The Control of Dicumarol Therapy in Myocardial Infarction by a Simple Blood Prothrombin Test

By Benjamin Manchester, M.D., and Boris Rabkin, M.D.

Effective anticoagulant therapy is dependent upon adequate and reliable blood prothrombin determinations. The initiation of such therapy usually requires hospitalization. The currently available blood prothrombin tests require special laboratory facilities and trained personnel. The authors of this report present the results of Dicumarol in myocardial infarction and a simple blood prothrombin test for the control of such anticoagulant therapy. The test has been employed for more than eight years. The method has proved to be simple, accurate, and practical, and has made anticoagulants possible for patients at home as well as in the hospital.

The value of Dicumarol and heparin in the prevention of thromboembolic disease and its complications seems well established. However, the indication for anticoagulant therapy in coronary occlusion with myocardial infarction has been challenged. The reduction in mortality because of Dicumarol is doubted; the need for anticoagulants by "good risk" patients is questioned. The hazard of bleeding or the development of sub-intimal hemorrhage and resultant extension of coronary occlusion have been offered as deterrents to the use of Dicumarol alone or with heparin.

Some observers have emphasized the difficulty of maintaining adequate, safe, therapeutic prothrombin levels. The difficulty of accurately performing the prothrombin test has not been overlooked. The one-stage method is too simple and the two-stage method too complicated. The Quick prothrombin time determination is found adequate by some, while others prefer a "modification" of the Quick prothrombin test. The whole-plasma and the plasma-dilution prothrombin time exponents each have their own followers. Finally, it is observed that the one-stage prothrombin time measures a complex made up chiefly of proconvertin and prothrombin.

Disagreement exists as to whether the prothrombin time should be expressed in seconds or per cent, as an index, or as the expression of a hyperbolic curve. The types of thromboplastin, the variability of thromboplastic activity, the inability to standardize a uniform thromboplastin have also presented problems which required study.

The added cost to the patient has been stressed. The requirement of trained technical personnel and adequate laboratory facilities have been considered to make the use of anticoagulants in the home difficult or even impracticable.

The psychologic factors, including the inconveniences to the patient and the psychic trauma produced by repeated venepunctures, have not been slighted.

Despite these hazards and objections, we have treated individuals with acute myocardial infarction with Dicumarol alone or with heparin, in the home and in the hospital. Since 1946, a total of 300 subjects with one or more myocardial infaracts have been studied. One hundred fifty without anticoagulants served as controls; the other 150 received Dicumarol and heparin. Both groups otherwise followed the same regimen and medication.

From the George Washington University School of Medicine, Department of Medicine, and the George Washington University Medical Service, District of Columbia General Hospital, Washington, D. C.

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TABLE 2.—A Comparison of the Bedside Prothrombin Test with the Quick, and the Link-Shapiro Methods*

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* Prothrombin time expressed in per cent.
Moreover, owing to inadequate laboratory facilities, lack of laboratory technicians and our awareness of the inaccuracy, variability, multiplicity and preferability of prothrombin methods, we employed a simple capillary blood prothrombin test, a modification of the Ziffren-Smith whole blood prothrombin test. The test was modified to a micromethod for bedside use; a procedure so simple that it can be performed by a completely inexperienced but conscientious, interested person. Two to three minutes are required to obtain a prothrombin time.

The purpose of this report is to describe a simple blood prothrombin test and to present the results of Dicumarol therapy regulated by this method.

MATERIALS AND METHODS

The 300 patients studied were under direct supervision of the authors either at home or in the hospital. Alternate cases in the first 224 patients received conventional therapy and constitute the "control" group, while the others received Dicumarol, alone or with heparin, in addition to conventional therapy and represent the anticoagulant group. The remaining 76 patients were selected according to the day first observed. Those first examined on the odd calendar date received anticoagulants while those seen on the even calendar date were placed in the control group. In addition to the clinical and laboratory findings, electrocardiographic confirmation of myocardial infarction was required for inclusion in the study.

Most of the patients were seen within 72 hours of the onset of their illness. Seventy-five subjects were seen one week after the onset of the acute coronary occlusion; 37 were in the control and 38 were in the anticoagulant group. All patients who died within the first 24 hours were not included in the present report.

A comparison of the patients in the two groups with regard to age, sex, previous infarction and severity of the present attack according to "good" and "poor" risk are shown in Table 1. The ages ranged from 31 to 81 years with a mean age of 58.5 for the anticoagulant and 61 for the control group. Forty-two and 48 per cent were 61 years old or over in the anticoagulant and control groups, respectively. Sixteen per cent in the treated group and 19.4 per cent in the control group were females.

A history of one or more previous myocardial infarctions was noted in 28 per cent in the anticoagulant group and in 23 per cent of the control group.

In the anticoagulant group 72 per cent received heparin and Dicumarol and 28 per cent received Dicumarol alone. The initial dose of Dicumarol was 200 to 300 mg. and thereafter 100 mg. daily until the prothrombin level was in the therapeutic range. For those who received heparin the prothrombin test was made three to four hours after the last dose or when the clotting time was normal. Daily prothrombin determinations were performed during the first 30 days, then repeated at weekly intervals for six or more weeks.

TECHNIC

The bedside method is a modified Ziffren-Smith prothrombin test. Two hemoglobin pipets, a concave slide, stop watch, physiologic saline solution and thromboplastin are the required materials. (See fig. 1.) The thromboplastin is prepared from acetone-desiccated rabbit brain as recommended by Quick. To 4 cc. of physiologic saline solution

Table 1.—Composition of Total Group: 300 Cases of Coronary Occlusion with Myocardial Infarction Surviving First Day of Illness

<table>
<thead>
<tr>
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<th>Anticoagulant</th>
<th>Control</th>
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<tr>
<td>No. of Cases</td>
<td>150</td>
<td>150</td>
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<tr>
<td>Av. Age</td>
<td>58.5</td>
<td>61</td>
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<tr>
<td>Males</td>
<td>126 (84%)</td>
<td>121 (80.6%)</td>
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<tr>
<td>With Previous Infarct</td>
<td>42 (28%)</td>
<td>34 (23%)</td>
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<tr>
<td>Good Risks</td>
<td>33 (22%)</td>
<td>47 (31%)</td>
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<tr>
<td>Poor Risks</td>
<td>117 (78%)</td>
<td>103 (69%)</td>
</tr>
<tr>
<td>Heparin and Dicumarol</td>
<td>108 (72%)</td>
<td>0</td>
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<tr>
<td>Dicumarol Alone</td>
<td>42 (28%)</td>
<td>0</td>
</tr>
<tr>
<td>Thromboembolic Complications</td>
<td>9 (6%)</td>
<td>26 (17.3%)</td>
</tr>
<tr>
<td>Mortality</td>
<td>18 (12%)</td>
<td>42 (26%)</td>
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0.15 Gm. of dried powdered rabbit brain is added. The mixture is then incubated for 20 minutes at 40 C.

Twenty cu. mm. of thromboplastin warmed to 37 C. are placed on a warm dry slide, and an equal amount of free-flowing capillary blood, obtained by a simple needle puncture of a finger, is added. The slide is tilted gently back and forth until a coagulum is formed. The time in seconds is the prothrombin time. The "total clotting time" for capillary blood is 15 to 18 seconds, with a standard deviation of 2.5 seconds. A normal blood prothrombin time on a control is always taken before it is determined on a patient. The therapeutic level is maintained at twice the normal (36 to 40 seconds). When the prothrombin time is expressed as a percentage of the normal the therapeutic level was maintained between 40 and 60 per cent. The equation for this determination is

Prothrombin index = \frac{\text{normal prothrombin time}}{\text{patient's prothrombin time}} \times 100

A comparison of this method with the Quick and Link-Shapiro blood prothrombin tests is shown in table 2. It compares favorably with the Link-Shapiro method. The values expressed in per cent in the Quick blood prothrombin test are based on a hyperbolic dilution curve. When the bedside prothrombin test, expressed in per cent, is 60 to 40, this corresponds to Quick prothrombin time expressed as 30 to 10 per cent, respectively. The bedside prothrombin test is discussed in greater detail in another report to be published.\(^{13}\)

**Results**

The subjects in both groups were classified with regard to prognosis according to the criteria of Russek and his co-workers\(^{11}\) as "good risk" and "poor risk" patients. Those who had previous myocardial infarction, angina pectoris, intractable pain, severe shock, cardiomegaly, congestive heart failure, auricular fibrillation or other serious arrhythmia, previous pulmonary embolism, or other states predisposing to thrombosis, were placed in the "poor risk" category. Patients without the above signs or symptoms were classified as "good risks." The grouping was made on the clinical examination excluding the electrocardiographic and other laboratory data.

The total mortality in the control group was 42, or 28 per cent, and in the anticoagulant group, 18 or 12 per cent (table 1). Clinical thromboembolic phenomena occurred in 26, or 17.3 per cent and in nine, or 6 per cent, in the control and anticoagulant groups, respectively.

Among the 47 good-risks in the control group, the mortality was six, or 12.8 per cent. Among the 33 good risks in the anticoagulant group there were three deaths, or 9.1 per cent.

Thromboembolism occurred in two of the good risks, or 4.2 per cent. Embolism was fatal in both of these cases. Death occurred 14 and 18 days, respectively, after the onset of illness and during otherwise uneventful convalescence. In the anticoagulant group thromboembolism also occurred in two patients, but the patients recovered from this complication.

The mortality in the 103 poor risks in the control group was 36, or 35 per cent, whereas in the anticoagulant group of 117 there were 15 deaths of 12.8 per cent. Thromboembolic complications in these poor risks showed a corresponding contrast. They occurred in 24, or 23.3 per cent, of the control group and in only seven, or 5.9 per cent, of the anticoagulant group. Death due to pulmonary embolism occurred 12 times among poor risks in the control group and once in the anticoagulant group. Pulmonary embolism in the remaining cases of both groups complicated by thromboembolism was the precipitating cause of severe congestive heart failure.

In poor risks with two or more myocardial

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<th>Table 3 — Mortality Rate and Incidence of Thromboembolic Complications in Control and Anticoagulant Groups</th>
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<td>Good Risk</td>
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<td>(^*) Fatal.</td>
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<td>(^†) Recovered.</td>
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infarctions treated with dicumarol the prognosis was better than in the comparable control patients. Among 42 such patients who received anticoagulant therapy, nine died, or 21.3 per cent (table 4). Embolization occurred four times, or in 9.9 per cent. In the control group of 36 subjects there were 21 fatalities, or 58.3 per cent, and embolism occurred in 14 subjects, or 38.8 per cent.

The causes of death in the control group of 150 were as follows: In 12 patients death followed pulmonary embolism; two patients died of ruptured hearts 14 and 20 days, respectively, after onset of the illness; 20 died of congestive heart failure; four died of extension of the myocardial infarct; and in four the cause of death was undetermined. Of 15 fatalities in the entire anticoagulant series of 150, one was due to pulmonary embolism, nine to congestive heart failure, three to sudden unexplained death, one to respiratory depression following intravenous morphine, and four to unknown causes.

Hemorrhagic complications were noted in 16, or 10.6 per cent of treated patients. The hemorrhagic manifestations were distributed as follows: epistaxis in two, ecchymoses on the body in eight, hematuria in four, and hema-
temesis and hemoptysis in two. If one excludes epistaxis and ecchymoses, the incidence of hemorrhagic complications would be six, or 4 per cent. There were no deaths from hemor-
raghe in the group treated with anticoagulants. Hemorrhagic complications were the cause of death in two, or 1.33 per cent of the control group, as a result of ventricular rupture and cardiac tamponade.

**Discussion**

The greatest deterrent to the use of dicumarol therapy is the fact that a simple, accurate and inexpensive method for measuring blood prothrombin activity has not been available. Methods currently employed require trained technical personnel and laboratory facilities. The present report is unique in one respect: dicumarol has been given to patients with coronary thrombosis and infarction in the home as well as in the hospital. Effective antithrombotic levels as measured by a simple blood prothrombin test were maintained without the increased hazard of bleeding.

Whole blood for performing a blood prothrombin test has been employed by many investigators in the past. A similar method employing capillary blood was first described by Quick in 1939.14 Tocantins15 has employed whole venous blood for the ziffren-smith prothrombin test in his routine control of anticoagulant therapy. Bruzelius16 in Sweden has used a similar micromethod for dicumarol therapy. Several modifications of a similar type of prothrombin test have been reported.17-21 So far as is known, the present report is the first to deal with a large series of patients with acute myocardial infarction in which dicumarol dosage has been controlled by such a simple blood prothrombin test.

A comparison of this bedside prothrombin test with current one-stage procedures shows it to have much in common with the latter. The term “prothrombin test” for such methods is a misnomer. Both measure more than prothrombin activity. It has been shown that the one-stage prothrombin test measures prothrombin, fibrinogen, and accelerator factors.22 The prothrombin time, therefore, is an accelerated “clotting test” and reflects more than prothrombin concentration.

The present method is not without its pitfalls. The accuracy and sensitivity of this test was dependent upon an active and reliable source of thromboplastin. While normal plasma yielded the same prothrombin time with different types of thromboplastin, dicumarol plasma behaved differently with various types of thromboplastin. The results reported here can only be reproduced if desiccated acetone-dehydrated rabbit brain is used as the source of thromboplastin. The thromboplastin activity may vary with the age, temperature and
amount employed. A control prothrombin time must always be determined first on a normal subject.

The described test has proved a valuable practical guide to Dicumarol therapy for the prevention of thromboembolic complications. At the same time it was possible to detect hypoprophrothrombinemia and to prevent hemorrhagic complications. The usefulness of the simple blood prothrombin test which we have employed for the control of Dicumarol therapy is reflected in the therapeutic efficacy and safety noted in this series. The results compare favorably with the reports of other investigators using other prothrombin tests.

Those who challenge the value of anticoagulant therapy have suggested that the favorable results noted in the literature may be due primarily to the added attention given to all patients who have received anticoagulant drugs. Every effort was made in the study to follow an identical medical regimen and provide the same attention to the patients in both groups.

It has been postulated that in addition to prevention of thromboembolic complication, anticoagulants prevent congestive failure, ventricular fibrillation and cardiac asystole by the prevention of intravascular coronary thrombosis. Gilbert and Nalefski have suggested that the favorable results observed from Dicumarol were due primarily to an increase in coronary blood flow. Gilchrist believed that in addition to the reduction in thromboembolism, anticoagulants had a favorable influence on the associated shock syndrome.

The collective statistics from the proponents of anticoagulant therapy have been critically probed for defects and inaccuracies. Those who challenge the value of anticoagulant therapy emphasize the comparable low incidence of mortality in good risks not treated with anticoagulants. The occasional thromboembolic complication would have little influence on the over-all mortality rate and hence would justify their view. However rare, this complication did occur and proved fatal to two in our control group. While the increased mortality from such a complication was only 4.2 per cent, hardly significant statistically, the unpredictability of such a complication in a good risk increased the responsibility of avoiding a preventable fatality from thromboembolism. To a family, the survival of such a patient assumes greater importance than any significant statistical figure. These observations are in agreement with Wright's earlier admonitions.

One critic has agreed that anticoagulants are indicated in the poor risk. The mortality in the control group was 35 per cent as against 12.3 per cent in the anticoagulant group. Death was nearly three times more frequent in the control group. Thromboembolic complications showed a decrease in the anticoagulant group. The prognosis in the poor risk group with two or more myocardial infarctions treated with Dicumarol was better than in the comparable control group. The mortality was reduced from 58.3 per cent to 21.3 per cent, and embolization from 38.8 to 9.3 per cent. These results have afforded an increased sense of security and a more favorable prognosis. It was not vitiated by either anxiety or fear of hemorrhage. The results of this study indicate that the advantages of Dicumarol therapy were greater than all the disadvantages reported to date.

The hazard of hemorrhage was nevertheless present. Without careful clinical observation, attention to detail, and an awareness of idiosyncrasies, many medicaments are dangerous and even fatal. The incidence of hemorrhagic complications was low and compares well with previous reports. Frequent prothrombin determinations made it possible to detect levels of hypoprothrombinemia before hemorrhagic complications developed. The withdrawal of Dicumarol and administration of vitamin K, orally or parenterally, was always effective in stopping these manifestations. It was unnecessary to hospitalize the patient or to administer blood. Bleeding usually ceased within 6 to 10 days. There were no deaths from this cause.

**Summary**

The control of Dicumarol therapy in acute myocardial infarction by a simple capillary blood prothrombin test has proved convenient,
practical and economical. It was possible to administer anticoagulant therapy to 150 patients with myocardial infarction at home and in the hospital. An additional 150 subjects who did not receive anticoagulants served as controls. Except for Dicumarol, alone or with heparin, both groups followed the same regimen and received the same medication.

Mortality in the anticoagulant group was 12 per cent; in the control group it was 28 per cent. Among 33 subjects in the “good risk” group treated with Dicumarol, there were three deaths (9.1 per cent); while in 47 of the good risks in the control group, the mortality rate was six (12.8 per cent). The mortality among 117 cases of the “poor risk” anticoagulant group was 15 (12.8 per cent). Among the poor risks of the control group of 103 cases, there were 36 deaths (35 per cent).

Thromboembolic complications developed in nine (6 per cent) of the treated patients as against 26 (17.3 per cent) in the control group.

Death due to pulmonary embolism occurred in one subject (0.66 per cent) in the treated group and in 12 (8 per cent) in the control group. Two of the deaths in the latter group occurred among the good risks. The prognosis in the poor risk group with two or more myocardial infarctions treated with Dicumarol was better than among poor risks of the control group.

Hemorrhagic complications were noted in 16 (10.6 per cent) of the treated and in two (1.33 per cent) of the control group.

The advantages of Dicumarol therapy, properly administered, were greater than all the disadvantages reported to date.

The value of the simple blood prothrombin test employed for the control of Dicumarol therapy is reflected in the therapeutic efficacy and safety noted in this series. It compares favorably with the reports of other investigators using other prothrombin tests.

**SUMARIO ESPAÑOL**

El control de la terapia de Dicumarol en el infarto del miocardio agudo por medio de una prueba sencilla de protrombina capilar sanguínea ha probado ser conveniente, práctico y económico. Fué posible administrar terapia anticoagulante a 150 pacientes con infartos del miocardio en su hogar y en el hospital. Unos 150 casos adicionales que no recibieron anticoagulantes sirvieron de controles. Excepto por Dicumarol, solo o con heparina, ambos grupos siguieron el mismo régimen y recibieron el mismo medicamento.

La mortalidad en el grupo a que se les administró anticoagulante fué de 12 por ciento; en el grupo control fué 28 por ciento. Entre 33 sujetos en el grupo “buen riesgo” tratados con Dicumarol, ocurrieron tres muertes (9.1 por ciento); mientras que en 47 de los buenos riesgos en el grupo control, la mortalidad fue de seis (12.8 por ciento). La mortalidad entre 117 casos de los riesgos pobres en el grupo tratado con anticoagulante fué 15 (12.8 por ciento). Entre los riesgos pobres en el grupo control de 103 casos, hibieron 36 muertes (35 por ciento). Complicaciones tromboembólicas se desarrollaron en nueve (6 por ciento) de los pacientes tratados en contraste a 26 (17.3 por ciento) del grupo control.

Muerte debida a embolismo pulmonar ocurrió en un sujeto (0.66 por ciento) en el grupo con anticoagulante y en 12 (8 por ciento) del grupo control. Dos de las muertes en este último grupo ocurrieron entre los buenos riesgos. El prognóstico en el grupo de riesgo pobre con dos o más infartos del miocardio tratados con Dicumarol fué mejor que en el grupo de pobres riesgos en el grupo control.

Complicaciones hemorrágicas fueron observadas en 16 (10.6 por ciento) de los tratados y en dos (1.33 por ciento) del grupo control. Las ventajas de la terapia con Dicumarol propiamente administrada, fueron mayores que todas las desventajas informadas hasta la fecha.

El valor de la prueba sencilla de protrombina sanguínea empleada en el control de la terapia con Dicumarol se refleja en la eficacia terapéutica y la inocuidad notada en esta serie. Compasa favorably con los informes de otros investigadores usando otras pruebas de protrombina.

**Acknowledgments**

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REFERENCES


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