itself 30 per cent. This extra 30 per cent mortality should be added to the death rate of the single infarct group, if patients can be protected from a second myocardial infarction.

We recognize the disadvantages of this form of therapy of coronary artery disease and have referred to many of them. The facilities of a good laboratory, where many prothrombin determinations are done, preferably by the same individual, are a vital part of the program and a large factor in its success. Infrequent prothrombin determinations will not permit adequate control, and too many technicians involved in the testing will add the factor of individual variation in reaction times to the possible sources of error. The physician who directs the procedure must be entirely familiar.
with the drugs used and fully capable of coping with any complication.

The danger of hemorrhage is constantly advanced as one of the chief objections to anticoagulant therapy, either long-term or short-term. In prolonged treatment, minor forms of bleeding occur frequently and are relatively unimportant. Since our knowledge of what constitutes prothrombin levels adequate for protection has increased, bleeding has been less of a problem. Death has not been directly the result of bleeding, although hemorrhagic phenomena may have eventually precipitated a chain of terminal events. All of the severe hemorrhagic manifestations occurred during the early stages of our work with this treatment, and we have every reason to believe their occurrence in the future will be extremely rare.

SUMMARY

Evidence for the value of long-term anticoagulant therapy in selected cases of coronary artery disease is presented. This form of treatment has been particularly effective in the group with recurrent infarcts.

The incidence of acute myocardial infarction among patients discontinuing therapy is high; the mortality rate among those having infarcts is 44 per cent.

Hemorrhagic manifestations do not constitute a contraindication to this form of therapy.

A trained anticoagulant team, working with a well-equipped laboratory, is necessary for the success of the treatment.

Bleeding episodes are an undesirable feature that we believe is less of a hazard to the patient with coronary disease than the risk from the disease itself. In over 5 years of prolonged anticoagulant therapy, what may be termed “serious” or “major” bleeding occurred in 13 per cent of the cases, minor bleeding episodes in 42 per cent. In the last 2 years of this study the incidence has been greatly reduced, to less than 5 per cent.

SUMMARIO IN INTERLINGUA

Es presentate datos indicante le valor del uso de therapia anticoagulante a longe duration in selegite casos de morbo de arteria coronari. Iste forma de tractamento se ha monstre specialmente efficace pro patientes con infarctos recurrente.

Inter le patientes qui discontinua le therapia il ha un alte frequentia de acute infarctos myocardial. Pro illes le mortalitate durante infarcto es 44 pro cento. Manifestationes hemorrhagic non es un indication contra iste forma de therapia.

Le successo del tractamento depende del disponibilitate de un ben-appunctate laboratorio e de un equipo de expertos in le dominio del anticoagulantes.

Episodios de sanguination es un eventualitate indesirabile que nos considera como minus hasardose pro le patiente con morbo coronari que le morbo mesme. In nostre experientia 5-enne con therapia anticoagulante a longe duration, sanguinationes que pote esser characterisate como “serie” o “major” occurreva in 13 pro cento del casos; episodios de sanguination minor in 42 pro cento del casos. In le curso del passate duo annos le frequentia de episodios hemorrhagic ha descendite marcamente. Pro ille periodo illo esseva infra 5 pro cento.

REFERENCES


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