Use of Anticoagulants in Acute Myocardial Infarction

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The scientific basis for the use of anticoagulants in the treatment of acute myocardial infarction was established by Solandt, Nassim, and Best in 1939. They produced mural thrombi in the hearts of dogs by injecting sodium ricinoleate into the myocardium after tying off a branch of the left coronary artery. Thrombus formation could be prevented by the injection of heparin intravenously. The authors concluded that a clinical trial of heparin in acute myocardial infarction was immediate undertaken. The discovery of this anticoagulant made available dicoumarol (bishydroxycoumarin) by Link made suitable for oral administration. In 1946, Wright and Nichol reported the use of this anticoagulant in acute myocardial infarction. The results were encouraging and led to the planning of a large-scale clinical trial.

Effect of Anticoagulant Therapy on Mortality

In 1948, a major clinical trial was instituted to determine the efficacy of anticoagulant therapy in acute myocardial infarction. The importance of this trial cannot be overestimated. Although Bradford Hill had detailed the methodology of the clinical trial in 1937, it had not been widely applied in the United States. Thus, the use of this technique in the evaluation of a new form of therapy represented a great advance. Unfortunately, a method for random selection of patients was chosen which was subject to error. Patients admitted to cooperating hospitals on odd days were given anticoagulants and those admitted on even days were given no anticoagulants. This method permits admitting physicians to predict the therapy to be used on any given day and to defeat the purpose of randomization by selecting the day of admission.

There was a distinct difference in mortality between the patients receiving dicoumarol and those receiving no anticoagulants. Of the untreated patients 23% died, as contrasted to 16% of the treated patients. This striking difference in mortality as well as the reduction in thromboembolic events in the treated patients led to widespread acceptance of this therapy in the United States. The potential significance of the flaw in the process of randomization was not widely appreciated.

There were no further reports of large-scale clinical trials of anticoagulant therapy in acute myocardial infarction until 1961 when Hilden reported the results of such a trial in Denmark. The method of random selection of patients was not ideal. Patients on two medical services were treated with anticoagulants. Those on two other services in the same hospital were not so treated. Midway through the study, the process was reversed. There was a very high mortality in the two groups of patients, particularly in the first 2 days. It appears reasonable to exclude these early deaths, as anticoagulants would have little influence at this time. The death rate after the first 48 hours was 23% in the treated group and 25% in the untreated group. The results of this study led to serious questioning of the efficacy
of anticoagulants in reducing mortality in acute myocardial infarction. Subsequently, three smaller clinical trials showed no significant difference in mortality.9-11

The results of another large-scale clinical trial12 was reported in 1969. This trial was planned with great care by the Medical Research Council of Great Britain. The envelope method was used for random allocation of patients. A large number of patients were included in the study (712 in the treated group and 715 in the control group). The mortality rate was 16% in the treated group and 18% in the control group. This difference was judged to be not significant and could have occurred as the result of chance. Unfortunately, the average daily dose of anticoagulants and the reduction in clotting factors were less than in previous studies.13 This was because of the use of the thrombostest method rather than the one-stage prothrombin time as a measure of degree of anticoagulation achieved.

Thus, none of the clinical trials has established that treatment with anticoagulants lowers mortality in acute myocardial infarction. In retrospect, this quandary could have been predicted. There are multiple reasons for death in acute myocardial infarction. Among these are arrhythmias, failure of the heart as a pump, cardiac rupture, and thromboembolic complications. It is reasonable to assume that only deaths from the latter cause would be influenced by anticoagulants. Deaths directly related to thromboembolic complications probably do not comprise more than 10-20% of the total deaths. Thus, the best that can be expected from anticoagulant therapy is a lowering by 2 or 3% the number of deaths among the patients treated (for example, from 20% mortality to 18%). To demonstrate conclusively such a difference in mortality would require a clinical trial involving many thousands of patients. It is unlikely that any such trial will be mounted.

Effect of Anticoagulant Therapy on the Incidence of Thromboembolic Complications

The evidence for reduction in thromboembolic complications as a result of anticoagulant therapy is easier to evaluate. There is little evidence that anticoagulants prevent recurrent infarction by preventing coronary thrombosis.12 On the other hand, there is reason to believe that anticoagulants may influence the incidence of venous thrombosis, pulmonary emboli, mural thrombosis, and systemic emboli. The first two are difficult to evaluate. Venous thrombosis is usually asymptomatic in acute myocardial infarction. Acute thrombophlebitis is rare. A recent study using 131I-tagged fibrinogen14 showed that asymptomatic thrombi in the leg veins were common in patients with acute myocardial infarction (34% of the patients studied).

Pulmonary emboli may also present difficulties in diagnosis. They may be asymptomatic or may accentuate symptoms of congestive heart failure or shock. If pulmonary infarction is present, it may be confused with pulmonary edema or pneumonia. Hence, the available statistics on the incidence of pulmonary emboli may not be entirely reliable and may underestimate the incidence of this complication. Recently the use of pulmonary scanning after the injection of radioisotope-tagged macroaggregates of albumin and pulmonary arteriography has greatly enhanced diagnostic accuracy. Pulmonary scanning was used routinely in a large-scale Veterans Administration cooperative study to be reported in 1972. This should permit a more accurate estimate of the frequency of pulmonary emboli. Both the study of Wright6 and the MRC study12 reported a reduction in the incidence of pulmonary emboli in the patients treated with anticoagulants. Hilden8 did not report a significant reduction of clinically diagnosed thromboembolic complications, although postmortem examination demonstrated fewer pulmonary emboli in the treated patients as
compared with those who did not receive anticoagulants. Mural cardiac thrombi cannot be identified during life; hence, one must depend on postmortem studies. Wright\(^6\) found mural thrombi in 62% of untreated cases and 32% of treated cases. Hilden\(^8\) found mural thrombi in 58% of untreated cases and 24% of treated cases.

The best evidence that anticoagulants are effective in reducing the incidence of thromboembolic complications is found in the study of peripheral emboli. Cerebral emboli and emboli to the arteries of the legs produce obvious clinical manifestations and are unlikely to be overlooked. Wright\(^6\) found an incidence of cerebral emboli of 4.9% in the untreated and 0.7% in the treated patients. The corresponding figures for leg and visceral emboli were 2.7 and 0.5%, respectively. In the MRC study\(^12\) there were 2.5% cerebral emboli in the untreated group and 1.1% in the treated patients. The corresponding figures for other peripheral emboli were 0.7 and 0.1%, respectively.

Thus, an excellent case can be made for the use of anticoagulants for the prevention of thromboembolic complications. There is ample evidence from many studies that anticoagulants are useful in preventing pulmonary emboli.\(^15\) The evidence already cited would indicate that anticoagulants greatly reduce the incidence of peripheral emboli in acute myocardial infarction. Two questions remain to be answered: The first is whether the risk of emboli is great enough to justify the risk of hemorrhage. Secondly, if anticoagulants are to be used, should they be given to all patients or to a selected group?

**Risk of Hemorrhage**

There is a significant risk from major bleeding in patients receiving anticoagulant therapy. In the study of Wright\(^6\) there were no severe hemorrhages in the control group and five severe hemorrhages in the treated group (589 cases). There were no deaths in this series from extracardiac hemorrhage. However, in two patients, hemopericardium without rupture of the heart was found on postmortem examination and was thought to be an important cause of death. In another, a large amount of serosanguineous fluid was found together with a recent extension of the infarct. The bleeding may have contributed to the death. In Hilden's series of 371 treated patients,\(^9\) three died of gastrointestinal bleeding including one who had unrecognized hepatic cirrhosis and bled to death from esophageal varices. In addition, there was a death from a subpleural hematoma. In the MRC study\(^12\) there were 10 instances of hematemesis or melena in the treated group and one in the untreated group. There were no deaths from hemorrhage.

Although more than one half of the hemorrhages in Wright's study\(^6\) occurred during a period when the prothrombin time was in the desired therapeutic range, bleeding was more common when the prothrombin time was markedly prolonged. Hemorrhage in patients receiving anticoagulants is often associated with occult lesions predisposing to hemorrhage. This applies particularly to gastrointestinal hemorrhage because of the frequency of ulcerating lesions of the bowel. Roos and van Joost\(^16\) reported on 220 bleeding episodes associated with anticoagulant therapy. Local disease of the bleeding organ was found in 64% of cases.

The available evidence indicates that the risk of fatal hemorrhage in acute myocardial infarction is not great if the prothrombin time is kept within a reasonable range (below three times the control value) and all patients with diseases predisposing to bleeding are excluded from therapy. In view of the limited beneficial effect of anticoagulants in acute myocardial infarction, patients with suspected or proven ulcerative lesions of the gastrointestinal tract, liver disease, azotemia, severe hypertension, or any other disease predisposing to hemorrhage should be excluded from therapy.
The occurrence of bloody pericardial effusion in patients with acute myocardial infarction receiving anticoagulants is cause for concern. Death can occur from massive bleeding in the pericardial cavity without rupture of the heart. In addition to the cases reported by Wright, there have been other recorded instances of this complication. In the studies of Hilden and the MRC, this did not appear as a problem. It is reasonable to assume that this feared complication is relatively uncommon; nevertheless, the diagnosis should be considered in a patient on anticoagulant therapy who suddenly develops shock.

Should Anticoagulant Therapy be Used Only in Selected Patients?

In 1953 Russek pointed out that patients with acute myocardial infarction could be divided into two groups. One group had a very low mortality and also a low incidence of thromboembolic complications, whereas the other had a high mortality rate. He suggested that anticoagulants be used only in the high-risk group since the others usually recover uneventfully. A high-risk patient is an individual with one or more of the following: previous infarction, a large infarct, cardiac enlargement, congestive heart failure, shock, serious arrhythmias, or complicating diseases.

There has not been uniform agreement on the identification of the good-risk and poor-risk categories. It has been pointed out that the determination of poor- and good-risk categories is considerably more difficult when done on a prospective rather than retrospective basis.

The data relating the incidence of thromboembolic complications to size of infarct, congestive heart failure, shock, arrhythmias, and previous infarction are inadequate. It is planned to analyze this relationship in the Veterans Administration study. It should be possible to identify a group of patients with myocardial infarction in whom the risk of thromboembolic complications is low. If mural thrombosis, congestive heart failure, and prolonged bed rest are related to these complications, one would suspect that patients with a small or intramural infarct without complications would have a low rate of thromboembolism.

Should Heparin be Used Initially?

Heparin has been used in many of the clinical trials of anticoagulant therapy to rapidly induce altered coagulability of the blood. It is usually given only during the first 2 or 3 days until the prothrombin time becomes elevated to the therapeutic range as a result of administration of the coumarin drugs. There is little evidence that the initial use of heparin is valuable.

A controlled study comparing heparin with Dicumarol therapy in acute myocardial infarction not only showed no advantage of heparin over Dicumarol therapy but favored Dicumarol therapy. Other studies have shown no advantage of early administration of heparin.

It is difficult to justify the initial use of heparin with the associated inconvenience on the basis of scientific evidence. On the other hand, some of the larger and better controlled clinical trials have utilized initial heparin therapy as part of the total anticoagulant therapy.

Control of Anticoagulant Therapy

The coumarin drugs produce a deficiency of factor VII, factor IX, factor X, and to a lesser extent factor II. Factor VII and factor IX are the first to become deficient after administration of the drug. Factor X deficiency develops at a slower rate. In the United States the Quick one-stage prothrombin time is usually employed to measure the change in coagulation factors. The test is sensitive to the deficiency of factor VII and factor X while factor IX deficiency has little influence. A major problem in the use of this test has been standardization of the thromboplastin reagent used. It has been shown that if serum from a patient treated with Dicumarol is tested with
a variety of commercial thrompoplastins different degrees of prolongation of Quick one-stage prothrombin time will be obtained. Because of this, a standard reagent has been developed in Great Britain.

Other tests have been used. These include the thrombotest and the prothrombin-proconvertin (P and P) method. Care must be used in comparing the results of these tests with the Quick one-stage method. For example, 6% P and P, 3.4% thrombotest, and 15.5% Quick one-stage method are equivalent. Another problem has been the expression of the results of these tests as percentage of normal using dilution curves to convert prothrombin time to percentage. The curves are sometimes prepared by dilution with saline and at other times by the use of barium sulfate absorbed plasma. These two curves are not identical and will give a different conversion factor.

The physician can best deal with these problems by using a single laboratory which consistently uses the same standard thromboplastin. The usual practice is to maintain the prothrombin time at two to two and one half times the level obtained with normal plasma using the Quick one-stage method.

Recently drug interaction has been found to be an important cause of unexplained fluctuation in prothrombin time. The barbiturates are common offenders and should be avoided in patients receiving coumarin anticoagulants. They increase the activity of the hepatic microsomal enzymes. These enzymes are responsible for the metabolism of the coumarin drugs. As a consequence, the plasma level achieved by a given dose of a coumarin drug is lower in patients receiving barbiturates than in those patients not receiving the sedative. If the dose of anticoagulant is increased to achieve an optimal prothrombin time, a dangerous degree of anticoagulation may result if the barbiturate administration is stopped. Chloral hydrate, glutethimide, meprobamate, ethchlorvynol, and griseofulvin have similar effects.

Other drugs may influence the effect of coumarins. One of these is phenylbutazone, which displaces the coumarin drug from its albumin binding site in serum and hence potentiates its activity. Drugs with a similar action include clofibrate, diphenylhydantoin, ethacrynic acid, and salicylates. Aspirin has an additive effect in prolonging the prothrombin time, and, in addition, alters platelet function and may produce gastric erosions. Other drugs with an additive hypoprothrombinemic effect include: aminosalicylic acid, propylthiouracil, methylthiouracil, quinidine, and quinine. Chloramphenicol, kanamycin, neomycin, streptomycin, sulfonamides, and tetracyclines may decrease vitamin K synthesis by gut bacteria, resulting in decreased prothrombin activity.

Thus, great care must be used in the choice of drugs in patients receiving coumarin anticoagulants. The choice of a sedative is difficult. Although chlordiazepoxide (Valium) has been reported as interacting with the coumarin, it has been used successfully with the coumarin drugs for treating anxiety and as a sedative. Clofibrate (Atromid-S) is commonly given to patients with coronary disease. In some patients it potentiates the effect of the coumarin drugs while in others it does not have this effect. Before a drug is given to a patient receiving anticoagulants, it should be considered for its interaction with the coumarins. None of these drugs is absolutely contraindicated in patients receiving coumarins but the interaction should be kept in mind and the dose of the anticoagulant adjusted as necessary to maintain the prothrombin time within a desirable therapeutic range.

When Should Anticoagulant Therapy Be Stopped?

The long-term use of anticoagulants in myocardial infarction is also a controversial subject. The two studies in which the majority of the patients have been followed for 5 or more years have shown no difference in mortality rate over this period of time. From this, one would be inclined to conclude...
that long-term anticoagulant therapy has no value. However, closer analysis of the well-designed clinical trials leads to a different conclusion. These trials have been analyzed in a recent paper. Examination of the data in this collaborative analysis together with reading of the individual papers leaves one with the strong feeling that anticoagulant therapy does reduce the mortality rate during the first year or two after an acute myocardial infarction. A recently published study not included in the analysis comes to the same conclusion. The use of anticoagulants was of particular benefit in patients with a history of prolonged angina or previous infarction.

Thus one is left with the paradox that while the evidence is poor that anticoagulants lower the mortality rate during the first few weeks after myocardial infarction there is good evidence that they do so during the first year after infarction. Thus, logic would lead one to conclude that if anticoagulants are to be given in acute myocardial infarction the drug should be continued for 1–2 years.

**A Summing Up**

The physician facing a decision regarding the treatment of a patient with acute myocardial infarction often has difficulty in deciding whether or not to use anticoagulants. The controversy which has surrounded this issue and the widely divergent opinions of experts in the field has confused the practicing physician. From this brief review it is evident that the evidence is inadequate to answer conclusively some of the questions. The defects in many of the studies of the use of anticoagulants in the treatment of acute myocardial infarction have been ably analyzed by Gifford and Feinstein. Nevertheless, certain conclusions can be drawn and a reasonable approach to therapy can be suggested.

There can be little doubt that extensive intravascular clotting occurs in some patients with acute myocardial infarction. This may include a thrombus in a coronary artery, thrombi in the veins of the legs, pulmonary emboli, mural thrombosis, and peripheral emboli. It is difficult to believe that such extensive intravascular coagulation does not increase morbidity and mortality.

The evidence that anticoagulants can influence the development of intravascular coagulation is good. There is an extensive literature on the effect of anticoagulants in venous thrombosis and pulmonary embolism. It is generally accepted that anticoagulants used prophylactically may prevent venous thrombosis and embolism, or if used in treatment may lower the incidence of recurrent pulmonary emboli. As has already been mentioned, there is good evidence that anticoagulants influence the development of mural thrombi in the heart and lower the incidence of systemic emboli.

There is justification for the use of anticoagulants in the treatment of acute myocardial infarction. One can make a case for the philosophy that improvement in mortality in acute myocardial infarction will not result from the discovery of a dramatic mode of treatment but from careful attention to all of the details of management. The question remains as to whether the use of these drugs should be recommended in all cases or only in a select few. I find it difficult to justify the use of anticoagulants in all cases. It is unlikely that intravascular clotting is extensive in patients with a questionable or small infarction exposed to only brief periods of bed rest. Therefore, it would seem reasonable to recommend the use of anticoagulants only in those patients with one of the following: (1) large infarct, (2) history of previous infarction, (3) congestive heart failure, or (4) complications requiring a prolonged period in bed. There is a good reason to continue anticoagulants for at least a year if a decision is made to employ them.

**References**


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