SPECIAL ARTICLE

Anticoagulant Therapy in Coronary Artery Disease

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The efficacy of anticoagulant therapy in the treatment and prophylaxis of coronary artery disease has been undergoing evaluation for more than a quarter of a century. Numerous clinical trials of variable statistical sophistication have been published and further trials are still in progress. Several reviews and innumerable editorials have attempted to provide reasonable interpretations for the large mass of data that has accumulated on this subject. Acceptance of therapy ranges from the position that anticoagulant compounds may decrease the incidence of pulmonary embolism during acute myocardial infarction to the view that the drugs are of value in patients with angina pectoris as well as in subjects with healed myocardial infarctions.

For many physicians it is understandably difficult to compare data obtained on populations of patients with profound disparities in the mortality rates of the respective control or untreated patients, large differences in the frequency of drug-induced hemorrhage, and dissimilar regimens for the regulation of therapy. While it might seem preferable to withhold anticoagulant therapy until the question of its value is conclusively resolved, the fact of the matter is that the physician must make his decision to use or withhold anticoagulants on the basis of current data; for to withhold treatment is as much a decision as to institute therapy.

Acute Myocardial Infarction

It is probably fair to say that the original expectations of the benefits of anticoagulant therapy in acute myocardial infarction were unrealistically high. It has been estimated that perhaps 30 to 40% of patients with acute infarction do not have a fresh occlusion and of those who do the initial intravascular obstruction that develops on an atheromatous plaque is a platelet nidus, the formation of which is affected neither by heparin or coumarin compounds in the therapeutic range. Only the coagulation or fibrin thrombus can be prevented by anticoagulant therapy and, except following shock, it is uncommon for these red thrombi to be multiple or to propagate significantly in the coronary arteries. Infarction secondary to obstruction from intimal hemorrhage or to ischemia from an excessive work load on an already compromised collateral circulation will be unaffected by anticoagulant agents. Similarly, demise from shock, congestive failure, or arrhythmias is not influenced by coumarin compounds. Nor has clear evidence been obtained that anticoagulant drugs affect favorably or adversely the incidence, respectively, of mural thrombi or myocardial rupture. Only in the area of pulmonary embolism is there essential agreement that therapy decreases this associated lesion in acute myocardial infarction. It has been suggested that anticoagulants may offer a 3 to 4% salvage from thrombotic death in acute myocardial infarction. Although the percentage figure is small, the population at risk is great. Of necessity one must balance this gain against the risk of fatal hemorrhage. Here again the physician is confronted with disagreement on the question of whether the net gain in mortality from thromboembolism outweighs the loss from drug-induced hemorrhage.

Until new anticoagulants are developed that can prevent platelet aggregation without compromising the hemostatic integrity of the...
vascular tree, or until thrombolytic therapy has been demonstrated to be of value in the therapy of acute coronary artery thrombosis, the physician will have to settle for the small gain from heparin and coumarin compounds or forego anticoagulation entirely.

Postmyocardial Infarction, Long-Term Treatment

A review of the better designed clinical trials provides no unanimity of opinion as to the value of long-term anticoagulant therapy for patients who have survived acute myocardial infarction. In general, when benefit has been recognized, this favorable response has been observed in men. On the other hand, no statistical evidence of harm has come from the long-term use of anticoagulants in these trials. Accordingly, and pending further data, anticoagulant therapy may be justified in men for 1 or 2 years following recovery from acute infarction.

Angina Pectoris and Coronary Insufficiency

On the basis of the scant data available, it would appear that men with angina pectoris of less than 2 years' duration (and without prior myocardial infarction) may be benefited by anticoagulant therapy.

Also, on the basis of limited data, patients with coronary insufficiency or coronary failure (that group of patients who fall between subjects with stable angina and overt infarction) are said to benefit from anticoagulant therapy although this position is not universally accepted.

As with long-term therapy following acute myocardial infarction, no statistical evidence of harm from the treatment of patients with angina pectoris or coronary insufficiency has been reported. Accordingly, the physician may be influenced by the duration of symptoms, the patient's age, or the family history of coronary disease in attempting to reach a decision on therapy in these individuals.

Peripheral Embolization Following Myocardial Infarction

Evidence is available to indicate that the expected 5-year recurrence rate of an acute embolus to a leg artery is 25% and that the expected incidence of thromboembolic visceral complications is of a similar order of magnitude. This study included patients with mural thrombi secondary to valvular disease as well as coronary artery disease and most patients had atrial fibrillation. Fewer emboli have been observed in patients with atrial fibrillation following acute myocardial infarction when anticoagulant drugs have been used. It would appear reasonable to recommend long-term prophylactic anticoagulant therapy for all patients with coronary disease who sustain peripheral emboli. There is general agreement that for all except cerebral emboli, treatment should be instituted immediately. For cerebral emboli data are conflicting and some authorities recommend a delay of several days after clinical recognition of a cerebral embolus before starting anticoagulant therapy. In the authors' experience, when the evidence for a cerebral embolus as opposed to a thrombus is readily determined clinically, no delay in the institution of anticoagulant therapy has been attempted. Clearly a definitive answer to this problem is not as yet available.

Management of Anticoagulant Therapy

It is evident that at best the gains from anticoagulant therapy in coronary artery disease are marginal, being most readily apparent in acute myocardial infarction and in the prophylaxis of peripheral emboli, of less clear-cut value in the long-term treatment of patients who have recovered from an infarct, and of least established merit in the treatment of patients with angina and of patients with coronary insufficiency. These views, coupled with the fact that the overriding hazard of therapy is hemorrhage, make control of therapy often the final arbiter of whether or not anticoagulant drugs will be used.

Selection of the Patient

An essential preliminary to anticoagulant therapy is a careful history to exclude actual or potential causes of hemorrhage.

The patient who denies a familial hemorrhagic tendency, nosebleeds, gingival bleeding, spontaneous ecchymoses, menorrhagia, or prolonged bleeding following dental surgery,
tonsillectomy, or trauma is unlikely to be a bleeder.

In addition to the recognition of a bleeding diathesis, a good history can suggest dietary defects leading to hemorrhage, such as lack of vitamin C, or evidence of prior overt bleeding such as bleeding from a peptic ulcer, esophageal varices, colitis, polyps, or past ocular or intracranial hemorrhage. The history may also reveal significant information concerning hypertensive, hepatic, and renal disease, each of which may be associated with hemorrhage, as well as the likelihood of major surgery in the immediate future. Finally, careful questioning will yield information concerning chronic medication, such as steroids, that may predispose to hemorrhage.

Minimal laboratory procedures should include a determination of the hemoglobin, a blood smear to establish the presence of an adequate number of platelets, urinalysis, and a stool examination for gross or occult blood. When doubts remain, these tests may be supplemented by a platelet count, prothrombin time, and kaolin-partial thromboplastin time.

This initial screening is simple and requires little additional time. The recognition of hemorrhage or a tendency to bleed, however, does not constitute a blanket contraindication to anticoagulant therapy. Clinical judgment is required at all times to balance the anticipated risk of hemorrhage against the threat of thrombotic episodes.

In general, anticoagulant drugs should not be employed under the following circumstances: a hemorrhagic diathesis, severe hypertension (diastolic blood pressure greater than 110 mm Hg), cerebral vascular hemorrhage, acute ulceration, or overt bleeding from the gastrointestinal, respiratory, genitourinary, or pulmonary tracts*, or recent surgery of the central nervous system.

Other contraindications are less stringent. Here the urgency of therapy must be balanced against the risk of hemorrhage involved. These include moderate hypertension, diabetes mellitus, vasculitis, subacute bacterial endocarditis, renal and liver disease, surgery in general, but particularly of the biliary tract in the presence of hepatic failure, and surgery of the lung and prostate. Pericarditis, associated with acute myocardial infarction, deserves careful and special consideration in view of the possibility of hemopericardium consequent to anticoagulant therapy. Excessive bleeding into the thyroid gland has also been observed in thyrotoxic patients who have received therapeutic 131I while on anticoagulant drugs.

It is important to recognize that these lists cannot be taken literally. The question as to whether in a given patient the need for anticoagulant therapy outweighs its hazards requires sound clinical judgment.

For long-term therapy, the patient must be both willing and able to cooperate—requirements which often preclude its use for patients with emotional disorders and inadequate intelligence.

Administration of the Anticoagulant Drugs

Heparin may be administered intravenously, subcutaneously, or intramuscularly. It is not absorbed in significant quantities through the buccal or rectal mucosa. The intramuscular administration of heparin may be painful, and with both intramuscular and subcutaneous administration there may be unpredictable lags in absorption. For these reasons, the authors prefer to administer heparin by intermittent intravenous injection through an indwelling plastic catheter. It has been noted by Douglas that there is no evidence has been collected to indicate that continuous heparin infusion is therapeutically more effective than intermittent injections. The minimum daily dose of heparin is uncertain and probably depends on the condition being treated. Stamm has suggested 40,000 units per day, intravenously, as the minimum dose when treating acute thrombophlebitis. It is common in Europe to administer heparin intravenously without laboratory control, giving four injections daily. This

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is usually safe when treating thrombophlebitis, but as this condition improves, the tolerance for heparin declines, so that a safe dose initially may be subsequently too high. For these reasons, the authors prefer to administer heparin at 4 hourly intervals in doses sufficient to keep the whole blood clotting time at double the normal time when measured immediately prior to the succeeding dose. Once the dose is stabilized, one clotting time daily is adequate. In general, heparin is used only until effective oral anticoagulant therapy has been established. Although an anticoagulant effect is achieved more rapidly by starting treatment with heparin, there are no data to indicate that this combined therapy is superior to using coumarin therapy alone.

The coumarin and indandione drugs affect the coagulation system by depressing the hepatic synthesis of factors II (prothrombin), VII (proconvertin), IX (PTC), and X (Stuart). The various drugs among these two classes of compounds vary in terms of dosage, absorption from the gut, and incidence of side effects other than hemorrhage. The commonly used agents are warfarin, dicumarol, and phenylindandione. The latter is used primarily in Europe and has occasional serious side effects such as granulocytopenia, hepatitis, proteinuria, and oral lesions. Warfarin is notable for being completely absorbed from the gut. For this reason, we prefer it to dicumarol which is irregularly and incompletely absorbed from the gut.

Numerous programs of administration of warfarin have been advocated. The one described by Douglas is quite satisfactory. A point seldom emphasized in anticoagulant reviews is that the skill with which the physician administers these drugs may be as decisive as the excellence of the laboratory control in determining the incidence of hemorrhage. Appreciation of both the lag effect and the need for small dose changes is necessary.

The pharmacology of warfarin has been carefully investigated by O'Reilly and his associates who demonstrated considerable variation in the rate at which the drug disappears from the plasma of normal individuals. This presumably accounts for the normal variation in response to a given dose of warfarin. Apart from this normal variation is the state of inherited resistance to warfarin described by O'Reilly and associates in a man who required 145 mg of warfarin daily for maintenance therapy. At the other end of the spectrum is the occasional patient who demonstrates extreme sensitivity to the coumarin drugs, responding to a single dose of 25 mg of warfarin with a prothrombin time prolongation to 180 seconds.

It is generally recommended that physicians be alert to increasing sensitivity to the orally administered anticoagulants in patients who are also receiving broad spectrum antibiotics. The usual explanation is the suppression of synthesis of vitamin K by intestinal bacteria. Recent studies have cast doubt on this hypothesis by showing that vitamin K is not absorbed from the cecum and that a vitamin K-free diet has a profound effect on the prothrombin time of patients receiving warfarin, suggesting that a major source of vitamin K in man is in the diet.

Patients taking anticoagulant drugs by mouth are generally cautioned not to take aspirin. In the patient not receiving coumarin therapy, aspirin in full therapeutic dosage does not produce a significant coagulation defect. In the patient who is receiving an anticoagulant agent by mouth, however, salicylates are said to increase the sensitivity to the drug, but their local irritative effect on the gastric mucosa is possibly of equal or greater importance.

Patients should be instructed to take any barbiturate medication at least 5 hours after their anticoagulant tablet, because simultaneous ingestion of barbiturate and anticoagulant drugs results in decreased plasma levels of the latter and a decreased anticoagulant effect. Other drugs to be avoided by the anticoagulated patient include steroids, ACTH, and clofibrate (Atromid).

There is insufficient information at present to advise the physician as to the manner in which oral anticoagulant therapy should be terminated. Reports noting an increase in
deaths and reinfarction following such cessation have given rise to the “rebound” theory which suggests that some unexplained thrombotic tendency is associated with abrupt termination of oral anticoagulant therapy. Accordingly, many physicians taper off the dose of a coumarin drug instead of stopping it precipitously. On the other hand, Merskey and Drapkin have recently reported the abrupt cessation of anticoagulant therapy in over 100 patients without observing any increased incidence of deaths or reinfarction.

**Laboratory Control**

For controlling the administration of heparin, the whole blood clotting time is quite satisfactory. A number of acceptable techniques have been described. The method chosen should utilize a two-syringe technique, 18 to 20 gauge needles, meticulously clean glassware, and a rigidly standardized procedure. Most textbooks and reviews suggest that capillary clotting times are less helpful than macro-clotting times.

For control of oral anticoagulant therapy, the three tests commonly used are the Quick one-stage prothrombin time (PT), the prothrombin and proconvertin test of Owren (P & P), and the thrombotest of Owren. In order to consider the manner in which these tests differ, it will be helpful to review the current concept of the coagulation system which is shown in table 1.

When freshly drawn blood is placed in a glass tube, clotting occurs in a few minutes. If tissue juice (tissue thromboplastin) is also added to the tube, clotting ensues in approximately 15 seconds. In both instances, prothrombin is converted to thrombin by prothrombin activator, and the thrombin initiates a sequence of events culminating in the appearance of a solid clot. Prothrombin activator is a proteolytic enzyme which may arise by either of two systems called, respectively, the “extrinsic” and “intrinsic” thromboplastin-forming systems. The intrinsic system consists of those factors necessary for prothrombin activator to be formed in the absence of tissue thromboplastin. For both systems calcium and factors V and X are required. Factor VII is required only for the extrinsic system and factors IX, XII, XI, and VIII function only in the intrinsic system. The oral anticoagulant compounds, by depressing the production of factors II, VII, IX, and X, affect both intrinsic and extrinsic systems. Both intrinsic and extrinsic systems have a final common pathway that commences with prothrombin activator. Tests such as the prothrombin time utilize the patient’s plasma in undiluted form and employ the solid fibrin clot as an endpoint. Therefore, any decline in fibrinogen (below 100 mg%) or the presence of an antithrombin such as heparin may cause a prothrombin time prolongation irrespective of any clotting factor deficiency induced by the oral anticoagulants.

The prothrombin time is performed by adding equal volumes of plasma, thromboplastin, and calcium chloride to a tube at 37°C and observing the clotting time. The clotting time is prolonged if there is a deficiency of factors VII, X, V, prothrombin, or fibrinogen. Two of these factors (fibrinogen and factor V) are not affected by anticoagulant therapy. The prothrombin time is also prolonged by heparin or the anticoagulant found in some patients with lupus erythematosus. Many laboratories use commercial thromboplastins for determining the prothrombin time. Some of these thromboplastins, such as those composed of lung extracts, have been shown to be relatively insensitive to a deficiency of factor X and are not as suitable for this test as are thromboplastins prepared from human brain. Another source of error is the shortening effect of glass contact on the prothrombin time. Plasma specimens allowed to stand in glass tubes for several hours will yield prothrombin times several seconds shorter than if kept in siliconized or plastic tubes. The mechanism of this effect is not understood, but it does not occur in Hageman factor-deficient plasma. This phenomenon varies in intensity from one patient to another,
and lusteroid tubes are recommended for the collection of blood specimens for prothrombin times. It should be noted that the prothrombin time reflects the extrinsic system since it employs the addition of tissue thromboplastin to plasma. It does not reflect the intrinsic system and, therefore, a complete deficiency of factor IX does not prolong this test. Prothrombin times are usually expressed in seconds and as a percentage of a normal standard. The latter is determined by reference to a calibration curve which is constructed by performing prothrombin times on normal plasma progressively diluted in either saline or BaSO₄ adsorbed plasma. Biggs and Macfarlane⁴² do not recommend dilution curves, and the present authors concur.

The P & P test utilizes BaSO₄ adsorbed bovine plasma as a source of factor V and fibrinogen.⁴³ The BaSO₄ adsorption removes the four clotting factors that are depressed by the coumarin drugs but leaves intact the fibrinogen and factor V. The test is performed by adding to a test tube equal volumes of adsorbed bovine plasma, a 1/10 dilution of the test plasma, human brain thromboplastin, and calcium chloride. The result is expressed as a per cent of a normal standard. The calibration curve is formed by diluting normal plasma with buffer 1/10 to 1/80 and performing P & P tests with these dilutions. Because the substrate bovine plasma is rich in fibrinogen and factor V, the test is not sensitive to variations in these factors in the patient’s plasma. Since the patient’s plasma is diluted 1/10, the test is not significantly sensitive to heparin. Because the test utilizes tissue thromboplastin, it reflects the extrinsic system, and al-

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Table 1

Current Concept of the Coagulation System

<table>
<thead>
<tr>
<th>Extrinsic System</th>
<th>Intrinsic System</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tissue thromboplastin</td>
<td>Surface</td>
</tr>
<tr>
<td>Factor VII (proconvertin)</td>
<td>Factor XII (Hageman)</td>
</tr>
<tr>
<td>Factor X (Stuart)</td>
<td>Factor XI (PTA)</td>
</tr>
<tr>
<td>Factor V (proaccelerin)</td>
<td>Factor IX (PTC)</td>
</tr>
<tr>
<td>Calcium++</td>
<td>Factor VIII (AHF)</td>
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<td></td>
<td>Factor X</td>
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<td></td>
<td>Factor V</td>
</tr>
<tr>
<td></td>
<td>Platelet phospholipids</td>
</tr>
<tr>
<td></td>
<td>Calcium++</td>
</tr>
</tbody>
</table>

Prothrombin + Prothrombin activator → Thrombin

Fibrinogen → Thrombin → Fibrin monomer + Fibrinopeptides A & B

Fibrin monomer → Spontaneous → Fibrin polymer

Fibrin polymer → Ca++ → Fibrin clot

FSF' ← Thrombin

FSF

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Circulation, Volume XXXIV, November 1966
though sensitive to factors II, VII, and X, it is not sensitive to factor IX. This is essentially the only drawback to this excellent test. It has been claimed\textsuperscript{15} that this test is expensive and time-consuming. However, bovine plasma is easily obtained from a local abattoir either free or at nominal cost and the plasma may be stored frozen for 3 to 6 months. Enough human brain thromboplastin to last a year can be made in a day for a few dollars worth of supplies.

The thrombotest was devised by Owren to cover the P & P test's lack of sensitivity to factor IX. Instead of human brain thromboplastin, a mixture of bovine brain thromboplastin and cephalin (a crude mixture of phospholipids which acts as a platelet substitute) is used. The dual nature of this thromboplastic agent allows both extrinsic and intrinsic systems to be reflected by the test. This statement is true, however, only if the extrinsic system is depressed as it is in the anticoagulant-treated patient. In the subject with congenital factor IX deficiency, the extrinsic system is intact and the thrombotest is only a few seconds prolonged. Thrombotest reagent is available in lyophilized form in ampules that cost about 20 cents per test. One significant advantage of the thrombotest over both the P & P assay and the determination of prothrombin time is that the thrombotest can be performed on capillary blood and thus permits anticoagulant therapy in patients whose veins can no longer be used for venipuncture. A disadvantage of both the thrombotest and the undiluted prothrombin time is that, in contrast to the P & P assay, these tests are sensitive to heparin.

Of the three tests, the prothrombin time is the most widely used in the United States, whereas the P & P test and the thrombotest have had more use in Europe. All three tests, properly performed, are capable of regulating coumarin therapy. The recommended therapeutic range is prolongation of the prothrombin time 1.8 to 2.2 times when human brain thromboplastin is used. For the P & P assay and the thrombotest 10 to 20% values are recommended. If interim surgery is to be performed, anticoagulant therapy should not be discontinued but should be adjusted to values 25 to 30% of normal.

Sevitt and Iones\textsuperscript{44} have noted that anticoagulant therapy of sufficient intensity to prolong the prothrombin time 2.5- to threefold is necessary to prevent the formation of all stasis thrombi in the leg veins of bedridden patients subsequently examined at necropsy. Therapy sufficient to achieve the usual thrombotest or P & P range of 10 to 20% did not prevent the formation of such thrombi. Merskey and Drapkin\textsuperscript{15} have suggested that a thrombotest range of 10 to 20% may represent inadequate therapy. This viewpoint must, however, be reconciled with the excellent results the Norwegian group has compiled in preventing both hemorrhage as well as recurrent emboli in patients with rheumatic heart disease who received oral anticoagulant therapy. This question has not finally been settled.

The levels to which the affected clotting factors must be suppressed before hemostasis breaks down has been determined by Owren’s group\textsuperscript{19} as follows: factor VII, less than 4 or 5% of normal; factor X, 5% of normal; factor IX, 7 to 8% of normal; and prothrombin about 9% of normal. Of the four factors, excessive depression of factors X and IX are most commonly associated with unexpected bleeding.\textsuperscript{19, 45} This is not surprising since factor X is poorly measured by the commercial thromboplastin in most common use, and factor IX is not measured at all by the prothrombin time.

The physician who prescribes oral use of anticoagulant drugs should recognize that the dose necessary to impair hemostasis is considerably greater than the dose required for effective anticoagulant therapy. When small vessel integrity is interrupted, platelets immediately congregate at that spot. ADP (adenosine diphosphate) is evolved and the platelets aggregate reversibly and proceed to form thrombin with the aid of plasma clotting factors adsorbed to their surfaces. With the formation of thrombin the platelet aggregation becomes irreversible and the platelet plug

\textit{Circulation, Volume XXXIV, November 1966}
is complete. Only later is fibrin formed in the plasma surrounding the area of injury. With clinically effective doses of coumarin or heparin drugs, the platelet plug formation is intact, but with doses of either anticoagulant above the therapeutic range, this phenomenon is suppressed and, with it, hemostatic integrity. If anticoagulants are to be given, however, they should be administered in full therapeutic doses since both laboratory and clinical evidence suggests that token therapy may be harmful.  

It should also be noted that neither the orally used anticoagulant agents nor heparin augment fibrinolysis or lyse clots. They do, however, prevent further thrombus formation and allow the body's normal fibrinolytic mechanisms to dispose of the thrombus. As indicated above, neither drug prevents the platelet thrombus unless excessive doses are given.

**Summary**

Information available at the present time allows the following conclusions to be drawn:

1. Anticoagulant therapy is clearly effective in treating and preventing venous thrombosis and pulmonary emboli.

2. If used in the treatment of acute myocardial infarction, anticoagulant drugs may salvage 3 to 4% of the treated population. This small gain is probably achieved by the prevention of thromboembolic episodes. While only a small percentage of patients are benefited, the actual number of persons salvaged is relatively great because of the large size of the population at risk. In the considerable majority of treated patients who do not benefit from coumarin drugs, the therapy need do no harm, if proper safeguards are employed in the selection of patients and the administration and laboratory control of the drug.

3. In long-term therapy of patients who have recovered from acute myocardial infarction, it appears that men, especially below age 60, may be helped for the first 1 or 2 years after infarction.

4. More data are required to evaluate the role of anticoagulant treatment in patients with angina pectoris or coronary insufficiency. For the present, the physician may reasonably be influenced in the use of anticoagulant therapy by the recent onset of symptoms, the patient's age, and the family history.

5. Although appropriately controlled studies are lacking, it appears as though patients with peripheral emboli secondary to coronary artery disease may be benefited by anticoagulant therapy.

**References**

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